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BICYCLE THERAPEUTICS LIMITED

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As confidentially submitted to the Securities and Exchange Commission on March 22, 2019 as Amendment No. 1 to the Confidential Submission dated December 21, 2018.
This draft registration statement has not been publicly filed with the Securities and Exchange Commission and all information herein remains strictly confidential.

Registration No. 333-

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

BICYCLE THERAPEUTICS LIMITED*

(Exact Name of Registrant as Specified in Its Charter)

England and Wales	**2834**	**Not Applicable**
(State or Other Jurisdiction of Incorporation or Organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

Bicycle Therapeutics Limited
B900, Babraham Research Campus
Cambridge CB22 3AT
United Kingdom
+44 1223 261503
(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

Bicycle Therapeutics Inc.
4 Hartwell Place
Lexington, Massachusetts 02421
Attention: Lee Kalowski
617-945-8155
(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent For Service)

Copies to:

Kristopher D. Brown **James Xu** **Jonathan A. Schur** **Goodwin Procter LLP** **620 Eighth Avenue** **New York, NY 02109** **(212) 813-8800**	**Graham Defries** **Goodwin Procter (UK) LLP** **100 Cheapside** **London EC2V 6DY** **United Kingdom** **+44 20 7447 4200**	**Ed Lukins** **Edward Dyson** **Cooley (UK) LLP** **Dashwood** **69 Old Broad Street** **London EC2M 1QS** **United Kingdom** **+44 20 7785 9355**	**Divakar Gupta** **Ryan Sansom** **Richard Segal** **Cooley LLP** **1114 Avenue of the Americas** **New York, NY 10036** **(212) 479-6000**

Approximate date of commencement of proposed sale to the public:
As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended, check the following box. o

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer o	Accelerated Filer o	Non-Accelerated Filer o	Smaller Reporting Company ☒ Emerging Growth Company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

CALCULATION OF REGISTRATION FEE

Title of each class of securities	**Proposed maximum**	**Amount of**

to be registered	aggregate offering price(1)	registration fee(2)
Ordinary shares, nominal value £0.01 per share(3)	$	$

(1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended. Includes the aggregate offering price of additional ordinary shares represented by American Depositary Shares, or ADSs, that the underwriters have the option to purchase.

(2) Calculated pursuant to Rule 457(o) under the Securities Act of 1933, as amended, based on an estimate of the proposed maximum aggregate offering price.

(3) These ordinary shares are represented by ADSs, each of which represents one ordinary share of the registrant. ADSs issuable upon deposit of the ordinary shares registered hereby are being registered pursuant to a separate registration statement on Form F-6 (File No. 333-).

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until this registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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* We intend to alter the legal status of our company under English law from a private limited company by re-registering as a public limited company and changing our name from Bicycle Therapeutics Limited to Bicycle Therapeutics plc prior to the completion of this offering.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion. Dated , 2019

American Depositary Shares

Representing Ordinary Shares

This is an initial public offering of the American Depositary Shares, or the ADSs, of Bicycle Therapeutics plc. We are offering ADSs. Each ADS represents one ordinary share, nominal value £0.01 per share.

Prior to this offering, there has been no public market for the ADSs or our ordinary shares. It is currently estimated that the initial public offering price per ADS will be between $ and $. We intend to apply to list the ADSs on the Nasdaq Global Market under the symbol "BCYC."

We are an "emerging growth company" as that term is used in the U.S. Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

See "Risk Factors" on page 15 to read about factors you should consider before buying the ADSs.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

	Per ADS	Total
Initial public offering price	$	$
Underwriting discounts[(1)]	$	$
Proceeds, before expenses, to Bicycle Therapeutics	$	$

(1) See the section titled "Underwriting" for compensation payable to the underwriters.

To the extent the underwriters sell more than ADSs, the underwriters have the option to purchase up to an additional ADSs from us at the initial public offering price less the underwriting discounts.

The underwriters expect to deliver the ADSs against payment in New York, New York on , 2019.

Goldman Sachs & Co. LLC **Jefferies** **Piper Jaffray**

Canaccord Genuity

Prospectus dated , 2019

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We have not, and the underwriters have not, authorized any person to provide you with information different from that contained in this prospectus or any related free-writing prospectus that we authorize to be distributed to you. This prospectus is not an offer to sell, nor is it seeking an offer to buy, these securities in any jurisdiction where the offer or sale is not permitted. The information in this prospectus speaks only as of the date of this prospectus unless the information specifically indicates that another date applies, regardless of the time of delivery of this prospectus or of any sale of the securities offered hereby.

For investors outside of the United States: We have not, and the underwriters have not, done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the United States. Persons outside of the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the ADSs and the distribution of this prospectus outside of the United States.

ABOUT THIS PROSPECTUS

Prior to the completion of this offering, we intend to re-register Bicycle Therapeutics Limited as a public limited company and to change our name from Bicycle Therapeutics Limited to Bicycle Therapeutics plc.

Unless otherwise indicated or the context otherwise requires, all references in this prospectus to the terms "Bicycle Therapeutics Limited," "Bicycle Therapeutics plc," "the company," "we," "us" and "our" refer to (i) Bicycle Therapeutics Limited and its wholly owned subsidiaries prior to the re-registration of Bicycle Therapeutics Limited as a public company, and (ii) Bicycle Therapeutics plc and its subsidiaries after the re-registration of Bicycle Therapeutics Limited as a public limited company, which shall occur prior to the completion of this offering. See "Share Capital Reorganization and Re-Registration" for more information.

We own various trademark registrations and applications, and unregistered trademarks, including our name and our corporate logo. All other trade names, trademarks and service marks of other companies appearing in this prospectus are the property of their respective holders. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend to use or display other companies' trademarks and trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

PRESENTATION OF FINANCIAL INFORMATION

We maintain the books and records of Bicycle Therapeutics Limited, and its wholly owned subsidiaries in the United Kingdom, BicycleTx Limited and BicycleRD Limited in pounds sterling. For financial reporting, our results are translated to U.S. dollars and we prepare our consolidated financial statements in accordance with generally accepted accounting principles in the United States, or U.S. GAAP, as issued by the Financial Accounting Standards Board. All references in this prospectus to "$" are to U.S. dollars and all references to "£" are to pounds sterling.

Unless otherwise indicated, certain pounds sterling amounts contained in this prospectus have been translated into U.S. dollars at the rate of $1.2763 to £1.00, which was the noon buying rate of the Federal Reserve Bank of New York on December 31, 2018, the last business day of the year ended December 31, 2018. These translations should not be considered representations that any such amounts have been, could have been or could be converted into pounds sterling at that or any other exchange rate as of that or any other date. See "Exchange Rate Information" for more information.

We have made rounding adjustments to some of the figures included in this prospectus. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them. We have historically conducted our business through Bicycle Therapeutics Limited's subsidiaries, BicycleRD Limited, BicycleTx Limited and Bicycle Therapeutics Inc., and therefore our historical consolidated financial statements present the consolidated results of operations of Bicycle Therapeutics Limited. After the re-registration of Bicycle Therapeutics Limited into Bicycle Therapeutics plc and following the completion of this offering, our consolidated financial statements will present the consolidated results of operations of Bicycle Therapeutics plc.

PROSPECTUS SUMMARY

Overview

We are a clinical-stage biopharmaceutical company developing a novel class of medicines, which we refer to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained to form two loops which stabilize their structural geometry. This constraint is designed to confer high affinity and selectivity and the relatively large surface area presented by the molecule allows targets to be drugged that have historically been intractable to non-biological approaches. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic, or PK, properties of a small molecule. *Bicycles* are excreted by the kidney rather than the liver and have shown no signs of immunogenicity to date, which we believe together support a favorable toxicological profile.

We have a novel and proprietary phage display screening platform which we use to identify *Bicycles* in an efficient manner. The platform initially displays linear peptides on the surface of engineered bacteriophages, or phages, before "on-phage" cyclization with a range of small molecule scaffolds which can confer differentiated physicochemical and structural properties. Our platform encodes quadrillions of potential *Bicycles* which can be screened to identify molecules for optimization to potential product candidates. We have used this powerful screening technology to identify our current portfolio of candidates in oncology and intend to use it in conjunction with our collaborators to seek to develop additional future candidates across a range of other disease areas.

Our initial internal programs are focused on oncology indications with high unmet medical need. Our lead product candidate, BT1718, is a *Bicycle* Toxin Conjugate, or BTC. This *Bicycle* is being developed to target tumors that express Membrane Type 1 matrix metalloprotease, or MT1-MMP. The *Bicycle* is chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK, or CRUK. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019. We are also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2, or EphA2, and Nectin-4, respectively, for oncology indications. BT5528 and BT8009 are being investigated for safety, activity and to establish a rationale for therapeutic use in preclinical studies. We are currently conducting Investigational New Drug application, or IND, -enabling activities for BT5528 and BT8009. Our discovery pipeline in oncology includes *Bicycle*-targeted innate immune activators, as well as T-cell modulators.

Beyond oncology, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas where we believe our proprietary *Bicycle* screening platform can identify therapies to treat diseases with significant unmet medical need. Our partnered programs outside of oncology include collaborations for anti-bacterial, cardiovascular, hematology, ophthalmology and respiratory indications.

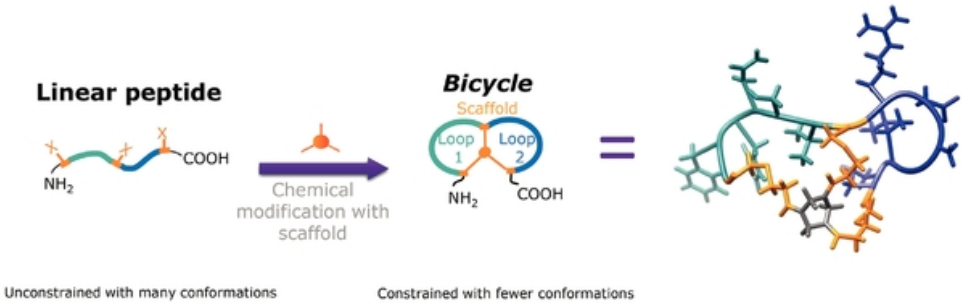
We were founded in 2009 based on innovative science conducted by Sir Greg Winter and Professor Christian Heinis. Sir Greg Winter is a pioneer in monoclonal antibodies and, in 2018, was awarded a Nobel prize in chemistry for the invention of the technology underpinning our proprietary phage display screening platform that we use to identify *Bicycles*. Since our founding, we have generated substantial intellectual property, including three patent families directed to novel scaffolds, 11 patent families directed to our platform technology, 52 patent families directed to bicyclic peptides and related conjugates, and four patent families directed to clinical indications. The work we have conducted in developing *Bicycles* and our proprietary screening platform have created substantial know-how that we believe provides us with a competitive advantage.

Introduction to *Bicycles*

Bicycles are fully synthetic, short peptides consisting of nine to 15 amino acids constrained to form two loops which stabilize the structural geometry of the peptide and facilitate target binding with high affinity and selectivity. *Bicycles* represent a unique therapeutic class, combining the pharmacological properties normally associated with a biologic with the manufacturing and PK advantages of a small molecule, with no signs of immunogenicity observed to date.

Drugs must bind to target proteins with high affinity and selectivity to achieve a therapeutic effect, while minimizing undesired effects on other proteins and physiological functions. Peptides exist in a number of folded states, only a few of which are able to bind to target proteins, and a key challenge for peptide therapeutics is designing structures that achieve these goals. We have designed our molecules to be highly constrained by linking a chemical connector compound, also known as a scaffold, to particular amino acids in the peptide chain. The resulting cyclized molecule, which we refer to as a *Bicycle*, is locked in the preferred state to bind to the target proteins.

Schematic of the Creation of a Cyclized Molecule Resulting in a Bicycle



We have expanded the diversity of the chemical space we can cover from approximately 10^{13} potential molecules in 2009 to 10^{17} today. We have applied our novel *Bicycle* modality to a growing range of targets, from a single target in 2009 to more than 90 today. We can create a wide range of *Bicycles* by varying four parameters:

- the number of amino acids in the two loops;
- the amino acid composition at each position;
- the symmetry of the two loops; and
- the small molecule scaffold used to cyclize the *Bicycle*.

Bicycles have a large surface area available for target binding, which is designed to allow high affinity and selectivity to the designated target. As short sequences of amino acids, or peptides, they have a low molecular weight, typically ranging from 1.5 kDa to 2.0 kDa. *Bicycles* have a readily adjustable PK profile with good plasma stability and rapid distribution from the vasculature into the extracellular space. This PK profile enables rapid tissue penetration and a renal route of elimination that minimizes liver exposure. Toxicity issues are observed with small molecules that are metabolized and eliminated by the liver. *Bicycle* peptides, by contrast, are not subject to metabolism or elimination by the liver but are metabolized in the peripheral circulation or kidney with subsequent rapid excretion in the urine. Consequently, by increasing excretion in urine, the liver exposure is minimized and the risk of liver toxicity is reduced. The modular nature of *Bicycles*

allows us to optimize therapeutic molecules for specific targets. To date, we have observed no signs of immunogenicity.

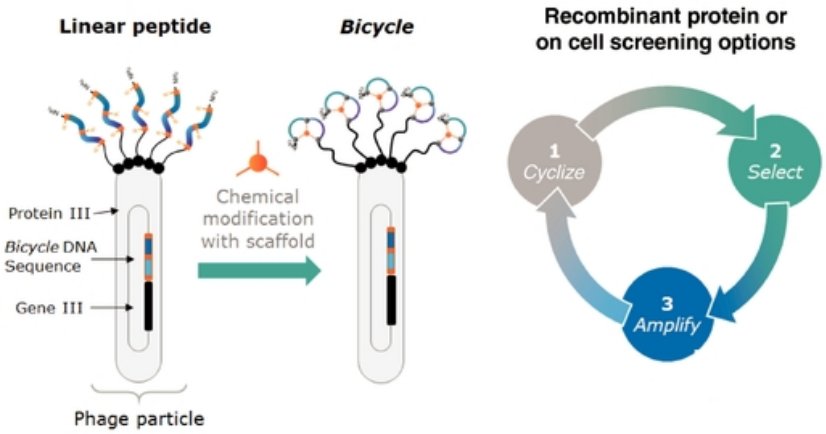
Compared to biologics, *Bicycles* have a lower cost of production and a simpler manufacturing process, and are recognized by regulatory authorities as small molecule new chemical entities. *Bicycles* can be readily identified to drug a wide spectrum of targets and target classes, including many that have so far been undruggable with small molecules, such as protein-protein interactions. Our novel and proprietary screening platform allows us to screen *Bicycles* against molecular targets quickly and efficiently, affording potentially reduced timelines and costs compared to other high-throughput screening approaches. Leveraging our platform, we can rapidly and efficiently identify a compound for development in only six to 12 months after a target has been selected.

Our Proprietary *Bicycle* Screening Platform

We utilize our novel and proprietary phage display screening platform to identify *Bicycles* that are potentially useful in medicine. We have used this technology to identify our current pipeline, and intend to leverage it to develop a broader portfolio of product candidates to address unmet medical needs across a wide range of diseases.

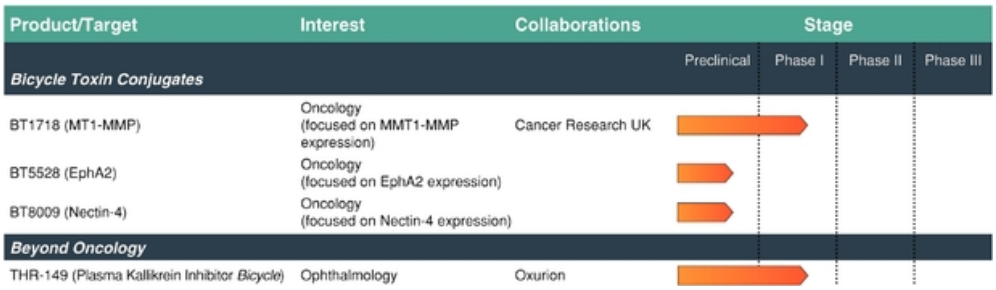
Our screening process self-selects for *Bicycles* that are amenable to attachment, commonly referred to as conjugation, to other molecular payloads such as cytotoxins, innate immune activators or other *Bicycles*. *Bicycles* can be linked together with synthetic ease to create complex molecules with combinatorial pharmacology. Alternatively, *Bicycles* in the form of multimers can also be used as standalone therapeutics, such as those that we are exploring in our T-cell modulator program. We believe that the flexibility of *Bicycles* and our powerful screening platform allow new therapeutics to be rapidly conceived and reduced to practice to potentially serve diverse therapeutic applications across a wide range of indications.

Schematic of our Proprietary Bicycle Screening Process



Our Pipeline

The following table summarizes key information about our pipeline programs.



***Bicycle* Toxin Conjugates**

BT1718

Our lead product candidate, BT1718, is a BTC that we are developing for oncology indications. The molecule is comprised of our MT1-MMP targeting *Bicycle*, a hindered disulphide cleavable linker and a cytotoxin DM1 payload.

MT1-MMP is a matrix metalloprotease involved in tissue remodeling and is generally expressed at relatively low levels in normal adult tissues. MT1-MMP has an established role in cell invasion and metastasis, and we believe that MT1-MMP is an attractive target for cytotoxin delivery due to its high level of expression on stromal and tumor cell subsets in various cancers, including breast, lung, sarcoma, gastric, bladder, endometrial and ovarian cancers.

In our preclinical studies, we observed that BT1718 was associated with the greatest anti-tumor effect when membrane staining for MT1-MMP was high. Tumors with lower levels of expression of MT1-MMP were observed to have reduced levels of response to BT1718. We are collaborating with leading cancer researchers to determine MT1-MMP expression levels across a panel of tumor types, which will help inform patient selection for further clinical development. One of the goals of our clinical trials is to better understand the relationship between the level of target expression and activity of BT1718.

BT1718 is being investigated in an ongoing Phase I/IIa open label dose escalation and expansion clinical trial sponsored by CRUK. Up to 40 patients with advanced solid tumors are being enrolled in the ongoing Phase I part of this trial at three sites in the United Kingdom in which two dosing regimens are being evaluated. Once a recommended Phase IIa dose has been determined, the Phase IIa part of the trial is expected to commence.

BT5528

BT5528 is a BTC designed to target EphA2. The molecule is comprised of our EphA2 targeting *Bicycle*, a valine-citrulline, or val-cit, cleavable linker and a cytotoxin MMAE payload.

EphA2 is a member of the Ephrin superfamily of receptor tyrosine kinases regulating cell migration, adhesion, proliferation and differentiation. EphA2 is expressed at relatively low levels in normal adult tissues but is overexpressed in numerous difficult to treat tumors including lung, breast, bladder, gastric, ovarian, endometrial, cervical, melanoma and glioma. In both cell-derived and patient-derived preclinical models, we observed target-dependent anti-tumor activity signals following administration of our EphA2 toxin conjugates.

Our IND-enabling preclinical studies for BT5528 are currently ongoing.

BT8009

BT8009 is a BTC designed to target Nectin-4. The molecule is comprised of our Nectin-4 targeting *Bicycle*, a val-cit cleavable linker, and a cytotoxin monomethyl auristatin E payload.

Nectin-4 (also known as PVRL4) is a cell adhesion molecule from the Nectin and Nectin-like family, members of which are integral to the formation of the homotypic and heterotypic cell junctions. Nectin-4 has been shown to be overexpressed in tumor cells and is believed to play a role in tumor cell growth and proliferation. High in normal embryonic and fetal tissue, Nectin-4 declines in adulthood, showing a limited distribution in healthy tissues. However, Nectin-4 is expressed on tumor cells in numerous cancer types including bladder, breast, gastric, lung and ovarian. In addition, we believe the favorable characteristics of BTC-targeted therapies may address some of the challenges in treating pancreatic cancer.

Our IND-enabling preclinical studies for BT8009 are currently ongoing.

Bicycle-Targeted Innate Immune Activators

Local activation of the innate immune system within tumors is a promising area for cancer drug discovery. Many of the current clinical programs require direct injection of molecules activating the innate immune system into tumors to avoid excessive systemic activation of the immune system and associated toxicity. Based on our experience with BTCs, we believe that *Bicycles* can systemically deliver activators of the innate immune system to tumors without activating the immune system in normal tissues. We believe that this approach has the potential to avoid the need for direct tumor injection and to allow inaccessible tumors to be reached, while enabling rapid systemic elimination of excess payloads in an inactive form.

Bicycle T-Cell Modulators

CD137

We are developing cytotoxic T-cell activators, designed to trigger an immune response to tumors. We have identified potent *Bicycle* activators of CD137, a tumor necrosis factor receptor, or TNFR, family member. We believe that *Bicycles* represent a differentiated approach to target CD137 that may confer several advantages over existing modalities due to the multivalency and PK characteristics of *Bicycles*. Our *Bicycle* T-cell modulators are designed to circumvent the limitations of antibody and biologic therapies, such as liver toxicity and limited efficacy, and to better enable combination therapy. We are also exploring CD137 in a bi-specific format linked to other *Bicycles* that bind tumor antigens, inhibit checkpoint proteins or otherwise activate the immune system.

Beyond Oncology

We have entered into several collaborations outside of our internal focus in oncology to leverage the broad applicability of *Bicycles*. Our strategic collaborations are based on the ability of *Bicycles* to address a wide variety of targets and we are working with collaborators with deep therapeutic expertise outside of oncology to enable us to more efficiently develop novel medicines for patients.

AstraZeneca. In November 2016, we entered into a research collaboration agreement with AstraZeneca AB, or AstraZeneca, with a focus on targets within respiratory, cardiovascular and metabolic disease.

Bioverativ. In August 2017, we entered into a collaboration agreement with Bioverativ, Inc., or Bioverativ, focused on hemophilia and sickle cell disease.

Oxurion. In August 2013, we entered into a research collaboration and license agreement with Oxurion NV (formerly ThromboGenics NV), or Oxurion, focused on ophthalmology. The lead molecule of the partnership is THR-149, a novel plasma kallikrein inhibitor, for the treatment of diabetic macular edema. A Phase I clinical trial of THR-149 is currently ongoing.

Our Strategy

Our mission is to become a leading biopharmaceutical company by pioneering *Bicycles* as a novel therapeutic modality to treat diseases that are inadequately addressed with existing treatment modalities. Specifically, we seek to execute on the following strategy to maximize the value of our novel technology and pipeline:

- ***Advance our lead product candidate, BT1718, through clinical development.*** BT1718 is being investigated in an ongoing Phase I/IIa clinical trial sponsored by CRUK. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019. We intend to advance development of this candidate aggressively across oncology indications in which the target MT1-MMP is expressed.

- ***Advance our other Bicycle Toxin Conjugate programs into clinical development.*** We intend to progress our IND-enabling activities for BT5528 and BT8009 to advance these programs into clinical development for oncology indications. Based on promising observations from our preclinical models, we believe EphA2 and Nectin-4 are attractive targets for cytotoxin delivery and that *Bicycles* provide a promising delivery modality.

- ***Pursue clinical development of our discovery programs.*** We intend to continue our ongoing discovery activities to screen and select promising candidates for oncology indications. For example, our discovery pipeline includes T-cell modulators, from which we expect to identify a development candidate. In addition, we are also developing *Bicycle*-targeted innate immune activators.

- ***Leverage our powerful proprietary screening platform and novel Bicycle modality to grow our pipeline.*** Our novel and proprietary phage display screening platform allows us to rapidly and efficiently identify potential candidates for development. We can incorporate a wide range of small molecule scaffolds into *Bicycles* to increase diversity and confer differentiated physicochemical and structural properties. We have used our powerful *Bicycle* screening platform to identify our current pipeline of promising BTCs, innate immune activators and T-cell modulators, and intend to use it to develop a broader pipeline of diverse product candidates.

- ***Collaborate strategically with leading organizations to access enabling technology and expertise in order to expand the application of our novel Bicycle modality to indications beyond oncology.*** We are collaborating with leading biopharmaceutical companies and organizations to apply our novel *Bicycle* modality to other disease areas, including anti-bacterial, cardiovascular, hematological, ophthalmological and respiratory indications. We may opportunistically enter into additional collaborations in the future to apply our technology to areas of unmet medical need.

- ***If approved, maximize the commercial potential of our product candidates by either establishing our own sales and marketing infrastructure or doing so through collaborations with others.*** Subject to receiving marketing approval, we intend to pursue the commercialization of our product candidates either by building internal sales and marketing capabilities or doing so through opportunistic collaborations with others.

Our Team

Our management team includes veterans in drug development with executive experience at leading pharmaceutical companies including GlaxoSmithKline, Novartis and Pfizer. Our board of directors and scientific advisory board include industry experts and seasoned investors, with extensive experience in immuno-oncology. We are supported by prominent healthcare-focused investment funds, including Ahren Innovation Capital, Atlas Venture Fund, Cambridge Innovation Capital, Longwood Fund, Novartis Venture Fund, S.R. One, Limited, SV Life Sciences, Tybourne Capital (HK) Management Limited and Vertex HC Ventures.

Our Intellectual Property

We have generated substantial intellectual property, including three patent families directed to novel scaffolds, 11 patent families directed to Bicycle's platform technology, 52 patent families directed to bicyclic peptides and related conjugates, and four patent families directed to clinical indications. The work we have conducted in developing *Bicycles* and our proprietary screening platform have created substantial know-how that we believe provides us with a competitive advantage.

Corporate History

In 2009, we were incorporated as a limited liability company under the laws of England and Wales. In 2017, we effected a reorganization to create a new holding company which, in connection with this offering, will be re-registered as a public limited company named Bicycle Therapeutics plc., which will be the issuer of the securities described in this prospectus. Bicycle Therapeutics plc will be the parent company of three wholly owned subsidiaries, two of which are based in Cambridge, England and one of which has its principal office in Lexington, Massachusetts, near Boston, that will carry on our business.

The English subsidiaries are BicycleTx Limited and BicycleRD Limited, and the U.S. subsidiary is Bicycle Therapeutics Inc. Our principal executive offices are located at B900, Babraham Research Campus, Cambridge, CB22 3AT, United Kingdom, and our phone number is +44 1223 261503. Our website address is http://www.bicycletherapeutics.com. The information contained in or accessible from our website is not incorporated into this prospectus, and you should not consider it part of this prospectus.

Share Capital Reorganization and Re-Registration

Prior to the consummation of this offering, Bicycle Therapeutics Limited will be re-registered as a public limited company and will change its name from Bicycle Therapeutics Limited to Bicycle Therapeutics plc. Please see the "Share Capital Reorganization and Re-Registration" section for more information.

Risks Affecting Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. You should carefully consider all of the information set forth in this prospectus and, in particular, should evaluate the specific factors set forth in the section titled "Risk Factors" before deciding whether to invest in our ADSs. Among these important risks are, but not limited to, the following:

- We have a history of significant operating losses and expect to incur significant and increasing losses for the foreseeable future, and we may never achieve or maintain profitability.

- Even if this offering is successful, we will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.
- Our product candidates and those of our collaborators will need to undergo preclinical and clinical trials that are time consuming and expensive, the outcomes of which are unpredictable, and for which there is a high risk of failure. If preclinical or clinical trials of our or their product candidates fail to satisfactorily demonstrate safety and efficacy to the FDA, the EMA and any other comparable regulatory authority, additional costs may be incurred or delays experienced in completing the development of these product candidates, or their development may be abandoned.
- Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate.
- We are at a very early stage in our development efforts, our product candidates and those of our collaborators represent a new category of medicines and may be subject to heightened regulatory scrutiny until they are established as a therapeutic modality.
- We may not be successful in our efforts to identify or discover additional product candidates.
- We face significant competition and if our competitors develop and market products that are more effective, safer or less expensive than the product candidates we develop, our commercial opportunities will be negatively impacted.
- As a company based outside of the United States, we are subject to economic, political, regulatory and other risks associated with international operations.
- For certain product candidates, we depend, or will depend, on development and commercialization collaborators to develop and conduct clinical trials, obtain regulatory approvals, and if approved, market and sell product candidates. If such collaborators fail to perform as expected, the potential for us to generate future revenue from such product candidates would be significantly reduced and our business would be harmed.
- If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.
- If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.
- Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.
- We do not know whether an active, liquid and orderly trading market will develop for our ADSs or what the market price of our ADSs will be. As a result, it may be difficult for you to sell your ADSs.

Implications of Being an Emerging Growth Company

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012. For so long as we remain an emerging growth company, we are permitted and intend to rely on certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments not previously approved. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock. See "Management's Discussion and Analysis of Financial Condition and Results of Operations — Emerging Growth Company Status."

We will remain an emerging growth company until the earlier to occur of (1) the last day of 2023, (2) the last day of the fiscal year in which we have total annual gross revenues of at least $1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a "large accelerated filer," under the rules of the U.S. Securities and Exchange Commission, or SEC, which means the market value of our equity securities that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (4) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of delayed adoption of new or revised accounting standards and, therefore, we will be subject to the same requirements to adopt new or revised accounting standards as other public companies that are not emerging growth companies.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our ordinary shares held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including exemption from the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

The Offering

ADSs offered by us	ADSs, each ADS representing one ordinary share.
Ordinary shares outstanding immediately after this offering	ordinary shares (or ordinary shares if the underwriters' option to purchase additional ADSs is exercised in full).
ADSs outstanding immediately after this offering	ADSs (or ADSs if the underwriters' option to purchase additional ADSs is exercised in full).
Underwriters' option to purchase additional ADSs	We have granted a 30-day option to the underwriters to purchase up to an aggregate of additional ADSs.
American Depositary Shares	Each ADS represents one ordinary share with a nominal value of £ per ordinary share. You will have the rights of an ADS holder as provided in the deposit agreement among us, the depositary and all holders and beneficial owners of ADSs issued thereunder. To better understand the terms of the ADSs, you should carefully read the section in this prospectus titled "Description of American Depositary Shares." We also encourage you to read the deposit agreement, which is filed as an exhibit to the registration statement that includes this prospectus.
Depositary	
Custodian	
Use of proceeds	We estimate that we will receive net proceeds from this offering of approximately $ million, or $ million, if the underwriters exercise their option to purchase additional ADSs in full, based upon an assumed initial public offering price of $ per ADS, which is the midpoint of the estimated price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. We expect to use the net proceeds from this offering to (i) complete preparation for Phase II and III clinical development of BT1718 and to advance BT5528 and BT8009 through Phase I clinical development and complete preparations for Phase II development activities; (ii) advance our CD137 programs through preclinical development and to advance one CD137 multimeric program through Phase I clinical development; and (iii) the remainder on drug discovery, further expansion of our infrastructure to support our pipeline as well as to fund working capital and other general corporate purposes. See "Use of Proceeds" for additional information.

Risk factors	You should carefully read "Risk Factors" and the other information in this prospectus for a discussion of factors that you should consider before deciding to invest in the ADSs.
Proposed Nasdaq Global Market trading symbol	"BCYC"

The number of ordinary shares to be outstanding after this offering is based on 628,902 ordinary shares (which includes 58,746 unvested restricted shares subject to repurchase by us) outstanding as of December 31, 2018, and gives effect to (i) the issuance of 80,385 Series B2 convertible preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A convertible preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 convertible preferred shares, and (iv) the automatic conversion of all outstanding convertible preferred shares as of December 31, 2018, plus the Series B2 convertible preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares, upon the completion of this offering, and excludes:

- 604,444 ordinary shares issuable upon the exercise of options to subscribe for ordinary shares outstanding as of December 31, 2018 at a weighted average exercise price of $1.44 per ordinary share;
- 485,985 ordinary shares reserved for future issuance as of December 31, 2018 in connection with equity awards;
- ordinary shares that will be made available for future issuance under our 2019 Share Option and Incentive Plan upon the effectiveness of the registration statement of which this prospectus forms a part; and
- ordinary shares that will be made available for future issuance under our 2019 Employee Share Purchase Plan, upon the effectiveness of the registration statement of which this prospectus forms a part.

Unless otherwise indicated, all information in this prospectus reflects or assumes the following:

- the effectiveness of the share capital reorganization prior to the completion of this offering, which is intended to have the effect of a 1-for- share split of our share capital. See "Share Capital Reorganization and Re-Registration;"
- the effectiveness of our amended and restated memorandum and articles of association upon the closing of this offering;
- the reclassification of the warrant liability into additional paid-in capital, upon the completion of this offering;
- the conversion of all of our outstanding convertible preferred shares, including 80,385 Series B2 convertible preferred shares issued in January 2019, plus 200,000 Series A convertible preferred shares, and 371,645 Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon the completion of this offering;
- no issuance or exercise of share options after December 31, 2018 (except for the exercise of warrants to subscribe for Series A and Series B1 convertible preferred shares, as described above); and
- no exercise by the underwriters of their option to purchase up to an additional ADSs in this offering.

Summary Consolidated Financial Data

The following tables present the summary consolidated financial data as of the dates and for the periods indicated for Bicycle Therapeutics Limited. We derived the summary consolidated statements of operations and comprehensive loss data for the years ended December 31, 2017 and 2018 and the consolidated balance sheet data as of December 31, 2018 from our audited consolidated financial statements included elsewhere in this prospectus. Our historical audited consolidated financial statements as of December 31, 2017 have been restated. See Note 1 to the audited consolidated financial statements included elsewhere in this prospectus. We prepare our consolidated financial statements in accordance with U.S. GAAP.

Our historical results are not necessarily indicative of the results that may be expected in the future. You should read this data together with our consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the sections titled "Selected Consolidated Financial Data", "Capitalization" and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

The functional currency of Bicycle Therapeutics Limited and its wholly owned subsidiaries in the United Kingdom, BicycleTx Limited and BicycleRD Limited, is the pound sterling. The functional currency of Bicycle Therapeutics Inc. is the U.S. dollar. For financial reporting purposes, the financial statements of Bicycle Therapeutics Limited, BicycleTx Limited and BicycleRD Limited, which are prepared using the functional currency, have been translated into U.S. dollars. Our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates and shareholders' (deficit) equity is translated based on historical exchange rates. Translation adjustments are not included in determining net loss but are included in foreign exchange translation adjustment within accumulated other comprehensive income (loss), a component of shareholders' (deficit) equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in general and administrative expense in the consolidated statements of operations and comprehensive loss.

As of December 31, 2018, the last business day of the year ended December 31, 2018, the representative exchange rate was $1.2763 = £1.00.

Prior to the completion of this offering, we intend to reorganize our share capital and to re-register as a public limited company and change our name from Bicycle Therapeutics Limited to Bicycle Therapeutics plc. See "Share Capital Reorganization and Re-Registration".

	Year ended December 31,	
	2017	2018
	(as restated) (in thousands, except share and per share data)	
Statement of Operations Data:		
Collaboration revenues	$ 2,060	$ 7,136
Operating expenses:		
Research and development	11,866	20,761
General and administrative	6,407	8,121
Total operating expenses	18,273	28,882
Loss from operations	(16,213)	(21,746)
Other income (expenses):		
Interest and other income	50	169
Other expense	(119)	(665)
Total other expense, net	(69)	(496)
Net loss before income tax provision	(16,282)	(22,242)
Benefit from income taxes	(23)	(396)
Net loss	$ (16,259)	$ (21,846)
Net loss attributable to ordinary shareholders	$ (16,259)	$ (21,846)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (69.74)	$ (71.13)
Weighted average ordinary shares outstanding, basic and diluted	233,134	307,123
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)		$ (2.76)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)		7,665,736

See Note 2 within the notes to our consolidated financial statements appearing at the end of this prospectus for a description of the method used to calculate basic and diluted net loss per share applicable to ordinary shareholders and unaudited pro forma basic and diluted net loss per share.

	As of December 31, 2018		
	Actual	Pro forma[1]	Pro forma as adjusted[2]
	(in thousands)		
Balance Sheet Data:			
Cash	$ 63,380	$ 64,983	
Working capital[3]	67,840	69,443	
Total assets	81,826	83,229	
Total deferred revenue	14,635	14,635	
Warrant liability	4,804	—	
Convertible preferred shares	122,197	—	
Total shareholders' (deficit) equity	$ (69,826)	58,778	

(1) The unaudited pro forma balance sheet data gives effect to (i) the issuance of 80,385 Series B2 convertible preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 preferred shares immediately prior to the completion of this offering, (iv) the

automatic conversion of all outstanding convertible preferred shares as of December 31, 2018, plus the Series B2 preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon completion of this offering, and (v) the reclassification of the warrant liability into additional paid-in capital, upon the completion of this offering.

(2) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of ADSs in this offering at an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. The pro forma as adjusted information discussed above is illustrative only and will change based on the actual initial public offering price and other terms of this offering determined at pricing. Each $1.00 increase (decrease) in the assumed initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, working capital, total assets and total shareholders' (deficit) equity by $ million, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. Each increase (decrease) of 1,000,000 in the number of ADSs offered by us, as set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, total assets and total shareholders' (deficit) equity by $ million, assuming no change in the initial public offering price per ADS.

(3) We define working capital as current assets less current liabilities.

RISK FACTORS

Investing in our ADSs involves a high degree of risk. Before deciding whether to invest, you should carefully consider the following risks and uncertainties, together with all other information in this prospectus, including our consolidated financial statements and related notes and "Management's Discussion and Analysis of Results of Operations and Financial Condition" before investing in our ADSs. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or growth prospects. In such an event, the market price of our ADSs could decline and you may lose all or part of your investment. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our ADSs could decline if one or more of these risks or uncertainties actually occur, causing you to lose all or part of the money you paid to buy our ADSs. Additional risks that we currently do not know about or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Special Note Regarding Forward-Looking Statements" in this prospectus.

Risks Related to Our Financial Position and Need for Additional Capital

We have a history of significant operating losses and expect to incur significant and increasing losses for the foreseeable future, and we may never achieve or maintain profitability.

We do not expect to generate revenue or profitability that is necessary to finance our operations in the short term. We incurred net losses of $16.3 million and $21.8 million for the years ended December 31, 2017 and 2018, respectively. In addition, our accumulated deficit as of December 31, 2018 was $69.9 million. To date, we have not commercialized any products or generated any revenues from the sale of products, and absent the realization of sufficient revenues from product sales, we may never attain profitability in the future. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical trials. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our shareholders' (deficit) equity and working capital.

We anticipate that our expenses will increase substantially if and as we:

- continue to develop and conduct clinical trials with respect to our lead product candidate, BT1718, and our other product candidates in our *Bicycle* Toxin Conjugate, or BTC, program;
- initiate and continue research, preclinical and clinical development efforts for any future product candidates;
- seek to discover and develop additional product candidates and further expand our clinical product pipeline;
- seek marketing and regulatory approvals for any product candidates that successfully complete clinical trials;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- expand our research and development infrastructure, including hiring and retaining additional personnel, such as clinical, quality control and scientific personnel;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize products for which we obtain marketing approval, if any;

- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization and help us comply with our obligations as a public company; and

- add equipment and physical infrastructure to support our research and development.

Our ability to become and remain profitable depends on our ability to generate revenue. Generating product revenue will depend on our or any of our collaborators' ability to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. Successful commercialization will require achievement of key milestones, including completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our collaborators, may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We and any collaborators may never succeed in these activities and, even if we do, or any collaborators do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our revenue to date has been primarily generated from our research collaborations with AstraZeneca AB, or AstraZeneca, Bioverativ, Inc., or Bioverativ, and Oxurion NV (formerly ThromboGenics NV), or Oxurion. There can be no assurance that we will generate revenue from these collaborations in the future.

Our failure to become and remain profitable would depress the market price of our ADSs and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If we continue to suffer losses, investors may not receive any return on their investment and may lose their entire investment.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Our business commenced operations in 2009. Our operations to date have been limited to financing and staffing our company, developing our technology, conducting preclinical research and early-stage clinical trials for our product candidates and pursuing strategic collaborations to advance our product candidates. We have not yet demonstrated an ability to successfully conduct late-stage clinical trials, obtain marketing approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical-stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they would be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will eventually need to transition from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our

control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Even if this offering is successful, we will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. For example, in the years ended December 31, 2017 and 2018, we used $1.4 million and $26.1 million, respectively, in net cash for our operating activities, substantially all of which related to research and development activities. We expect our expenses to increase in connection with our ongoing activities, particularly as we initiate new clinical trials of, initiate new research and preclinical development efforts for and seek marketing approval for, our current product candidates or any future product candidates. In addition, if we obtain marketing approval for any of our product candidates, we may incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of a collaborator. Furthermore, following the completion of this offering, we expect to incur significant additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We plan to use the net proceeds of this offering primarily to complete preparation for Phase II and III clinical development of BT1718 and to advance BT5528 and BT8009 through Phase I clinical development and complete preparations for Phase II development activities, advance our CD137 programs through preclinical development and to advance at least one CD137 multimeric program through Phase I clinical development, and the remainder on drug discovery, further expansion of our infrastructure to support our pipeline as well as to fund working capital and other general corporate purposes. We will be required to expend significant funds in order to advance the development of the product candidates in our pipeline, as well as other product candidates we may seek to develop. In addition, while we may seek one or more collaborators for future development of our product candidates, we may not be able to enter into a collaboration for any of our product candidates for such indications on suitable terms, on a timely basis or at all. In any event, the net proceeds of this offering and our existing cash will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of any of our product candidates. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. We do not have any committed external source of funds. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that the net proceeds from this offering, together with our existing cash of $ million as of will enable us to fund our operating expenses and capital expenditure requirements for . Our estimate may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of, and research and preclinical development efforts for, our current and future product candidates;

- our ability to enter into, and the terms and timing of, any collaborations, licensing or other arrangements;
- our ability to identify one or more future product candidates for our pipeline;
- the number of future product candidates that we pursue and their development requirements;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for any of our product candidates that receive marketing approval to the extent such costs are not the responsibility of any collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approval, revenue, if any, received from commercial sales of our current and future product candidates;
- our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights including enforcing and defending intellectual property related claims; and
- the costs of operating as a public company.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or cause us to relinquish valuable rights.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances, licensing arrangements or monetization transactions. To the extent that we raise additional capital through the sale of equity, convertible debt securities or other equity-based derivative securities, your ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect your rights as a shareholder. Any indebtedness we incur would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline and existing shareholders may not agree with our financing plans or the terms of such financings. If we raise additional funds through strategic partnerships and alliances, licensing arrangements or monetization transactions with third parties, we may have to relinquish valuable rights to our technologies, or our product candidates, or grant licenses on terms unfavorable to us. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to the Discovery, Development and Regulatory Approval of Our Product Candidates

We are substantially dependent on the success of our internal development programs and of our product candidates from our BTC program which may not successfully complete clinical trials, receive regulatory approval or be successfully commercialized.

Our future success will depend heavily on the success of our internal development programs and of product candidates from our BTC program.

Within our BTC program, we are investigating BT1718 for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with the Centre for Drug Development of Cancer Research UK, or CRUK. Upon the completion of the Phase I/IIa clinical trial for BT1718, we have the right to obtain a license to the results of the clinical trial from CRUK upon the payment of a milestone, in cash and ordinary shares with a combined value in a mid six digit dollar amount. If we do not exercise our right to obtain a license to the results of the clinical trial or we fail to obtain a license, our ability to continue development of BT1718 would be negatively impacted. BT1718 is designed to target tumors that express MT1-MMP. We are also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2, or EphA2, and Nectin-4, respectively, for oncology indications. These target proteins have an established role in cell invasion and metastasis and are overexpressed in many solid tumors, but there can be no assurance our BTCs will ever demonstrate evidence of safety or effectiveness for any use or receive U.S. or E.U. regulatory approval in any indication. Even if clinical trials show positive results, there can be no assurance that the FDA in the U.S., EMA in Europe or similar regulatory authorities will approve our BTCs or any of our other product candidates for any given indication for several potential reasons, including the failure to follow Good Clinical Practice, or GCP, a negative assessment of the risks and benefits, insufficient product quality control and standardization, failure to have Good Manufacturing Practices, or GMP, compliant manufacturing facilities, or the failure to agree with regulatory authorities on clinical endpoints.

Our ability to successfully commercialize our BTCs and our other product candidates will depend on, among other things, our ability to:

- successfully complete preclinical studies and clinical trials;
- receive regulatory approvals from the FDA, the EMA and other similar regulatory authorities;
- establish and maintain collaborations with third parties for the development and/or commercialization of our product candidates, or otherwise build and maintain strong development, sales, distribution and marketing capabilities that are sufficient to develop products and launch commercial sales of any approved products;
- obtain coverage and adequate reimbursement from payors such as government health care systems and insurance companies and achieve commercially attractive levels of pricing;
- secure acceptance of our product candidates from physicians, health care payors, patients and the medical community;
- produce, through a validated process, in manufacturing facilities inspected and approved by regulatory authorities, including the FDA, sufficiently large quantities of our product candidates to permit successful commercialization;
- manage our spending as expenses increase due to clinical trials and commercialization; and
- obtain and enforce sufficient intellectual property rights for any approved products and product candidates.

Of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a new drug application, or NDA, to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market our product candidates, any such approval may be subject to limitations on the indicated uses or patient populations for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure you that our product candidates will be successfully developed or commercialized. If we are unable to develop, or obtain regulatory approval for, or, if approved, to successfully commercialize our product candidates, we may not be able to generate sufficient revenue to continue our business.

We are at a very early stage in our development efforts, our product candidates and those of our collaborators represent a new category of medicines and may be subject to heightened regulatory scrutiny until they are established as a therapeutic modality.

Bicycles represent a new therapeutic modality of peptide compounds intended to combine targeting abilities of antibodies with performance of small molecules. Our product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess. We have not yet succeeded and may never succeed in demonstrating efficacy and safety for these or any other product candidates in clinical trials or in obtaining marketing approval thereafter.

Regulatory authorities do not have experience with *Bicycles* and may require evidence of safety and efficacy that goes beyond what we and our collaborators have included in our development plans. In such a case, development of *Bicycle* product candidates may be more costly or time-consuming than expected, and our candidate products and those of our collaboration partners may not prove to be viable.

If we are unsuccessful in our development efforts, we may not be able to advance the development of our product candidates, commercialize products, raise capital, expand our business or continue our operations.

Our product candidates and those of our collaborators will need to undergo preclinical and clinical trials that are time consuming and expensive, the outcomes of which are unpredictable, and for which there is a high risk of failure. If preclinical or clinical trials of our or their product candidates fail to satisfactorily demonstrate safety and efficacy to the FDA, the EMA and any other comparable regulatory authority, additional costs may be incurred or delays experienced in completing, the development of these product candidates, or their development may be abandoned.

The FDA in the United States, the EMA in the European Union and the European Economic Area, and any other comparable regulatory authorities in other jurisdictions must approve new product candidates before they can be marketed, promoted or sold in those territories. We have not previously submitted an IND or NDA to the FDA or similar drug approval filings to comparable foreign regulatory authorities for any of our product candidates. We must provide these regulatory authorities with data from preclinical studies and clinical trials that demonstrate that our product candidates are safe and effective for a specific indication before they can be approved for commercial distribution. We cannot be certain that our clinical trials for our product candidates will be successful or that any of our other product candidates will receive approval from the FDA, the EMA or any other comparable regulatory authority.

Preclinical studies and clinical trials are long, expensive and unpredictable processes that can be subject to extensive delays. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. It may take several years and require significant

expenditures to complete the preclinical studies and clinical trials necessary to commercialize a product candidate, and delays or failure are inherently unpredictable and can occur at any stage. We may also be required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we contemplate, which may lead to us incurring additional unplanned costs or result in delays in clinical development. In addition, we may be required to redesign or otherwise modify our plans with respect to an ongoing or planned clinical trial, and changing the design of a clinical trial can be expensive and time consuming. An unfavorable outcome in one or more trials would be a major setback for our product candidates and for us. An unfavorable outcome in one or more trials may require us to delay, reduce the scope of or eliminate one or more product development programs, which could have a material adverse effect on our business, financial position, results of operations and future growth prospects.

Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of marketing approval for our product candidates. The FDA, EMA or any other comparable regulatory authority may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

In connection with clinical trials of our product candidates, we face a number of risks, including risks that:

- a product candidate is ineffective or inferior to existing approved products for the same indications;
- a product candidate causes or is associated with unacceptable toxicity or has unacceptable side effects;
- patients may die or suffer adverse effects for reasons that may or may not be related to the product candidate being tested;
- the results may not confirm the positive results of earlier trials;
- the results may not meet the level of statistical significance required by the FDA, the EMA or other relevant regulatory agencies to establish the safety and efficacy of our product candidates for continued trial or marketing approval; and
- our collaborators may be unable or unwilling to perform under their contracts.

Furthermore, we sometimes estimate for planning purposes the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies, clinical trials, the submission of regulatory filings or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the completion of an ongoing clinical trial, the initiation of other clinical programs, the receipt of marketing approval or a commercial launch of a product. The achievement of many of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions, which may cause the timing of achievement of the milestones to vary considerably from our estimates. If we fail to achieve milestones in the timeframes we expect, the commercialization of our product candidates may be delayed, we may not be entitled to receive certain contractual payments, which could have a material adverse effect on our business, financial position, results of operations and future growth prospects.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our clinical trials because of negative publicity from adverse events related to novel therapeutic approaches, competitive clinical trials for similar patient populations, the existence of current treatments or for other reasons. Enrollment risks are heightened with respect to certain indications that we may target for one or more of our product candidates that may be rare diseases, which may limit the pool of patients that may be enrolled in our planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with the required or desired characteristics, to complete our clinical trials in a timely manner. For example, due to the nature of the indications that we are initially targeting, patients with advanced disease progression may not be suitable candidates for treatment with our product candidates and may be ineligible for enrollment in our clinical trials. Therefore, early diagnosis in patients with our target diseases is critical to our success. Patient enrollment and trial completion is affected by factors including the:

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- safety profile, to date, of the product candidate under study;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of our approach to treatment of diseases;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject's disease at the time of enrollment;
- proximity and availability of clinical trial sites for prospective subjects;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

In addition, clinical testing of BT1718 is currently taking place outside of the U.S. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;

- the absence in some countries of established groups with sufficient regulatory expertise for review of protocols related to our novel approach;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in the results of completed clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. For example, the Phase I/IIa trial of BT1718 is being conducted by CRUK at up to six sites in the United Kingdom, and the findings may not be replicated in future trials at global clinical trial sites in a later stage clinical trial conducted by us or our collaborators. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval.

Preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

Failure to successfully validate, develop and obtain regulatory approval for companion diagnostics could harm our drug development strategy.

We may employ companion diagnostics to help us more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics are subject to regulation by the FDA and comparable foreign regulatory authorities as medical devices and require separate regulatory approval prior to commercialization. We do not develop companion diagnostics internally and thus we will be dependent on the sustained cooperation and

effort of our third-party collaborators in developing and obtaining approval for these companion diagnostics. There can be no guarantees that we will successfully find a suitable collaborator to develop companion diagnostics. We and our collaborators may encounter difficulties in developing and obtaining approval for the companion diagnostics, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by our collaborators to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates. In addition, our collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics, and both they and we may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community. If such companion diagnostics fail to gain market acceptance, our ability to derive revenues from sales of any products, if approved, will be adversely affected. In addition, the diagnostic company with whom we contract may decide to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our product candidates or our relationship with such diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

Our current or future product candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs that could halt their clinical development, prevent their marketing approval, limit their commercial potential or result in significant negative consequences.

Undesirable or clinically unmanageable side effects could occur and cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. Results of our trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. To date, subjects exposed to BT1718 in the ongoing Phase I/IIa clinical trial have experienced drug-related side effects including fatigue, liver function abnormalities and muscle pain.

If unacceptable side effects arise in the development of our product candidates, we, the FDA or comparable foreign regulatory authorities, the Institutional Review Boards, or IRBs, or independent ethics committees at the institutions in which our studies are conducted, or the Data Safety Monitoring Board, or DSMB, could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete the trial, or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We may be required to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may prevent us from achieving or maintaining market acceptance of the affected product candidate and may harm our business, financial condition and prospects significantly.

Our product candidates are currently undergoing safety testing in the form of Phase I/IIa clinical trials. None of our products have completed this testing to date. While our current and future product candidates will undergo safety testing to the extent possible and, where applicable, under such conditions discussed with regulatory authorities, not all adverse effects of drugs can be

predicted or anticipated. Unforeseen side effects could arise either during clinical development or, if such side effects are more rare, after our products have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. So far, we have not demonstrated, and we cannot predict if ongoing or future clinical trials will demonstrate, that BT1718 or any other of our product candidates are safe in humans.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following consequences could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any collaborators, may need to recall the product, or be required to change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a boxed warning or a contraindication;
- we, or any collaborators, may be required to create a medication guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

If any of our current or future product candidates fail to demonstrate safety and efficacy in clinical trials or do not gain marketing approval, we will not be able to generate revenue and our business will be harmed. Any of these events could harm our business and operations, and could negatively impact the price of our ADSs.

We may not be successful in our efforts to identify or discover additional product candidates.

Although we intend to utilize our *Bicycle* screening platform to explore other therapeutic opportunities in addition to the product candidates that we are currently developing, we may fail to identify other product candidates for clinical development for a number of reasons. For example, our research methodology may not be successful in identifying potential product candidates or those we identify may be shown to have harmful side effects or other characteristics that make them unmarketable or unlikely to receive regulatory approval. A key part of our strategy is to utilize our screening technology to identify product candidates to pursue in clinical development. Such product candidates will require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development. If we fail to identify and develop additional potential product candidates, we may be unable to grow our business and our results of operations could be materially harmed.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the impairment of our business reputation;
- the withdrawal of clinical trial participants;
- substantial monetary awards to patients or other claimants;
- costs due to related litigation;
- the distraction of management's attention from our primary business;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We believe our product liability insurance coverage is sufficient in light of our current commercial and clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage each time we commercialize an additional product; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our ADS price to decline and, if

judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by certain of our product candidates, such as our lead indications in oncology, are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

We may seek designations for our product candidates with the FDA and other comparable regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, but there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and other comparable regulatory authorities offer certain designations for product candidates that are intended to encourage the research and development of pharmaceutical products addressing conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. There can be no assurance that we will successfully obtain such designation for any of our other product candidates. In addition, while such designations could expedite the development or approval process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

For example, we may seek a Breakthrough Therapy Designation for one or more of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, if preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of

our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

We may also seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

We may seek priority review designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, in particular if such product candidate has received a Breakthrough Therapy Designation, the FDA may decide not to grant it. Moreover, a priority review designation does not result in expedited development and does not necessarily result in expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

Obtaining and maintaining marketing approval of our current and future product candidates in one jurisdiction does not mean that we will be successful in obtaining marketing approval of our current and future product candidates in other jurisdictions.

Obtaining and maintaining marketing approval of our current and future product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain marketing approval in any other jurisdiction, while a failure or delay in obtaining marketing approval in one jurisdiction may have a negative effect on the marketing approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval. We do not have experience in obtaining reimbursement or pricing approvals in international markets.

Obtaining marketing approvals and compliance with regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our

products in certain countries outside of the United Kingdom and the United States. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

Risks Related to Commercialization of Our Product Candidates and Other Regulatory Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate.

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. Varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends

non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or other regulatory authority. The FDA or other regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or other regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or other regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. For example, regulatory agencies may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. Regulators may approve a product candidate for a smaller patient population, a different drug formulation or a different manufacturing process, than we are seeking. If we are unable to obtain necessary regulatory approvals, or more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

Any delay in obtaining or failure to obtain required approvals could negatively impact our ability to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact the price of our ADSs.

We currently have no marketing, sales or distribution infrastructure with respect to our product candidates. If we are unable to develop our sales, marketing and distribution capability on our own or through collaborations with marketing partners, we will not be successful in commercializing our product candidates.

We currently have no marketing, sales or distribution capabilities and have limited sales or marketing experience within our organization. If one or more of our product candidates is approved, we intend either to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize that product candidate, or to outsource this function to a third party. There are risks involved with either establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services.

Recruiting and training an internal commercial organization is expensive and time consuming and could delay any product launch. Some or all of these costs may be incurred in advance of any approval of any of our product candidates. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire a sales force in the United States or other target market that is sufficient in size or has adequate expertise in the medical markets that we intend to target.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- the inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell any product candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates.

The market opportunities for any current or future product candidate we develop, if and when approved, may be limited to those patients who are ineligible for established therapies or for whom prior therapies have failed, and may be small.

Cancer therapies are sometimes characterized as first-line, second-line, or third-line, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy, immunotherapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We may initially seek approval of BT1718 and any other product candidates we develop as a therapy for patients who have received one or more prior treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval potentially as a first-line therapy, but there is no guarantee that product candidates we develop, even if approved, would be approved for first-line therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

The number of patients who have the cancers we are targeting may turn out to be lower than expected. Additionally, the potentially addressable patient population for our current programs or future product candidates may be limited, if and when approved. Even if we obtain significant market share for any product candidate, if and when approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications, including use as first- or second-line therapy.

Even if we receive marketing approval of a product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products, if approved.

Any marketing approvals that we receive for any current or future product candidate may be subject to limitations on the approved indicated uses for which the product may be marketed or the

conditions of approval, or contain requirements for potentially costly post-market testing and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval of any product candidate, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. If the FDA or a comparable foreign regulatory authority approves a product candidate, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import and export and record keeping for the product candidate will be subject to extensive and ongoing regulatory requirements. These requirements include, among others, prohibitions on the promotion of an approved product for uses not included in the product's approved labeling, submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current Good Manufacturing Practice, or cGMP, and Good Clinical Practice, or GCP, for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with any approved candidate, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the labeling, distribution, marketing or manufacturing of the product, withdrawal of the product from the market, or product recalls;
- untitled and warning letters, or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications we filed or suspension or revocation of license approvals;
- requirements to conduct post-marketing studies or clinical trials;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- product seizure or detention, or refusal to permit the import or export of the product; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay marketing approval of a product. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

We face significant competition and if our competitors develop and market products that are more effective, safer or less expensive than the product candidates we develop, our commercial opportunities will be negatively impacted.

The life sciences industry is highly competitive. We are currently developing therapeutics that will compete, if approved, with other products and therapies that currently exist, are being developed or will in the future be developed, some of which we may not currently be aware.

We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, universities and other research institutions. Many of our competitors

have significantly greater financial, manufacturing, marketing, product development, technical and human resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining marketing approvals, recruiting patients and manufacturing pharmaceutical products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or marketing approval or discovering, developing and commercializing products in our field before we do.

There is a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. These treatments consist both of small molecule drug products, such as traditional chemotherapy, as well as novel immunotherapies. For example, a number of multinational companies as well as large biotechnology companies, including Astellas Pharma Inc., Seattle Genetics, Inc., AstraZeneca, GlaxoSmithKline plc and Merrimack Pharmaceuticals, Inc., are developing programs for the targets that we are exploring for our BTC programs. Furthermore, Agenus Inc., Bristol-Myers Squibb Company, Pfizer Inc., Roche Holding AG, or Roche, have or are developing programs for CD137, and Amgen Inc., Pieris Pharmaceuticals, Inc. and Roche are developing bi-specifics.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe effects, are more convenient, have a broader label, are marketed more effectively, are reimbursed or are less expensive than any products that we may develop. Our competitors also may obtain FDA, EMA or other marketing approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Even if the product candidate we develop achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness.

Smaller and other early stage companies may also prove to be significant competitors. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. In addition, the biopharmaceutical industry is characterized by rapid technological change. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our product candidates obsolete, less competitive or not economical.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, payors and others in the medical community.

We have never commercialized a product, and even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting products based on our *Bicycle* peptides in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors and others in the medical community. Physicians are often reluctant to switch their patients from existing

therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the frequency and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the frequency and severity of any side effects resulting from follow-up requirements for the administration of our product candidates;
- the relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage and adequate reimbursement.

Even if a product candidate displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical community and payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors, particularly due to the novelty of our *Bicycle* approach. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We currently focus our research and product development on treatments for oncology indications and our product candidates are designed to target specific tumor antigens. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, we may not address the entirety of the opportunity we are seeking.

In addition, the tumor antigens that our product candidates target may not be expressed as broadly as we anticipate. Further, if companion diagnostics are not developed alongside our product candidates, testing patients for the tumor antigens may not be possible, which would hamper our ability to identify patients who could benefit from treatment with our product candidates.

As a result, the number of patients we are able to identify in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to access, all of which would adversely affect our business, financial condition, results of operations and prospects.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

We expect the cost of our product candidates to be substantial, when and if they achieve market approval. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by private payors, such as private health coverage insurers, health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health care programs, such as Medicare and Medicaid. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, even if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as the CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for novel products such as ours, as there is no body of established practices and precedents for these new products. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is: (1) a covered benefit under its health plan; (2) safe, effective and medically necessary; (3) appropriate for the specific patient; (4) cost-effective; and (5) neither experimental nor investigational. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Third-party payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the approved drugs for a particular indication.

Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of product candidates. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates may have a higher cost of goods than conventional therapies, and may require long-term follow-up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater. There is significant uncertainty related to insurance

coverage and reimbursement of newly approved products. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, cost containment initiatives and additional legislative changes.

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union. These countries have broad discretion in setting prices and we cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be lawfully marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. To obtain reimbursement or pricing approval in some countries, we, or any collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

Moreover, efforts by governments and payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate reimbursement for our product candidates. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

If the FDA or comparable foreign regulatory authorities approve generic versions of any of our product candidates that receive marketing approval, or such authorities do not grant such products appropriate periods of data exclusivity before approving generic versions of such products, the sales of such products could be adversely affected.

Once a NDA is approved, the product covered thereby becomes a "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning, in part, that it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference-listed drug may be typically lost to the generic product, and the price of the branded product may be lowered.

The FDA may not accept for review or approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. It is unclear whether the FDA will treat the active ingredients in our product candidates as NCEs and, therefore, afford them five years of NCE data exclusivity if they are approved. If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Three year exclusivity is given to a non-NCE drug if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the NDA. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws health information privacy and security laws, and other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and

regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, or Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. "Remuneration" has been interpreted broadly to include anything of value. A person or entity does not need to have actual knowledge of the Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act, or FCA, or federal civil money penalties. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

- the federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which impose criminal and civil penalties against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The FCA also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;

- the beneficiary inducement provisions of the CMP Law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the Anti-Kickback Statute, a person or entity does not need to have actual

knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their respective business associates, individuals and entities that perform services on their behalf that involve the use or disclosure of individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- the U.S. federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payer. Many U.S. states have adopted laws similar to the Anti-Kickback Statute and False Claims Act, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will

involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in the United States, the ACA was enacted in 2010 which, among other things, subjects biologic products to potential competition by lower-cost biosimilars; addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increases the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extends the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjects manufacturers to new annual fees and taxes for certain branded prescription drugs; and provides incentives to programs that increase the federal government's comparative effectiveness research.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the current administration to repeal or replace certain aspects of the ACA. Further, since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provision of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. In addition, CMS recently issued a final rule that will give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

Concurrently, Congress has considered legislation that would repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the

annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device exercise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." More recently, in July 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. Congress also could consider additional legislation to repeal or replace other elements of the ACA. Thus, the full impact of the ACA, any law repealing or replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and due to subsequent legislative amendments, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Also, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. For example, the current administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. For example, in November 2018, CMS issued a proposed rule for comment that would, among other things, provide Medicare prescription drug plans under Part D more transparency in pricing and greater flexibility to negotiate discounts for, and in certain circumstances exclude, drugs in the six "protected" formulary classes and allow Medicare Advantage plans to use certain drug management tools such as step therapy for physician-administered drugs. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Additionally, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program.

There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of these governments and other payors to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

We are subject to the U.K. Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have

an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our activities in the United States subject us to various laws relating to foreign investment and the export of certain technologies, and our failure to comply with these laws or adequately monitor the compliance of our suppliers and others we do business with could subject us to substantial fines, penalties and even injunctions, the imposition of which on us could have a material adverse effect on the success of our business.

Because we have a U.S. subsidiary and substantial operations in the United States, we are subject to U.S. laws that regulate foreign investments in U.S. businesses and access by foreign persons to technology developed and produced in the United States. These laws include section 721 of the Defense Production Act of 1950, as amended by the Foreign Investment Risk Review Modernization Act of 2018, and the regulations at 31 C.F.R. Parts 800 and 801, as amended, administered by the Committee on Foreign Investment in the United States; and the Export Control Reform Act of 2018, which is being implemented in part through Commerce Department rulemakings to impose new export control restrictions on "emerging and foundational technologies" yet to be fully identified. Application of these laws, including as they are implemented through regulations being developed, may negatively impact our business in various ways, including by restricting our access to capital and markets; limiting the collaborations we may pursue; regulating the export our products, services, and technology from the United States and abroad; increasing our costs and the time necessary to obtain required authorizations and to ensure compliance; and threatening monetary fines and other penalties if we do not.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and

regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

Risks Related to Our International Operations

As a company based outside of the United States, we are subject to economic, political, regulatory and other risks associated with international operations.

As a company based in the United Kingdom, our business is subject to risks associated with conducting business outside of the United States. Many of our suppliers and clinical trial relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

European data collection is governed by restrictive regulations governing the use, processing, and cross-border transfer of personal information.

The collection and use of personal health data in the European Union is was governed by the provisions of the Data Protection Directive, and which, as of May 25, 2018, has been superseded by the GDPR. These directives impose several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The Data Protection Directive and GDPR also impose strict rules on the transfer of personal data out of the European Union to the United States. Failure to comply with the requirements of the Data Protection Directive, the GDPR, and the related national data protection laws of the European Union Member States may result in fines and other administrative penalties. While the Data Protection Directive did not apply to organizations based outside the EU, the GDPR has expanded its reach to include any business, regardless of its location, that provides goods or services to residents in the EU. This expansion would incorporate any potential clinical trial activities in EU member states. The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "sensitive information" which includes health and genetic information of data subjects residing in the EU. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedies in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the European Union to the United States or other regions that have not been deemed to offer "adequate" privacy protections. Failure to comply with the requirements of the GDPR and the related national data protection laws of the European Union Member States, which may deviate slightly from the GDPR, may result in fines of up to 4% of global revenues, or € 20,000,000, whichever is greater. As a result of the implementation of the GDPR, we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our ADSs.

In June 2016, a majority of voters in the United Kingdom voted to withdraw from the European Union in a national referendum, commonly referred to as Brexit. On March 29, 2017, the U.K. Prime Minister formally delivered the notice of withdrawal. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the notice of withdrawal, unless the European Council, in agreement with the United Kingdom, unanimously decides to extend this period or the United Kingdom unilaterally withdraws its notification of its intention to withdraw from the European Union under Article 50 of the Treaty on European Union. The United Kingdom and the European Council have agreed to an extension until May 22, 2019 conditional upon endorsement of the Withdrawal Agreement (agreed between the United Kingdom and the European Union on November 14, 2018) by the United Kingdom House of Commons by March 29, 2019. If the Withdrawal Agreement is not so endorsed, the period will be unconditionally extended until April 12, 2019 instead. This withdrawal has involved a process of lengthy negotiations between the United Kingdom and EU

Member States to determine the future terms of the United Kingdom's relationship with the European Union.

These developments have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in the United Kingdom and Europe. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the EEA overall could be diminished or eliminated.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of Brexit, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may result in increased trade barriers that could make our doing business in Europe more difficult. In addition, currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the United Kingdom, or what, if any, role the EMA may have in the approval process.

Exchange rate fluctuations may materially affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Risks Related to Our Dependence on Third Parties

For certain product candidates, we depend, or will depend, on development and commercialization collaborators to develop and conduct clinical trials with, obtain regulatory approvals for, and if approved, market and sell product candidates. If such collaborators fail to perform as expected, the potential for us to generate future revenue from such product candidates would be significantly reduced and our business would be harmed.

For certain products candidates, we depend, or will depend, on our development and commercial collaborators to develop, conduct clinical trials of, and, if approved, commercialize product candidates.

Under our collaborations with AstraZeneca, Bioverativ and Oxurion, we are responsible for identifying and optimizing *Bicycle* peptides related to collaboration targets and our collaborators are responsible for further development and product commercialization after we complete the defined research screening and compound optimization. As part of our collaboration with Cancer Research Technology Limited and CRUK, CRUK's Centre for Drug Development is sponsoring and funding a Phase I/IIa clinical trial of our lead product candidate, BT1718, in patients with advanced solid tumors. We depend on these collaborators to develop and, where applicable, commercialize products based on *Bicycle* peptides, and the success of their efforts directly impacts the milestones and royalties we will receive. We cannot assure you that our collaborators will be successful in or that they will devote sufficient resources to the development or commercialization of their products. If our current or future collaboration and commercialization partners do not perform in the manner we expect or fail to fulfill their responsibilities in a timely manner, or at all, if our agreements with them terminate or if the quality or accuracy of the clinical data they obtain is compromised, the clinical development, regulatory approval and commercialization efforts related to their and our product candidates and products could be delayed or terminated and it could become necessary for us to assume the responsibility at our own expense for the clinical development of such product candidates.

Our current collaborations and any future collaborations that we enter into are subject to numerous risks, including:

- collaborators have significant discretion in determining the efforts and resources that they will apply to the collaborations;
- collaborators may not perform their obligations as expected or fail to fulfill their responsibilities in a timely manner, or at all;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on preclinical studies or clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay preclinical studies or clinical trials, provide insufficient funding for clinical trials, stop a preclinical study or clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our shareholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- The collaborations may not result in product candidates to develop and/or preclinical studies or clinical trials conducted as part of the collaborations may not be successful;
- product candidates developed with collaborators may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to stop commercialization of our product candidates;

- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate; and

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation.

In addition, certain collaboration and commercialization agreements provide our collaborators with rights to terminate such agreements, which rights may or may not be subject to conditions, and which rights, if exercised, would adversely affect our product development efforts and could make it difficult for us to attract new collaborators. In that event, we would likely be required to limit the size and scope of efforts for the development and commercialization of such product candidates or products; we would likely be required to seek additional financing to fund further development or identify alternative strategic collaborations; our potential to generate future revenue from royalties and milestone payments from such product candidates or products would be significantly reduced, delayed or eliminated; and it could have an adverse effect on our business and future growth prospects. Our rights to recover tangible and intangible assets and intellectual property rights needed to advance a product candidate or product after termination of a collaboration may be limited by contract, and we may not be able to advance a program post-termination.

If conflicts arise with our development and commercialization collaborators or licensors, they may act in their own self-interest, which may be adverse to the interests of our company.

We may in the future experience disagreements with our development and commercialization collaborators or licensors. Conflicts may arise in our collaboration and license arrangements with third parties due to one or more of the following:

- disputes with respect to milestone, royalty and other payments that are believed due under the applicable agreements;

- disagreements with respect to the ownership of intellectual property rights or scope of licenses;

- disagreements with respect to the scope of any reporting obligations;

- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities, or to permit public disclosure of these activities; and

- disputes with respect to a collaborator's or our development or commercialization efforts with respect to our products and product candidates.

For example, we are involved in ongoing litigation with Pepscan Systems B.V., or Pepscan, related to a non-exclusive patent license agreement that we entered into with Pepscan in 2009. Pursuant to the patent license agreement, we licensed rights related to the scaffold used for *Bicycles* contained in certain of our product candidates, including our lead product candidate, BT1718. The agreement required us to enter into a framework services agreement with Pepscan for Pepscan to provide certain *Bicycles* not produced by us. In 2010, we entered into such a framework services agreement. In 2014, we terminated the framework services agreement in accordance with its terms. Subsequently, in 2016, Pepscan terminated the patent license agreement. We instituted proceedings in the District Court of The Hague to contest the right of Pepscan to terminate the patent license agreement. In response, Pepscan claimed, among other

things, that the termination of the framework services agreement and alleged breach by us of confidentiality obligations constituted grounds for the termination of the patent license agreement. In a preliminary judgement delivered in April 2018, the District Court of the Hague rejected Pepscan's claim that it was entitled to terminate the patent license agreement on the basis of a breach of a purported exclusive supply obligation. The District Court of the Hague reserved for further proceedings the question of whether Pepscan was entitled to terminate the patent license agreement on the basis of allegations that we had breached our confidentiality obligations. The District Court of the Hague gave us an opportunity to submit proof to the contrary through written evidence and further hearings.

In July 2018, Pepscan appealed the decision of the District Court of the Hague and the proceedings before the District Court of the Hague have been stayed pending a decision in the appeal brought by Pepscan. While we intend to vigorously defend ourselves the appeal and any further proceedings, there can be no assurance that we will prevail. Our failure to successfully defend our use of the patent rights in question would delay the timing of our ability to commercialize our product candidates, including our lead product candidate BT1718, which could have a material adverse effect on our business and operating results.

In addition, in January 2013, Pepscan filed a notice of opposition in respect of European patent 2 257 624, which is a foundational patent that is directed to our technology platform. In April 2015, Pepscan filed a notice of opposition in respect of European patent 2 474 613, which is a divisional patent that is directed to extensions of our technology platform. As of the date of this prospectus, no final decision has been issued by the European Patent Office. If we are unable to prevail against these challenges, our intellectual property estate may be materially harmed, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections. See "Business — Legal Proceedings."

Conflicts with our development and commercialization collaborators or licensors could materially adversely affect our business, financial condition or results of operations and future growth prospects.

We rely on third parties, including independent clinical investigators and CROs, to conduct and sponsor some of the clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for our product candidates.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators, academic partners, regulatory affairs consultants and third-party CROs, to conduct our preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to engage with regulatory authorities and monitor and manage data for our ongoing preclinical and clinical programs. For example, CRUK currently sponsors and funds the Phase I/IIa clinical trial of our lead product candidate, BT1718, in patients with advanced solid tumors. We also utilize CROs to perform toxicology studies related to our preclinical activities. While we will have agreements governing the activities of such third parties, we will control only certain aspects of their activities and have limited influence over their actual performance. Given the breadth of clinical therapeutic areas for which we believe *Bicycles* may have utility, we intend to continue to rely on external service providers rather than build internal regulatory expertise.

Any of these third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. In addition, there is a natural transition period when a new contract research organization begins work. As a result, delays would likely occur, which could negatively

impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects.

We remain responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we fail to exercise adequate oversight over any of our academic partners or CROs or if we or any of our academic partners or CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon a regulatory inspection of us, our academic partners or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under applicable CGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

Furthermore, the third parties conducting clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time, skill and resources to our ongoing development programs. These contractors may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities, which could impede their ability to devote appropriate time to our clinical programs. If these third parties, including clinical investigators, do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

In addition, with respect to investigator-sponsored trials that may be conducted, we would not control the design or conduct of these trials, and it is possible that the FDA or EMA will not view these investigator-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. We expect that such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the investigator-sponsored trials. However, we would not have control over the timing and reporting of the data from investigator-sponsored trials, nor would we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the firsthand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or EMA may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional preclinical, manufacturing, or clinical data.

We intend to rely on third parties to manufacture product candidates, which increases the risk that we will not have sufficient quantities of such product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate manufacturing facilities for the production of clinical or commercial supplies of the product candidates that we are developing or evaluating in our development programs. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our product candidates on a clinical or commercial scale. We rely on third parties for supply of our product candidates, and our strategy is to outsource all manufacturing of our product candidates and products to third parties.

In order to conduct clinical trials of product candidates, we will need to have them manufactured in potentially large quantities. Our third-party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities and at any other time. For example, ongoing data on the stability of our product candidates may shorten the expiry of our product candidates and lead to clinical trial material supply shortages, and potentially clinical trial delays. If these third-party manufacturers are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed or infeasible, and regulatory approval or commercial launch of that product candidate may be delayed or not obtained, which could significantly harm our business.

Our use of new third-party manufacturers increases the risk of delays in production or insufficient supplies of our product candidates as we transfer our manufacturing technology to these manufacturers and as they gain experience manufacturing our product candidates. Even after a third-party manufacturer has gained significant experience in manufacturing our product candidates or even if we believe we have succeeded in optimizing the manufacturing process, there can be no assurance that such manufacturer will produce sufficient quantities of our product candidates in a timely manner or continuously over time, or at all.

We may be delayed if we need to change the manufacturing process used by a third party. Further, if we change an approved manufacturing process, then we may be delayed if the FDA or a comparable foreign authority needs to review the new manufacturing process before it may be used.

We operate an outsourced model for the manufacture of our product candidates, and contract with good manufacturing practice, or GMP, licensed pharmaceutical contract development and manufacturing organizations. While we have engaged several third-party vendors to provide clinical and non-clinical supplies and fill-finish services, we do not currently have any agreements with third-party manufacturers for long-term commercial supplies. In the future, we may be unable to enter into agreements with third-party manufacturers for commercial supplies of any product candidate that we develop, or may be unable to do so on acceptable terms. Even if we are able to

establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails risks, including:

- reliance on third-parties for manufacturing process development, regulatory compliance and quality assurance;
- limitations on supply availability resulting from capacity and scheduling constraints of third-parties;
- the possible breach of manufacturing agreements by third-parties because of factors beyond our control; and
- the possible termination or non-renewal of the manufacturing agreements by the third-party, at a time that is costly or inconvenient to us.

Third-party manufacturers may not be able to comply with cGMP requirements or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and/or criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. In addition, some of the product candidates we intend to develop, including BT1718, use toxins or other substances that can be produced only in specialized facilities with specific authorizations and permits, and there can be no guarantee that we or our manufacturers can maintain such authorizations and permits. These specialized requirements may also limit the number of potential manufacturers that we can engage to produce our product candidates, and impair any efforts to transition to replacement manufacturers.

Our future product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP requirements that might be capable of manufacturing for us.

If the third parties that we engage to supply any materials or manufacture product for our preclinical tests and clinical trials should cease to continue to do so for any reason, we likely would experience delays in advancing these tests and trials while we identify and qualify replacement suppliers or manufacturers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our product candidates or the substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to develop product candidates and commercialize any products that receive marketing approval on a timely and competitive basis.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our product candidates, and because we collaborate with various organizations and academic institutions on the development of our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements

with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on research, manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. As of December 1, 2018, our intellectual property portfolio includes three patent families covering novel scaffolds, 11 patent families directed to our platform technology, 52 patent families covering bicyclic peptides and related conjugates, and four patent families directed to clinical indications.

In certain situations and as considered appropriate, we have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, or whether the claims of any resulting patents will provide us with a competitive advantage or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain

patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection. It is possible that defects of form in the preparation or filing of patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If there are material defects in the form, preparation, prosecution or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents.

Even if they are unchallenged, our patents and patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, a third party may develop a competitive therapy that provides benefits similar to one or more of our product candidates but that falls outside the scope of our patent protection. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected.

Other parties, many of whom have substantially greater resources and have made significant investments in competing technologies, have developed or may develop technologies that may be related or competitive with our approach, and may have filed or may file patent applications and may have been issued or may be issued patents with claims that overlap or conflict with our patent applications, either by claiming the same compositions, formulations or methods or by claiming subject matter that could dominate our patent position. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. As a result, any patents we may obtain in the future may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our products and product candidates.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that our patents are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

In the future, one or more of our products and product candidates may be in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better financed competitors having established development, manufacturing and distribution capabilities, to make competing products or impact our ability to

develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

In addition to patent protection, we expect to rely heavily on trade secrets, know-how and other unpatented technology, which are difficult to protect. Although we seek such protection in part by entering into confidentiality agreements with our vendors, employees, consultants and others who may have access to proprietary information, we cannot be certain that these agreements will not be breached, adequate remedies for any breach would be available, or our trade secrets, know-how and other unpatented proprietary technology will not otherwise become known to or be independently developed by our competitors. If we are unsuccessful in protecting our intellectual property rights, sales of our products may suffer and our ability to generate revenue could be severely impacted.

Issued patents covering our products and product candidates could be found invalid or unenforceable if challenged in court or in administrative proceedings. We may not be able to protect our trade secrets in court.

If we initiate legal proceedings against a third-party to enforce a patent covering one of our products or product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product or product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, inter partes review and equivalent proceedings in foreign jurisdictions. An adverse determination in any of the foregoing proceedings could result in the revocation or cancellation of, or amendment to, our patents in such a way that they no longer cover our products or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our products and product candidates. Such a loss of patent protection could have a material adverse impact on our business.

For example, in January 2013, Pepscan filed a notice of opposition in respect of European patent 2 257 624, which is a foundational patent that is directed to our technology platform. In April 2015, Pepscan filed a notice of opposition in respect of European patent 2 474 613, which is a divisional patent that is directed to extensions of our technology platform. As of the date of this prospectus, no final decision has been issued by the European Patent Office. If we are unable to prevail against these challenges, our intellectual property estate may be materially harmed, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections. See "Business — Legal Proceedings."

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect

trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach.

In addition, our trade secrets may otherwise become known or be independently discovered by competitors. Competitors and other third parties could purchase our products and product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe, misappropriate or otherwise violate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected or sufficient to provide an advantage over our competitors, our competitive position could be adversely affected, as could our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets.

We may be subject to claims challenging the inventorship or ownership of the patents and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own or such assignments may not be self-executing or may be breached. We could be subject to ownership disputes arising, for example, from conflicting obligations of employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. The terms of one or more

licenses that we enter into the future may not provide us with the ability to maintain or prosecute patents in the portfolio, and must therefore rely on third parties to do so.

If we do not obtain patent term extension and data exclusivity for our products and product candidates, our business may be materially harmed.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

In the future, if we obtain an issued patent covering one of our present or future product candidates, depending upon the timing, duration and specifics of any FDA marketing approval of such product candidates, such patent may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, for example, failure to obtain a granted patent before approval of a product candidate, failure to exercise due diligence during the testing phase or regulatory review process, failure to apply within applicable deadlines, failure to apply prior to expiration of relevant patents or otherwise our failure to satisfy applicable requirements. A patent licensed to us by a third party may not be available for patent term extension. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products and product candidates.

Changes in either the patent laws or the interpretation of the patent laws in the United States or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. When implemented, the Leahy-Smith Act included several significant changes to U.S. patent law that impacted how patent rights could be prosecuted, enforced and defended. In particular, the Leahy-Smith Act also included provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allowed third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed new

regulations and procedures governing the administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. It remains unclear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent rulings from the U.S. Court of Appeals for the Federal Circuit and the U.S. Supreme Court have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

We cannot assure you that our efforts to seek patent protection for one or more of our products and product candidates will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact courts' decisions in historical and future cases may have on the ability of life science companies to obtain or enforce patents relating to their products in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, maintaining, defending and enforcing patents on products and product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products. There can be no assurance that we will obtain or maintain patent rights in or outside the United States under any future license agreements. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we pursue patent protection, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology and pharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of

competing products in violation of our proprietary rights generally. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. While we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds, methods of manufacturing compounds and/or methods of use for the treatment of the disease indications for which we are developing our product candidates. If any third-party patents or patent applications are found to cover our product candidates or their methods of use or manufacture, we and our collaborators or sublicensees may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all. We may also be required to indemnify our collaborators or sublicensees in such an event.

For example, we are involved in ongoing litigation with Pepscan in relation to a patent license agreement, pursuant to which we licensed rights related to the scaffold used for *Bicycles* contained in certain of our product candidates, including our lead product candidate, BT1718. While we intend to continue to vigorously defend our rights in this proceeding, there can be no assurance that we will prevail. If the outcome of these proceedings results in our inability to use the scaffold contained in certain of our product candidates, our ability to commercialize the affected product candidates, including our lead product candidate BT1718 would be impaired, which could have a material adverse effect on our business and operating results.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our products candidates, including interference and post-grant proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the composition, use or manufacture of our product candidates. We cannot guarantee that any of our patent searches or analyses including, but not limited to, the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us

based intellectual property rights that exist now or arise in the future. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use or manufacture. The scope of protection afforded by a patent is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us; alternatively or additionally it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our current and former employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, including some which may be competitors or potential competitors. Some of these employees may be subject to proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. For example, in the ongoing litigation with Pepscan, Pepscan claimed that we had breached certain confidentiality obligations, which was alleged to constitute sufficient grounds for the termination of our patent license agreement with Pepscan. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. In addition, our patents may become, involved in inventorship, priority, or validity disputes. To counter or defend against such claims can be expensive and time-consuming, and our adversaries may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both.

In an infringement proceeding, a court may decide that a patent is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating intellectual property rights we own or control. An adverse result in any litigation proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly. Further, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Even if resolved in our favor, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our ADSs. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities.

We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

If we fail to comply with our obligations under any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

In connection with our efforts to build our product candidate pipeline, we may enter into license agreements in the future. We expect that such license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market any product that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could negatively impact the value of the product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our marks of interest and our business may be adversely affected.

Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We rely on both registration and common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Employee Matters and Managing Growth

We only have a limited number of employees to manage and operate our business.

As of March 1, 2019, we had 60 full-time or part-time employees. Our focus on the development of our product candidates requires us to optimize cash utilization and to manage and operate our business in a highly efficient manner. We cannot assure you that we will be able to hire or retain adequate staffing levels to develop our product candidates or run our operations or to accomplish all of the objectives that we otherwise would seek to accomplish.

Cyber-attacks or other failures in telecommunications or information technology systems could result in information theft, data corruption and significant disruption of our business operations.

We utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks, the confidentiality and the availability and integrity of our data. For example, in 2018, we were the target of a cyber-attack. The cyber-attack comprised a phishing incident where two email accounts were accessed that resulted in the automatic forwarding of emails, to an unauthorized third party. Promptly after discovery of this cyber-attack, we performed a third-party investigation and determined that no further action was required under either U.S. or state law. This incident was reported to the U.K. information

commissioners' office, who deemed no further action was required under GDPR regulations. The 2018 cyber-attack did not have a material impact to our business or financial condition. While we believe we responded appropriately, including implementing remedial measures to stop this cyber-attack and with the goal of preventing similar ones in the future, there can be no assurance that we will be successful in these remedial and preventative measures or successfully mitigating the effects of future cyber-attacks. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to respond appropriately to such breaches and to implement further data protection measures.

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives. Furthermore, replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully.

Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials may make it more challenging to recruit and retain qualified personnel.

In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited.

The inability to recruit or the loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

Our employees, independent contractors, consultants, collaborators and contract research organizations may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (1) FDA regulations or similar regulations of

comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities, (2) manufacturing standards, (3) federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, and (4) laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, bribery and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee or collaborator misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. In connection with this offering, we intend to adopt a code of conduct and business ethics, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, imprisionment, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations.

We expect to expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug manufacturing, regulatory affairs and sales, marketing and distribution, as well as to support our public company operations. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Moreover, our expected growth could require us to relocate to geographic areas beyond those where we have been historically located. For example, we maintain an office in Lexington, Massachusetts, at which many of our finance, management and administrative personnel work. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion or relocation of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion or relocation of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates.

Risks Related to this Offering and Ownership of Our Securities

We do not know whether an active, liquid and orderly trading market will develop for our ADSs or what the market price of our ADSs will be. As a result, it may be difficult for you to sell your ADSs.

This offering constitutes the initial public offering of our ADSs, and no public market has previously existed for our ADSs or ordinary shares. We intend to apply to have our ADSs listed on The Nasdaq Global Market, or Nasdaq, and we expect our ADSs to be quoted on Nasdaq, subject to completion of customary procedures in the United States. Any delay in the commencement of trading of the ADSs on Nasdaq would impair the liquidity of the market for the ADSs and make it more difficult for holders to sell the ADSs.

If the ADSs are listed and quoted on Nasdaq, there can be no assurance that an active trading market for the ADSs will develop or be sustained after this offering is completed. The initial offering price was determined by negotiations among the lead underwriters and us. Among the factors considered in determining the initial public offering price were our future prospects and the prospects of our industry in general, our revenue, net income and certain other financial and operating information in recent periods, and the market prices of securities and certain financial and operating information of companies engaged in activities similar to ours. However, there can be no assurance that, following the completion of this offering, the ADSs will trade at a price equal to or greater than the public offering price.

The market price of our ADSs may be highly volatile, and you may not be able to resell your ADSs at or above the initial public offering price.

The market price of our ADSs following this offering is likely to be highly volatile. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your ADSs at or above the initial public offering price. The market price for our ADSs may be influenced by many factors, including:

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in products similar or perceived to be similar to those we are developing or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us to identify additional product candidates for our pipeline;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial projections we may provide to the public;

- failure by us to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- sales of our ADSs or ordinary shares by us or our shareholders in the future; and
- the trading volume of our ADSs.

In addition, companies trading in the stock market in general, and Nasdaq in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our ADS price and trading volume could decline.

The trading market for our ADSs will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. We do not currently have research coverage, and there can be no assurance that analysts will cover us, or provide favorable coverage. Securities or industry analysts may elect not to provide research coverage of our ADSs after this offering, and such lack of research coverage may negatively impact the market price of our ADSs. In the event we do have analyst coverage, if one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

Concentration of ownership of our ordinary shares (including ordinary shares in the form of ADSs) among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

Our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately % of our ordinary shares and, upon closing of this offering, that same group will beneficially own approximately % of our outstanding ordinary shares. Depending on the level of attendance at our general meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and amendments to our Articles of Association. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that you may believe are in your best interest as one

of our shareholders. Some of these persons or entities may have interests different than yours. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs are being sold in this offering and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

Future sales, or the possibility of future sales, of a substantial number of our securities could adversely affect the price of the shares and dilute shareholders.

Sales of a substantial number of our ADSs in the public market could occur at any time, subject to certain restrictions described below. If our existing shareholders sell, or indicate an intent to sell, substantial amounts of our securities in the public market, the trading price of the ADSs could decline significantly and could decline below the public offering price in this offering. Upon completion of this offering, we will have outstanding ordinary shares (including ordinary shares represented by the ADSs), approximately of which are subject to a 180-day contractual lock-up or otherwise restricted from resale as a result of securities laws. The representatives of the underwriters may permit us and the holders of the lock-up shares to sell shares or ADSs prior to the expiration of the lock-up agreements. See "Shares and American Depositary Shares Eligible for Future Sale." After the lock-up agreements pertaining to this offering expire, these additional ordinary shares will be eligible for sale in the public market, though shares are held by directors and executive officers and other affiliates and will be subject to volume limitations under Rule 144 under the Securities Act of 1933, as amended, or the Securities Act, for sales in the United States. In addition, ordinary shares subject to outstanding options under our equity incentive plans and the ordinary shares reserved for future issuance under our equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

Moreover, after this offering, holders of an aggregate of ordinary shares will have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other shareholders, as well as to cooperate in certain public offerings of such ordinary shares. In addition, we intend to register all ordinary shares that we may issue under our equity compensation plans. Once we register these ordinary shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Shares and American Depositary Shares Eligible for Future Sale" section of this prospectus.

Holders of ADSs are not treated as holders of our ordinary shares.

By participating in this offering you will become a holder of ADSs with underlying ordinary shares in a company incorporated under English law. Holders of ADSs are not treated as holders of our ordinary shares, unless they withdraw the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of our ordinary shares, other than the rights that they have pursuant to the deposit agreement. See "Description of American Depositary Shares."

Holders of ADSs may be subject to limitations on the transfer of their ADSs and the withdrawal of the underlying ordinary shares.

ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. The depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or

the depositary think it is advisable to do so because of any requirement of law, government or governmental body, or under any provision of the deposit agreement, or for any other reason, subject to the right of ADS holders to cancel their ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of your ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders' meeting or we are paying a dividend on our ordinary shares. In addition, ADS holders may not be able to cancel their ADSs and withdraw the underlying ordinary shares when they owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities. See "Description of American Depositary Shares."

We are entitled to amend the deposit agreement and to change the rights of ADS holders under the terms of such agreement, or to terminate the deposit agreement, without the prior consent of the ADS holders.

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depositary may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depositary. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depositary. In the event that the terms of an amendment are materially disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to direct the depositary to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but will have no right to any compensation whatsoever.

ADSs holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that, to the fullest extent permitted by law, holders and beneficial owners of ADSs irrevocably waive the right to a jury trial of any claim they may have against us or the depositary arising out of or relating to the ADSs or the deposit agreement.

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether

to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs. It is advisable that you consult legal counsel regarding the jury waiver provision before entering into the deposit agreement.

If you or any other holders or beneficial owners of ADSs bring a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and/or the depositary. If a lawsuit is brought against us and/or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any substantive provision of the U.S. federal securities laws and the rules and regulations promulgated thereunder.

You will not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise your right to vote.

Except as described in this prospectus and the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depositary to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the depositary, upon timely notice from us, will notify ADS holders of the upcoming vote and arrange to deliver our voting materials to them. Upon our request, the depositary will mail to holders a shareholder meeting notice that contains, among other things, a statement as to the manner in which voting instructions may be given. We cannot guarantee that ADS holders will receive the voting materials in time to ensure that they can instruct the depositary to vote the ordinary shares underlying their ADSs. A shareholder is only entitled to participate in, and vote at, the meeting of shareholders, provided that it holds our ordinary shares as of the record date set for such meeting and otherwise complies with our Articles of Association. In addition, the depositary's liability to ADS holders for failing to execute voting instructions or for the manner of executing voting instructions is limited by the deposit agreement. As a result, holders of ADSs may not be able to exercise their right to give voting instructions or to vote in person or by proxy and they may not have any recourse against the depositary or us if their ordinary shares are not voted as they have requested or if their shares cannot be voted.

You may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

The depositary for the ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses. You will receive these distributions in proportion to the number of our ordinary shares your ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders

of ADSs. We have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that you may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have an adverse effect on the value of your ADSs.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be declared and paid. Therefore, we must have distributable profits before declaring and paying a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs will be your sole source of gains for the foreseeable future, and you will suffer a loss on your investment if you are unable to sell your ADSs at or above the initial public offering price. Investors seeking cash dividends should not purchase our ADSs in this offering.

If you purchase our ADSs in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing ADSs in this offering will pay a price per ordinary share that substantially exceeds the pro forma book value per share of our tangible assets after subtracting our liabilities. As a result, investors purchasing ADSs in this offering will incur immediate dilution of $ per ADS, based on the assumed initial public offering price of $ per ADS, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, representing the difference between the assumed initial public offering price and our pro forma as adjusted net tangible book value as of December 31, 2018 after giving effect to this offering. Further, investors purchasing ADSs in this offering will contribute approximately % of the total amount invested by shareholders since our inception, but will own only approximately % of the ordinary shares outstanding. Furthermore, if the underwriters exercise their over-allotment option or our previously issued options to acquire ordinary shares at prices below the assumed initial public offering price are exercised, you will experience further dilution. For additional information on the dilution that you will experience immediately after this offering, see the section titled "Dilution."

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled "Use of Proceeds," and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States.

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether U.K. courts would entertain original actions brought in the United Kingdom against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our ADSs less attractive to investors.

We are an emerging growth company and we will remain an emerging growth company until the earlier to occur of (1) the last day of 2023, (2) the last day of the fiscal year in which we have total annual gross revenues of at least $1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a "large accelerated filer," under the rules of the U.S. Securities and Exchange Commission, or SEC, which means the market value of our equity securities that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (4) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;
- not being required to comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to provide only two years of audited financial statements in this initial registration statement, in addition to any required unaudited interim financial statements,

with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;

- reduced disclosure obligations regarding executive compensation; and
- an exemption from the requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this prospectus. In particular, we have not included all of the executive compensation information that would be required if we were not an EGC. We cannot predict whether investors will find our ADSs less attractive if we rely on certain or all of these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and our ADS price may be more volatile.

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our ordinary shares held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including exemption from the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

We will incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management will be required to devote substantial time to new compliance initiatives.

As a U.S. public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as

appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

We have identified a material weakness in our internal control over financial reporting. If we are unable to remedy the material weakness, or if we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our ADS price.

We have historically been a private limited company, and as such, have not historically been subject to the reporting requirements of Section 404 or an audit performed in accordance with auditing standards issued by the PCAOB. However, in connection with the preparation of our consolidated financial statements for the year ended December 31, 2018, we identified an error in our previously reported financial statements due to a material weakness in our internal control over financial reporting related to the valuation of our warrant liability. The material weakness is attributable to a deficiency in the design and operating effectiveness of our review of the respective third party valuation reports. Specifically, the findings relate to our internal control infrastructure that existed as of December 31, 2017 and September 30, 2018 where we did not design or implement sufficient processes, controls or other review processes to ensure that the liquidation preferences of our Series A and Series B1 warrants per our articles of association were properly reflected as an input in the valuations during the year ended December 31, 2017, or for the nine month periods ended September 30, 2018 as previously reported. As a result, the financial statements for those periods required restatement.

We have implemented and are continuing to implement measures designed to improve our internal control over financial reporting to remediate the material weakness, including formalizing our processes and internal control documentation and strengthening supervisory reviews by our financial management; hiring additional qualified accounting and finance personnel and engaging financial consultants to enable the implementation of internal control over financial reporting and segregating duties amongst accounting and finance personnel. We commenced efforts to enhance our control structure by hiring a full-time corporate controller with significant U.S. GAAP, SEC reporting and biotechnology industry experience in the second quarter of 2018, as well as by engaging financial consultants to assist with the evaluation and documentation of technical accounting matters. We expect to hire additional senior accounting staff, including those with expertise in SEC reporting and internal controls upon becoming a public company.

We expect to incur additional costs to remediate the material weakness, though there can be no assurance that our efforts will be successful or avoid potential future material weaknesses. In addition, neither our management nor an independent registered public accounting firm has ever performed an evaluation of our internal control over financial reporting in accordance with the provisions of the Sarbanes-Oxley Act because no such evaluation has been required. Had we or our independent registered public accounting firm performed an evaluation of our internal control over financial reporting in accordance with the provisions of the Sarbanes-Oxley Act, additional material weaknesses may have been identified. If we are unable to successfully remediate our existing or any future material weaknesses in our internal control over financial reporting, or if we identify any additional material weaknesses, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our ADS price may

decline as a result. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

Our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an EGC, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an EGC for up to five years. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Upon completion of this offering, we will become subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law the TCJA, which makes significant changes to the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation and other changes that may impact our operations, in particular the operations of our wholly owned U.S. subsidiary, Bicycle Therapeutics Inc. We continue to examine the impact the TCJA may have on our business, though the effect of the TCJA on our business is uncertain. We urge investors to consult with their legal

and tax advisers regarding the implications of the TCJA on an investment in our ordinary shares or ADSs.

If we are a controlled foreign corporation, there could be adverse U.S. federal income tax consequences to certain U.S. holders.

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income" and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents, royalties, "global intangible low-taxed income," gains from the sale of securities and income from certain transactions with related parties. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of the total combined voting power of all classes of stock entitled to vote or 10% or more of the total value of all classes of stock of such corporation.

We believe that we were not a CFC in the 2018 taxable year and we do not expect to be a CFC in the current taxable year. However, the determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. U.S. Holders (as defined below under "Material Income Tax Considerations—Material U.S. Federal Income Tax Considerations for U.S. Holders") should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC.

If we are a PFIC, there could be adverse U.S. federal income tax consequences to U.S. holders.

Under the Code, we will be a PFIC, for any taxable year in which (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. Holder holds our shares, the U.S. Holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

Based on our analysis of our income, assets, activities and market capitalization, we believe that we were a PFIC in the 2018 taxable year. We have not yet determined our PFIC status for the current taxable year, but we may be a PFIC. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by

reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how we spend the cash we raise in any offering, including this offering.

In certain circumstances, a U.S. Holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a "qualified electing fund," or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute "marketable" securities under the Code). A U.S. Holder would be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code. However, a U.S. Holder may make a QEF election with respect to our ordinary shares or ADSs only if we agree to furnish such U.S. Holder annually with required information. If we determine that we are a PFIC for this taxable year or any future taxable year, we currently expect that we would make available the information necessary for U.S. Holders to make a QEF Election.

For further discussion of the PFIC rules and the adverse U.S. federal income tax consequences in the event we are classified as a PFIC, see the section of this prospectus entitled "Material Income Tax Considerations — Material U.S. Federal Income Considerations for U.S. Holders."

We may be unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable U.K. tax legislation.

As a U.K. incorporated and tax resident entity, we are subject to U.K. corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any U.K. corporation tax. As of December 31, 2018, we had cumulative carryforward tax losses of $29.1 million in the U.K. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure program, or RDEC Program. Where available, under the SME Program, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these SME Program tax credit cash rebate claims. On October 29, 2018, the U.K. government proposed that from April 1, 2020 the amount of payable credit that a qualifying loss-making SME business can receive through R&D relief in any one year will be capped at three times the company's total PAYE and NICs liability for that year.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in

combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

Future changes to tax laws could materially adversely affect our company and reduce net returns to our shareholders.

The tax treatment of the company is subject to changes in tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, as well as tax policy initiatives and reforms related to the Organisation for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, HM Revenue & Customs, or HMRC, the Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

Shareholder protections found in provisions under the U.K. City Code on Takeovers and Mergers, or the Takeover Code, will not apply if our place of management and control is considered to change to outside the United Kingdom.

Prior to the consummation of this offering, we will re-register as a public limited company incorporated in England and Wales. Our place of central management and control is currently in the United Kingdom. Accordingly, we are currently subject to the Takeover Code and, as a result, our shareholders are entitled to the benefit of certain takeover offer protections provided under the Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted. If, at the time of a takeover offer, the Panel on Takeovers and Mergers determines that we do not have our place of central management and control in the United Kingdom, then the Takeover Code would not apply to us and our shareholders would not be

entitled to the benefit of the various protections that the Takeover Code affords. In particular, we would not be subject to the rules regarding mandatory takeover bids. The following is a brief summary of some of the most important rules of the Takeover Code:

- when any person acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares already held by that person and an interest in shares held or acquired by persons acting in concert with him or her) carry 30% or more of the voting rights of a company that is subject to the Takeover Code, that person is generally required to make a mandatory offer to all the holders of any class of equity share capital or other class of transferable securities carrying voting rights in that company to acquire the balance of their interests in the company;

- when any person who, together with persons acting in concert with him or her, is interested in shares representing not less than 30% but does not hold more than 50% of the voting rights of a company that is subject to the Takeover Code, and such person, or any person acting in concert with him or her, acquires an additional interest in shares which increases the percentage of shares carrying voting rights in which he or she is interested, then such person is generally required to make a mandatory offer to all the holders of any class of equity share capital or other class of transferable securities carrying voting rights of that company to acquire the balance of their interests in the company;

- a mandatory offer triggered in the circumstances described in the two paragraphs above must be in cash (or be accompanied by a cash alternative) and at not less than the highest price paid within the preceding 12 months to acquire any interest in shares in the company by the person required to make the offer or any person acting in concert with him or her;

- in relation to a voluntary offer (i.e. any offer which is not a mandatory offer), when interests in shares representing 10% or more of the shares of a class have been acquired for cash by an offeror (i.e., a bidder) and any person acting in concert with it in the offer period and the previous 12 months, the offer must be in cash or include a cash alternative for all shareholders of that class at not less than the highest price paid for any interest in shares of that class by the offeror and by any person acting in concert with it in that period. Further, if an offeror acquires for cash any interest in shares during the offer period, a cash alternative must be made available at not less than the highest price paid for any interest in the shares of that class;

- if the offeror acquires an interest in shares in an offeree company (i.e., a target) at a price higher than the value of the offer, the offer must be increased to not less than the highest price paid for the interest in shares so acquired;

- the offeree company must obtain competent advice as to whether the terms of any offer are fair and reasonable and the substance of such advice must be made known to all the shareholders, together with the opinion of the board of directors of the offeree company;

- special or favorable deals for selected shareholders are not permitted, except in certain circumstances where independent shareholder approval is given and the arrangements are regarded as fair and reasonable in the opinion of the financial adviser to the offeree;

- all shareholders must be given the same information;

- each document published in connection with an offer by or on behalf of the offeror or offeree must state that the directors of the offeror or the offeree, as the case may be, accept responsibility for the information contained therein;

- profit forecasts, quantified financial benefits statements and asset valuations must be made to specified standards and must be reported on by professional advisers;

- misleading, inaccurate or unsubstantiated statements made in documents or to the media must be publicly corrected immediately;
- actions during the course of an offer by the offeree company, which might frustrate the offer are generally prohibited unless shareholders approve these plans. Frustrating actions would include, for example, lengthening the notice period for directors under their service contract or agreeing to sell off material parts of the target group;
- stringent and detailed requirements are laid down for the disclosure of dealings in relevant securities during an offer, including the prompt disclosure of positions and dealing in relevant securities by the parties to an offer and any person who is interested (directly or indirectly) in 1% or more of any class of relevant securities; and
- employees of both the offeror and the offeree company and the trustees of the offeree company's pension scheme must be informed about an offer. In addition, the offeree company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

The rights of our shareholders may differ from the rights typically offered to shareholders of a U.S. corporation.

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. See "Description of Share Capital and Articles of Association — Differences in Corporate Law" in this prospectus for a description of the principal differences between the provisions of the Companies Act applicable to us and, for example, the Delaware General Corporation Law relating to stockholders' rights and protections.

The principal differences include the following:

- under English law and our articles of association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings;
- under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. You should be aware, however, that the voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank
- under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise;
- under English law and our articles of association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the articles of association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other significant transactions;

- in the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, for so long as we continue to be subject to the Takeover Code, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a "squeeze out" to obtain 100% control of us. Accordingly, acceptances of 90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting for approval;

- under English law and our articles of association, shareholders and other persons whom we know or have reasonable cause to believe are, or have been, interested in our shares may be required to disclose information regarding their interests in our shares upon our request, and the failure to provide the required information could result in the loss or restriction of rights attaching to the shares, including prohibitions on certain transfers of the shares, withholding of dividends and loss of voting rights. Comparable provisions generally do not exist under U.S. law; and

- the quorum requirement for a shareholders' meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder which is a corporation, represented by a duly authorized officer. Under U.S. law, a majority of the shares eligible to vote must generally be present (in person or by proxy) at a shareholders' meeting in order to constitute a quorum. The minimum number of shares required for a quorum can be reduced pursuant to a provision in a company's certificate of incorporation or bylaws, but typically not below one-third of the shares entitled to vote at the meeting.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the sections titled "Prospectus Summary," "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business," contains forward-looking statements that are based on our management's belief and assumptions and on information currently available to our management. Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements in this prospectus include, but are not limited to, statements about:

- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- our ability to advance our product candidates into, and successfully complete, clinical trials;
- our reliance on the success of our product candidates in our BTC program and our other pipeline programs;
- our ability to utilize our screening platform to identify and advance additional product candidates into clinical development;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- our ability to develop sales and marketing capabilities;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- our ability to operate our business without infringing the intellectual property rights and proprietary technology of third parties;
- cost associated with defending intellectual property infringement, product liability and other claims;
- regulatory development in the United States, under the laws and regulations of England and Wales, and other jurisdictions;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations or obtain additional grant funding;
- the rate and degree of market acceptance of any approved products;
- developments relating to our competitors and our industry, including competing therapies;
- our ability to effectively manage our anticipated growth;

- our ability to attract and retain qualified employees and key personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act;
- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance;
- our expected use of proceeds of this offering;
- the future trading price of the ADSs and impact of securities analysts' reports on these prices; and
- other risks and uncertainties, including those listed under the caption "Risk Factors."

In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue" or the negative of these terms or other comparable terminology. These statements are only predictions. You should not place undue reliance on forward-looking statements because they involve known and unknown risks, uncertainties and other factors, which are, in some cases, beyond our control and which could materially affect results. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under "Risk Factors" and elsewhere in this prospectus. If one or more of these risks or uncertainties occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those implied or projected by the forward-looking statements. No forward-looking statement is a guarantee of future performance. You should read this prospectus and the documents that we reference in this prospectus and have filed with the SEC as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements.

The forward-looking statements in this prospectus represent our views as of the date of this prospectus. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should therefore not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this prospectus.

MARKET, INDUSTRY AND OTHER DATA

This prospectus contains estimates, projections and other information concerning our industry, our business and the markets for our product candidates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties, and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from our own internal estimates and research as well as from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in the section titled "Risk Factors." These and other factors could cause our future performance to differ materially from those expressed in the industry publications, as well as from our assumptions and estimates. See the section titled "Special Note Regarding Forward-Looking Statements."

USE OF PROCEEDS

We estimate that the net proceeds to us from the sale of ADSs in this offering will be approximately $ million based upon an assumed initial public offering price of $ per ADS, the midpoint of the price range set forth on the cover of this prospectus, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional ADSs in full, we estimate that our net proceeds will be approximately $ million, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Each $1.00 increase (decrease) in the assumed initial public offering price of $ per ADS would increase (decrease) the net proceeds to us from this offering by approximately $ million, assuming the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 1,000,000 ADSs offered by us would increase (decrease) the net proceeds to us from this offering by approximately $ million, assuming the assumed initial public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The principal purposes of this offering are to create a public market for the ADSs, and to facilitate our future access to the public equity markets and obtain additional capital. We currently expect to use the net proceeds from this offering, together with our existing cash, as follows:

- approximately $ million to $ million to complete preparation for Phase II and III clinical development of BT1718, including manufacturing activities, and to advance BT5528 and BT8009 through Phase I clinical development and complete preparations for Phase II development activities;
- approximately $ million to $ million to advance our CD137 programs through preclinical development, including IND-enabling studies, and to advance one CD137 multimeric program through Phase I clinical development; and
- the remainder on drug discovery, further expansion of our infrastructure to support our pipeline as well as to fund working capital and other general corporate purposes.

This expected use of the net proceeds from this offering and our existing cash represents our intentions based upon our current plans and business conditions. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. The amounts and timing of our actual expenditures and the extent of clinical development may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from preclinical studies and any ongoing clinical trials or clinical trials we may commence in the future, as well as any collaborations that we may enter into with third parties for our product candidates and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering and may change the allocation of use of these proceeds among the uses described above. An investor will not have the opportunity to evaluate the economic, financial or other information on which we base our decisions on how to use the proceeds.

We may use a portion of the net proceeds of this offering for the acquisition or licensing, as the case may be, of additional technologies, other assets or businesses, or for other strategic investments or opportunities, although we have no current understandings, agreements or commitments to do so at this time. Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments, or hold as cash.

DIVIDEND POLICY

We have not declared or paid any dividends to our shareholders on our ordinary shares or our convertible preferred shares. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Investors should not purchase the ADSs with the expectation of receiving cash dividends.

Any future determination to pay dividends will be made at the discretion of our board of directors and may be based on a number of factors, including our future operations and earnings, capital requirements and surplus, general financial condition, contractual restrictions and other factors that our board of directors may deem relevant. In addition, our ability to pay dividends may be limited under English law. See "Risk Factors—Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment." If we pay any dividends, we will pay the ADS holders to the same extent as holders of our ordinary shares, subject to the terms of the deposit agreement, including the fees and expenses payable thereunder. See "Description of American Depositary Shares." Cash dividends on our ordinary shares, if any, will be paid in U.S. dollars.

SHARE CAPITAL REORGANIZATION AND RE-REGISTRATION

The share capital reorganization described below shall be implemented prior to the completion of this offering so that ordinary shares of £ nominal value each shall be in issue prior to the completion of this offering. We shall re-register Bicycle Therapeutics Limited as a public limited company and rename it Bicycle Therapeutics plc. Therefore, investors in this offering will acquire, and this prospectus only describes the offering of, ADSs each representing ordinary shares of Bicycle Therapeutics plc.

Share Capital Reorganization

To effect the share capital reorganization, Bicycle Therapeutics Limited shall capitalize a certain sum standing to the credit of Bicycle Therapeutics Limited's share premium account, and apply such sum in paying up newly issued fully paid shares by means of a bonus share issue. The calculation of the number of bonus shares to be issued will be determined based on the final price per ADS in this offering. The issue of bonus shares will vary the share capital of the Company and will also results in an adjustment to the number of: (a) warrant shares granted pursuant to the existing warrant instruments; and (b) options under the option agreements in each case to maintain the percentage interest in the Company's fully diluted share capital held by each warrant holder and option holder before the bonus shares were issued.

Reorganization of the Share Capital and Re-registration of Bicycle Therapeutics Limited as Bicycle Therapeutics plc

Prior to completion of this offering, Bicycle Therapeutics Limited will re-register as a public limited company. Such re-registration will require the passing of special resolutions by the shareholders of Bicycle Therapeutics Limited to approve the re-registration as a public company, the name change to Bicycle Therapeutics plc and the adoption of a new set of articles of association for Bicycle Therapeutics plc.

Certain further resolutions will be required to be passed by the shareholders of the Company prior to the completion of this offering, details of which are set out in the section titled "Description of Share Capital and Articles of Association."

Conditional upon and effectively immediately prior to completion of this offering, assuming an initial public offering price of $ per ADS, each class of shares in the issued share capital of Bicycle Therapeutics plc will be reorganized and re-designated into an aggregate of shares of a single class of ordinary shares of nominal value £0.01 per ordinary share of Bicycle Therapeutics plc.

In the event of a $1.00 increase in the assumed initial public offering price per ADS to $ per ADS, the shareholders of Bicycle Therapeutics plc immediately before completion of the offering will hold an aggregate of ordinary shares of Bicycle Therapeutics plc. In the event of a $1.00 decrease in the assumed initial public offering price per ADS to $ per ADS, the shareholders of Bicycle Therapeutics plc immediately before completion of the offering will hold an aggregate of ordinary shares of Bicycle Therapeutics plc.

CAPITALIZATION

The following table sets forth our cash and capitalization as of December 31, 2018 on:

- an actual basis;
- a pro forma basis to give effect to (i) the issuance of 80,385 Series B2 convertible preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A convertible preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 convertible preferred shares immediately prior to the completion of this offering, (iv) the automatic conversion of all outstanding convertible preferred shares as of December 31, 2018, plus the Series B2 convertible preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon the completion of this offering, and (v) the reclassification of the warrant liability into additional paid-in capital, upon the completion of this offering; and
- on a pro forma as adjusted basis giving effect to the pro forma adjustments set forth above and to give further effect to the sale of ADSs in this offering.

The pro forma as adjusted calculations assume an initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this information together with our audited consolidated financial statements and related notes appearing elsewhere in this prospectus and the information set forth under the sections titled "Selected Consolidated Financial Data," "Exchange Rate Information," "Use of

Proceeds" and "Management's Discussion and Analysis of Financial Condition and Results Of Operations."

	As of December 31, 2018		
	Actual	Pro Forma[1]	Pro Forma As Adjusted[2]
	(in thousands, except share and per share data)		
Cash	$ 63,380	$ 64,983	
Warrant liability	4,804	—	
Series A convertible prefered shares, £0.01 nominal value; 3,000,001 shares authorized, 2,800,001 shares issued and outstanding at December 31, 2018, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	41,820	—	
Series B1 convertible prefered shares, £0.01 nominal value: 4,690,485 shares authorized, 3,947,198 shares issued and outstanding at December 31, 2018, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	54,621	—	
Series B2 convertible preferred shares, £0.01 nominal value; 1,403,633 shares authorized, 1,323,248 shares issued and outstanding at December 31, 2018, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	25,756	—	
Shareholders' (deficit) equity:			
Ordinary shares, £0.01 nominal value; 10,813,450 shares authorized, 628,902 shares issued and 570,156 shares outstanding at December 31, 2018, actual: 8,905,805 shares authorized, 9,351,377 shares issued and 9,292,631 shares outstanding at December 31, 2018, pro forma; shares authorized, shares issued and shares outstanding, pro forma as adjusted	8	119	
Additional paid-in capital	1,859	130,352	
Accumulated other comprehensive loss	(1,751)	(1,751)	
Accumulated deficit	(69,942)	(69,942)	
Total shareholders' (deficit) equity	(69,826)	58,778	
Total capitalization	$ 57,175	$ 58,778	

(1) The number of ordinary shares to be outstanding after this offering is based on 628,902 shares (which includes 58,746 unvested restricted shares subject to repurchase by us) outstanding as of December 31, 2018, and gives effect to (i) the issuance of 80,385 Series B2 convertible preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A convertible preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 convertible preferred shares immediately prior to the completion of this offering, (iv) the automatic conversion of all outstanding convertible preferred shares as of December 31, 2018, plus the Series B2 convertible preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon the completion of this offering, and (v) the reclassification of the warrant liability into additional paid-in capital, upon the completion of this offering, and excludes:

- 604,444 ordinary shares issuable upon the exercise of options to subscribe for ordinary shares outstanding as of December 31, 2018 at a weighted average exercise price of $1.44 per ordinary share;
- 485,985 ordinary shares reserved for future issuance as of December 31, 2018 in connection with equity awards;
- ordinary shares that will be made available for future issuance under our 2019 Share Option and Incentive Plan upon the effectiveness of the registration statement of which this prospectus forms a part; and
- ordinary shares that will be made available for future issuance under our 2019 Employee Share Purchase Plan, upon the effectiveness of the registration statement of which this prospectus forms a part.

(2) The pro forma as adjusted information discussed above is illustrative only and will change based on the actual initial public offering price and other terms of this offering determined at pricing. Each $1.00 increase (decrease) in the assumed initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, total shareholders' (deficit) equity and total capitalization by $ million, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. Each increase (decrease) of 1,000,000 in the number of ADSs offered by us, as set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, total shareholders' (deficit) equity and total capitalization by $ million, assuming no change in the initial public offering price per ADS.

DILUTION

If you invest in the ADSs in this offering, your interest will be diluted to the extent of the difference between the initial public offering price per ADS and the pro forma as adjusted net tangible book value per ordinary share/ADS immediately after this offering. Dilution results from the fact that the initial public offering price per ADS is substantially in excess of the net tangible book value per ordinary share/ADS.

Our net tangible book value as of December 31, 2018 was $(71.5) million, or $(113.64) per ordinary share/ADS. Net tangible book value represents our total assets less our total liabilities and the carrying value of our convertible preferred shares, excluding deferred offering costs, and net tangible book value per share as of December 31, 2018 represents net tangible book value divided by the 628,902 ordinary shares outstanding, including 58,746 unvested restricted shares subject to repurchase by us.

Our pro forma net tangible book value as of December 31, 2018 was $57.1 million, or $6.11 per share/ADS. Pro forma net tangible book value per share is calculated after giving effect to (i) the issuance of 80,385 Series B2 convertible preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A convertible preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 convertible preferred shares immediately prior to the completion of this offering, (iv) the automatic conversion of all outstanding preferred shares as of December 31, 2018, plus the Series B2 convertible preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon the completion of this offering, and (v) the reclassification of the warrant liability into additional paid-in capital, upon the completion of this offering.

After giving further effect to our issuance and sale of ADSs in this offering at the assumed initial public offering price of $ per ADS, the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of December 31, 2018 would have been $ million, or $ per share/ADS.

This represents an immediate increase in pro forma as adjusted net tangible book value per ordinary share of $ to existing shareholders and immediate dilution in pro forma as adjusted net tangible book value per ADS of $ to new investors purchasing ADSs in this offering. Dilution per ADS to new investors is determined by subtracting pro forma as adjusted net tangible book value per ADS after this offering from the initial public offering price per ADS paid by new investors. The following table illustrates this dilution:

Assumed initial public offering price		$
Historical net tangible book value per ADS as of December 31, 2018	$ (113.64)	
Pro forma increase in net tangible book value per ADS as of December 31, 2018	119.75	
Pro forma net tangible book value per ADS as of December 31, 2018	6.11	
Increase in pro forma net tangible book value per ADS attributable to new investors		
Pro forma as adjusted net tangible book value per ADS after this offering		
Dilution per ADS to investors participating in this offering		$

Each $1.00 increase (decrease) in the assumed initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the dilution to new investors by $ per ADS, assuming the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same, and after deducting estimated underwriting discounts and commissions and estimated expenses payable by us. An increase of 1,000,000 ADSs offered by us would decrease the dilution to new investors by $ per ADS, assuming the assumed initial public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated expenses payable by us. A decrease of 1,000,000 ADSs offered by us would increase the dilution to new investors by $ per ADS, assuming the assumed initial public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated expenses payable by us.

If the underwriters exercise their option to purchase additional ADSs in full, the pro forma as adjusted net tangible book value would be $ per ordinary share/ADS, and the dilution in pro forma as adjusted net tangible book value to investors in this offering would be $ per ADS.

The following table summarizes, on a pro forma as adjusted basis as of December 31, 2018, the differences between existing shareholders, including holders of our convertible preferred shares, and new investors with respect to the number of ordinary shares (in the form of ADSs or shares) purchased from us, the total consideration paid and the average price per ordinary share/ADS paid before deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, at an assumed initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover of this prospectus.

The total number of ordinary shares does not include ordinary shares underlying the ADSs issuable upon the exercise of the option to purchase additional ADSs granted to the underwriters.

	Ordinary Shares (ADSs) Purchased		Total Consideration		Average Price per Ordinary Share	Average Price per ADS
	Number	Percent	Amount	Percent		
Existing shareholders		%	$	%	$	$
New investors						
Total		100%	$	100%		

The tables and calculations above are based on 628,902 shares (which includes 58,746 unvested restricted shares subject to repurchase by us) outstanding as of December 31, 2018, and gives effect to (i) the issuance of 80,385 Series B2 preferred shares in January 2019 for aggregate consideration of $1.6 million, (ii) the exercise of warrants to subscribe for 200,000 Series A convertible preferred shares immediately prior to the completion of this offering, (iii) the exercise of warrants to subscribe for 371,645 Series B1 convertible preferred shares immediately prior to the completion of this offering, and (iv) the automatic conversion of all outstanding convertible preferred shares as of December 31, 2018, plus the Series B2 convertible preferred shares issued in January 2019, plus the Series A convertible preferred shares and Series B1 convertible preferred shares underlying the warrants described above, into an aggregate of 8,722,477 ordinary shares upon completion of this offering, and excludes:

- 604,444 ordinary shares issuable upon the exercise of options to subscribe for ordinary shares outstanding as of December 31, 2018 at a weighted average exercise price of $1.44 per ordinary share;

- 485,985 ordinary shares reserved for future issuance as of December 31, 2018 in connection with equity awards;
- ordinary shares that will be made available for future issuance under our 2019 Share Option and Incentive Plan upon the effectiveness of the registration statement of which this prospectus forms a part; and
- ordinary shares that will be made available for future issuance under our 2019 Employee Share Purchase Plan, upon the effectiveness of the registration statement of which this prospectus forms a part.

The pro forma information discussed above is illustrative only. Our net tangible book value following the closing of this offering is subject to adjustment based on the actual initial public offering price of the ADSs and other terms of this offering determined at pricing.

To the extent that outstanding options and warrants are exercised, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our shareholders.

SELECTED CONSOLIDATED FINANCIAL DATA

The following tables present the selected consolidated financial data as of the dates and for the periods indicated for Bicycle Therapeutics Limited. We derived the selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2017 and 2018 and the consolidated balance sheet data as of December 31, 2017 and 2018 from our audited consolidated financial statements included elsewhere in this prospectus. Our historical audited consolidated financial statements as of and for the year ended December 31, 2017 have been restated. See Note 1 to the audited consolidated financial statements included elsewhere in this prospectus. We prepare our consolidated financial statements in accordance with U.S. GAAP.

Our historical results are not necessarily indicative of our future results. You should read this data together with our consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the sections titled "Capitalization" and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

The functional currency of Bicycle Therapeutics Limited and its wholly owned subsidiaries in the United Kingdom, BicycleTx Limited and BicycleRD Limited, is the pound sterling. The functional currency of Bicycle Therapeutics Inc. is the U.S. dollar. For financial reporting purposes, the financial statements of Bicycle Therapeutics Limited, BicycleTx Limited and BicycleRD Limited, which are prepared using the functional currency, have been translated into U.S. dollars. Our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates and shareholders' (deficit) equity is translated based on historical exchange rates. Translation adjustments are not included in determining net loss but are included in foreign exchange translation adjustment within accumulated other comprehensive income (loss), a component of shareholders' (deficit) equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in general and administrative expense in the consolidated statements of operations and comprehensive loss.

As of December 31, 2018, the last business day of the year ended December 31, 2018, the representative exchange rate was $1.2763 = £1.00.

Prior to the completion of this offering, we intend to reorganize our share capital and re-register Bicycle Therapeutics Limited as a public limited company and to change our name from Bicycle Therapeutics Limited to Bicycle Therapeutics plc. See "Share Capital Reorganization and Re-Registration."

	Year ended December 31,	
	2017	2018
	(as restated)	
	(in thousands, except share and per share data)	
Statement of Operations Data:[1]		
Collaboration revenues	$ 2,060	$ 7,136
Operating expenses:		
Research and development	11,866	20,761
General and administrative	6,407	8,121
Total operating expenses	18,273	28,882
Loss from operations	(16,213)	(21,746)
Other income (expenses):		
Interest and other income	50	169
Other expense	(119)	(665)
Total other expense, net	(69)	(496)
Net loss before income tax provision	(16,282)	(22,242)
Benefit from income taxes	(23)	(396)
Net loss	$ (16,259)	$ (21,846)
Net loss attributable to ordinary shareholders	$ (16,259)	$ (21,846)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (69.74)	$ (71.13)
Weighted average ordinary shares outstanding, basic and diluted	233,134	307,123
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)		$ (2.76)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)		7,665,736

See Note 2 within the notes to our consolidated financial statements appearing at the end of this prospectus for a description of the method used to calculate basic and diluted net loss per share applicable to ordinary shareholders and unaudited pro forma basic and diluted net loss per share.

	As of December 31,	
	2017	2018
	(in thousands)	
	(as restated)	
Balance Sheet Data:[1]		
Cash	$ 67,663	$ 63,380
Working capital	62,061	67,840
Total assets	74,001	81,826
Total deferred revenue	14,467	14,635
Warrant liability	4,411	4,804
Convertible preferred shares	96,441	122,197
Total shareholders' (deficit) equity	$ (47,184)	$ (69,826)

(1) The Company has also disclosed the impact of restatements to the previously issued consolidated financial statements as of September 30, 2018 and for the nine month periods ended September 30, 2017 and 2018. See "Management's Discussion and Analysis of Financial Condition and Results of Operations — Restatement of previously reported financial information" and Note 1 to the audited consolidated financial statements included elsewhere in this prospectus.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read this discussion and analysis of our financial condition and consolidated results of operations together with the consolidated financial statements, related notes and other financial information included in this prospectus. Our historical consolidated financial statements as of and for the year ended December 31, 2017 have been restated. The Company has also disclosed the impact of this restatement to the previously issued consolidated financial statements as of September 30, 2018 (unaudited) and for the nine month periods ended September 30, 2017 and 2018 (unaudited). See Note 1 to the consolidated financial statements included elsewhere in this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including statements of our plans, objectives, expectations and intentions, contain forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Please also see the section titled "Special Note Regarding Forward-Looking Statements."

Overview

We are a clinical-stage biopharmaceutical company developing a novel class of medicines, which we refer to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained to form two loops which stabilize their structural geometry. This constraint is designed to confer high affinity and selectivity and the relatively large surface area presented by the molecule allows targets to be drugged that have historically been intractable to non-biological approaches. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic, or PK, properties of a small molecule. *Bicycles* are excreted by the kidney rather than the liver and have shown no signs of immunogenicity to date, which we believe together support a favorable toxicological profile.

We have a novel and proprietary phage display screening platform which we use to identify *Bicycles* in an efficient manner. The platform initially displays linear peptides on the surface of engineered bacteriophages, or phages, before "on-phage" cyclization with a range of small molecule scaffolds which can confer differentiated physicochemical and structural properties. Our platform encodes quadrillions of potential *Bicycles* which can be screened to identify molecules for optimization to potential product candidates. We have used this powerful screening technology to identify our current portfolio of candidates in oncology and intend to use it in conjunction with our collaborators to seek to develop additional future candidates across a range of other disease areas.

Our initial internal programs are focused on oncology indications with high unmet medical need. Our lead product candidate, BT1718, is a *Bicycle* Toxin Conjugate, or BTC. This *Bicycle* is being developed to target tumors that express Membrane Type 1 matrix metalloprotease, or MT1-MMP. MT1-MMP is expressed in approximately 76% to 96% of the ovarian, bladder, endometrial and triple negative breast cancer samples we have tested, depending on cancer type. The *Bicycle* is chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK, or CRUK. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019. We are also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2, or EphA2, and Nectin-4, respectively, for oncology indications. BT5528 and BT8009 are being investigated for safety, activity and to establish a rationale for therapeutic use in preclinical studies. We are currently conducting

Investigational New Drug application, or IND, -enabling activities for BT5528 and BT8009. Our discovery pipeline in oncology includes *Bicycle*-targeted innate immune activators as well as T-cell modulators.

Beyond oncology, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas where we believe our proprietary *Bicycle* screening platform can identify therapies to treat diseases with significant unmet medical need. Our partnered programs outside of oncology include collaborations for anti-bacterial, cardiovascular, hematology, ophthalmology and respiratory indications.

Financial Overview

Since our inception, we have devoted substantially all of our resources to developing our *Bicycle* platform and our lead product candidates, BT1718, BT5528 and BT8009, conducting research and development of our product candidates and preclinical programs, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of convertible preferred shares, as well as proceeds received from upfront payments, research and development payments, and development milestone payments from our collaboration agreements with Oxurion, AstraZeneca and BioVerativ (a Sanofi Company). Through December 31, 2018, we have received gross proceeds of $126.4 million from the sale of convertible preferred shares, and $20.7 million of payments under our collaboration revenue arrangements including $4.1 million from Oxurion, $2.3 million from AstraZeneca and $14.3 million from BioVerativ. In January 2019, we received $1.6 million of proceeds from the sale of Series B2 convertible preferred shares as well as an additional $5.0 million that was paid to us by AstraZeneca. We do not have any products approved for sale and have not generated any revenue from product sales.

Since our inception, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability will depend on the successful development and eventual commercialization of one or more of our product candidates. Our net losses were $16.3 million and $21.8 million for the years ended December 31, 2017 and December 31, 2018, respectively. As of December 31, 2018, we had an accumulated deficit of $69.9 million. These losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

We anticipate that our expenses and capital requirements will increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and, if any product candidates are approved, pursue the commercialization of such product candidates by building internal sales and marketing capabilities. In addition, we expect to incur additional costs associated with operating as a public company following the completion of this offering, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company. We expect that our expenses and capital requirements will increase substantially if and as we:

- continue our development of our product candidates, including conducting future clinical trials of BT1718;
- progress the preclinical and clinical development of BT5528 and BT8009;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing to commercial scale;

- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, commercial and scientific personnel;
- acquire or in-license other products and technologies;
- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and
- add operational, financial and management information systems and personnel, including personnel to support our research and development programs, any future commercialization efforts and our transition to operating as a public company following the completion of this offering.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain marketing approval for one or more of our product candidates, which we expect will take many years and is subject to significant uncertainty. We have no commercial-scale manufacturing facilities of our own, and all of our manufacturing activities have been and are planned to be contracted out to third parties. Additionally, we currently utilize third-party contract research organizations, or CROs, to carry out our clinical development activities. If we seek to obtain marketing approval for any of our product candidates from which we obtain promising results in clinical development, we expect to incur significant commercialization expenses as we prepare for product sales, marketing, manufacturing, and distribution.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances, charitable grants, monetization transactions or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back, or discontinue the development and commercialization of one or more of our product candidates.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2018, we had cash of $63.4 million. We believe that the anticipated net proceeds from this offering, together with our existing cash, will enable us to fund our operating expenses and capital expenditure requirements . We have based this estimate on assumptions that may prove to be wrong, and we could deplete our available capital resources sooner than we expect. See "— Liquidity and Capital Resources." To finance our operations beyond that point, we will need to raise additional capital, which cannot be assured.

Components of Our Results of Operations

Collaboration Revenues

To date, we have not generated any revenue from product sales and we do not expect to generate any revenue from product sales for the foreseeable future. Our revenue consists of collaboration revenue under our arrangements with AstraZeneca, Bioverativ and Oxurion, including amounts that are recognized related to upfront payments, milestone payments and amounts due to us for research and development services. In the future, revenue may include additional milestone payments, option exercise payments, and royalties on any net product sales under our collaborations. We expect that any revenue we generate will fluctuate from period to period as a result of the timing and amount of license, research and development services, and milestone and other payments.

Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research and development activities, including our discovery efforts, and the development of our product candidates, which include:

- employee-related expenses including salaries, benefits, and share-based compensation expense;
- expenses incurred under agreements with third parties that conduct research and development, preclinical activities, clinical activities and manufacturing on our behalf;
- the cost of consultants;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical study materials and clinical trial materials;
- costs related to compliance with regulatory requirements; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other operating costs.

Research and development costs are expensed as incurred. Costs for certain activities are recognized based on an evaluation of the progress to completion of specific tasks. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our consolidated financial statements as a prepaid expense or accrued research and development expenses. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

U.K. research and development tax credits are recorded as an offset to research and development expense. See "—Benefit from Income Taxes."

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations, or CMOs, in connection with our preclinical and clinical development activities. Costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. Costs incurred prior to designating a product candidate are included in other discovery and platform related expense. We do not allocate employee costs, costs associated with our

discovery efforts, laboratory supplies, and facilities, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

In December, 2016, we entered into a Clinical Trial and License Agreement with the Cancer Research Technology Limited, or CRTL and Cancer Research UK, or CRUK, whereby the CRUK's Centre for Drug Development is sponsoring and funding a Phase I/IIa clinical trial for our lead product candidate, BT1718, in patients with advanced solid tumors. CRUK has designed and prepared and is carrying out and sponsoring the clinical trial at its own cost. Upon the completion of the Phase I/IIa clinical trial, we have the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and we decide to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, we will assign or grant to Cancer Research Technology Limited an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case we will receive tiered royalties of 70% to 90% of the net revenue depending on the stage of development when the license is granted is less certain costs, as defined by the agreement). The CRUK agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a single digit percentage on net sales of products developed. Upon the completion of the Phase IIa part of the clinical trial, we expect research and development expenses to increase significantly as we expect to fund the continued development of BT1718, as well as incur additional development milestone payments.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as a result of our expanded portfolio of product candidates and as we: (i) continue the clinical development and obtain marketing approval for our product candidates, including BT1718; (ii) initiate clinical trials for our product candidates, including BT5528 and BT8009; and (iii) build our in-house process development and analytical capabilities and continue to discover and develop additional product candidates.

The successful development of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development of these product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from our product candidates. This is due to the numerous risks and uncertainties associated with developing products, including the uncertainty of:

- completing research and preclinical development of our product candidates, including conducting future clinical trials of BT1718;
- progressing the preclinical and clinical development of BT5528 and BT8009;
- establishing an appropriate safety profile with IND-enabling studies to advance our preclinical programs into clinical development;
- identifying new product candidates to add to our development pipeline;
- successful enrollment in, and the initiation and completion of clinical trials;

- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with others;
- establishing commercial manufacturing capabilities or making arrangements with third party manufacturers;
- the development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials;
- addressing any competing technological and market developments, as well as any changes in governmental regulations;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how, as well as obtaining and maintaining regulatory exclusivity for our product candidates;
- continued acceptable safety profile of the drugs following approval; and
- attracting, hiring and retaining qualified personnel.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, the FDA, EMA or another regulatory authority may require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or we may experience significant trial delays due to patient enrollment or other reasons, in which case we would be required to expend significant additional financial resources and time on the completion of clinical development. In addition, we may obtain unexpected results from our clinical trials and we may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, corporate and business development and administrative functions. General and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

Foreign currency transactions in currencies different from the functional currency of our UK entities are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates in foreign currencies are recorded in general and administrative expense in the statement of operations and comprehensive loss. As such, our operating expenses may be impacted by future changes in exchange rates. See "*Quantitative and Qualitative Disclosures About Market Risks*" for further discussion.

We expect that our general and administrative expenses will increase in the future as we increase our general and administrative headcount to support our continued research and development and potential commercialization of our portfolio of product candidates. We also expect to incur increased expenses associated with being a public company, including costs of accounting, audit, information systems, legal, regulatory and tax compliance services, director and officer insurance costs and investor and public relations costs.

Other Income (Expense)

Interest and Other Income

Interest and other income consists primarily of interest earned on our cash held in operating accounts.

Other Expense

Other expense, consists primarily of changes in the fair value associated with the remeasurement of the warrant liability for warrants we issued to purchase Series A and Series B1 convertible preferred shares. We will continue to remeasure the warrant liability at fair value at each reporting period. We expect the warrant liability to increase until the completion of this offering. Upon the completion of this offering, the respective warrants will expire or will be exercised, and as such, we do not expect to incur additional expense related to the remeasurement of the warrant liability subsequent to this offering.

Benefit From Income Taxes

We are subject to corporate taxation in the United States and the United Kingdom. We have generated losses since inception and have therefore not paid United Kingdom corporation tax. The income tax benefit (provision) presented in our consolidated statements of operations and comprehensive loss represents the tax impact from our operating activities in the United States, which has generated taxable income in certain periods based on intercompany service arrangements.

The research and development tax credit received in the U.K. is recorded as a reduction to research and development expenses. The U.K. research and development tax credit, as described below, is fully refundable to us after surrendering tax losses and is not dependent on current or future taxable income. As a result, we have recorded the entire benefit from the U.K. research and development tax credit as a reduction to research and development expenses and is not reflected as part of the income tax provision. If, in the future, any U.K. research and development tax credits generated are needed to offset a corporate income tax liability in the U.K., that portion would be recorded as a benefit within the income tax provision and any refundable portion not dependent on taxable income would continue to be recorded as a reduction to research and development expenses.

As a company that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax credit cash rebate regimes: The Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure program, or RDEC Program. Qualifying expenditures largely comprise employment costs for research staff, consumables expenses incurred under agreements with third parties that conduct research and development, preclinical activities, clinical activities and manufacturing on our behalf and certain internal overhead costs incurred as part of research projects.

Based on criteria established by U.K. law, a portion of expenditures being carried out in relation to our pipeline research and development, clinical trials management and manufacturing development activities are to be eligible for the RDEC Program for the year ended December 31, 2018. We will assess whether it is possible to qualify under the more favorable SME regime for future accounting periods, but this will be affected as a result of becoming a large company by reference to our staff headcount and/or our financial results. public company listed in the United States.

Unsurrendered U.K. losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of U.K. taxable profits. After accounting for tax credits receivable, we had accumulated tax losses for carry forward in the U.K. of $29.1 million as of December 31, 2018.

Value Added Tax, or VAT, is broadly charged on all taxable supplies of goods and services by VAT-registered businesses. Under current rates, an amount of 20% of the value, as determined for VAT purposes, of the goods or services supplied is added to all sales invoices and is payable to HMRC. Similarly, VAT paid on purchase invoices is generally reclaimable from HMRC.

Results of Operations

Comparison of the Years Ended December 31, 2017 and 2018

The following table summarizes our results of operations for the years ended December 31, 2017 and 2018:

	Year Ended December 31,		
	2017 (as restated)	2018	Change
	(in thousands)		
Collaboration revenues	$ 2,060	$ 7,136	$ 5,076
Operating expenses:			
Research and development	11,866	20,761	8,895
General and administrative	6,407	8,121	1,714
Total operating expenses	18,273	28,882	10,609
Loss from operations	(16,213)	(21,746)	(5,533)
Other income (expenses):			
Interest and other income	50	169	119
Other expense	(119)	(665)	(546)
Total other expense, net	(69)	(496)	(427)
Net loss before income tax provision	(16,282)	(22,242)	(5,960)
Benefit from income taxes	(23)	(396)	(373)
Net loss	$ (16,259)	$ (21,846)	$ (5,587)

Collaboration Revenues

Collaboration revenues increased by $5.1 million during the year ended December 31, 2018 compared to the year ended December 31, 2017, primarily due to increases of $3.7 million of revenue from our collaboration with Bioverativ and $0.5 million of revenue under the AstraZeneca collaboration agreement as the year ended December 31, 2017 included less than a year of

collaboration activities for both arrangements. In addition, revenue under our collaboration agreement with Oxurion increased by $0.9 million due to $0.5 million of additional research services performed in the year ended December 31, 2018 pursuant to an amendment to the collaboration agreement, as well as incremental revenue related to the achievement of developmental milestones of $0.4 million for the advancement of the research by Oxurion into a Phase I clinical trial.

Research and Development Expenses

The table below summarizes our research and development expenses for the period:

	Year Ended December 31,		
	2017 (as restated)	2018	Change
	(in thousands)		
BT1718 (MT1)	$ 2,361	$ 1,804	$ (557)
BT5528 (EphA2)	—	4,649	4,649
BT8009 (Nectin-4)	—	2,847	2,847
Other discovery and platform related expense	7,796	8,018	222
Employee and contractor related expenses	3,784	7,994	4,210
Facility expenses	798	1,328	530
Research and development incentives	(2,873)	(5,879)	(3,006)
Total research and development expenses	$ 11,866	$ 20,761	$ 8,895

Research and development expense increased by $8.9 million in the year ended December 31, 2018 as compared to the prior year, primarily due to increases of $4.6 million and $2.8 million in the BT5528 and BT8009 program spending, respectively, as we nominated candidates for these development programs in 2018, as well as an increase of $0.2 million in other unallocated discovery and platform related expense, an increase of $4.2 million in employee and contractor related expenses, and an increase of $0.5 million in facilities related expenses due to an increase in headcount as we expanded our operations in the United States and the United Kingdom. These expenses were offset by a decrease in program spending on BT1718 of $0.6 million due to the timing of clinical material manufacturing, as well as an increase in the research and development tax credit reimbursement of $3.0 million, due to the corresponding increase in research and development spending in the United Kingdom.

We begin to separately track program expenses at candidate nomination, at which point we will accumulate all costs to support that program to date. Through December 31, 2018, since the candidate nominations of BT1718, BT5528 and BT8009, we have incurred approximately $11.3 million, $4.6 million and $2.8 million of direct expenses for the development of these programs, respectively.

General and Administrative Expenses

General and administrative expenses were $8.1 million for the year ended December 31, 2018, compared to $6.4 million for the year ended December 31, 2017. The increase of $1.7 million primarily reflected increases of $1.5 million in personnel related costs, $0.2 million in facilities related costs, and $1.0 million in professional fees. These increases were due to the hiring of additional personnel in our general and administrative functions as we expanded our operations in the United States and the United Kingdom. These amounts were offset by an increase in gains from the effect of foreign exchange rates of $0.9 million during year ended December 31, 2018.

Other Expense, net

Other expense, net increased by $0.4 million during the year ended December 31, 2018, compared to year ended December 31, 2017, primarily due to additional expense of $0.7 million related to the re-measurement associated with changes in the fair value of the warrant liability for warrants to subscribe for Series A and Series B1 convertible preferred shares. This was offset by an increase in interest income as a result of higher cash balances in 2018 following the closing of our Series B1 financings in May and October of 2017 and Series B2 financing in December 2018.

Restatement of previously reported financial information

We have also elected to disclose the impact of this restatement to the previously reported unaudited condensed consolidated financial data as of September 30, 2018 and for the nine month periods ended September 30, 2017 and 2018. See Note 1 to the audited consolidated financial statements included elsewhere in this prospectus.

The consolidated statements of operations data for the nine months ended September 30, 2017 and 2018 and the consolidated balance sheet data as of September 30, 2018 is unaudited. The unaudited interim consolidated financial information have been prepared on the same basis as the audited consolidated financial statements. In the opinion of management, the unaudited data reflects all adjustments, consisting only of normal recurring adjustments, necessary for a fair statement of the financial information contained in those statements.

Restated Results of Operations

	Nine Months Ended September 30,	
	2017	2018
	(as restated) (in thousands, except share and per share data)	
Statement of Operations Data:		
Collaboration revenues	$ 1,405	$ 6,079
Operating expenses:		
Research and development	7,380	14,268
General and administrative	3,866	6,015
Total operating expenses	11,246	20,283
Loss from operations	(9,841)	(14,204)
Other income (expenses):		
Interest and other income	27	75
Other expense	(119)	(1,472)
Total other expense, net	(92)	(1,397)
Net loss before income tax provision	(9,933)	(15,601)
Benefit from income taxes	(23)	(396)
Net loss	$ (9,910)	$ (15,205)
Net loss attributable to ordinary shareholders	$ (9,910)	$ (15,205)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (43.19)	$ (52.08)
Weighted average ordinary shares outstanding, basic and diluted	229,431	291,979

See Note 2 within the notes to our consolidated financial statements appearing at the end of this prospectus for a description of the method used to calculate basic and diluted net loss per

share applicable to ordinary shareholders and unaudited pro forma basic and diluted net loss per share.

	As of September 30, 2018
	(in thousands) (as restated)
Balance Sheet Data:	
Cash	$ 47,922
Working capital	51,855
Total assets	62,597
Total deferred revenue	15,944
Warrant liability	5,721
Convertible preferred shares	96,441
Total shareholders' (deficit) equity	$ (62,970)

Comparison of the Nine Months Ended September 30, 2017 and 2018 (Restated)

The following table summarizes our results of operations for the nine months ended September 30, 2017 and 2018:

	Nine months Ended September 30,		
	2017	2018 (as restated)	Change
		(in thousands)	
Collaboration revenues	$ 1,405	$ 6,079	$ 4,674
Operating expenses:			
Research and development	7,380	14,268	6,888
General and administrative	3,866	6,015	2,149
Total operating expenses	11,246	20,283	9,037
Loss from operations	(9,841)	(14,204)	(4,363)
Other income (expenses):			
Interest and other income	27	75	48
Other expense	(119)	(1,472)	(1,353)
Total other expense, net	(92)	(1,397)	(1,305)
Net loss before income tax provision	(9,933)	(15,601)	(5,668)
Benefit from income taxes	(23)	(396)	(373)
Net loss	$ (9,910)	$ (15,205)	$ (5,295)

Collaboration Revenues

Collaboration revenues increased by $4.7 million in the nine months ended September 30, 2018 compared to the nine months ended September 30, 2017, primarily due to increases of $0.5 million of revenue under the AstraZeneca collaboration and $3.3 million from our collaboration with Bioverativ as the nine month periods ended September 30, 2017 only include a partial period of the year of collaboration activities. In addition, revenue under our collaboration agreement with Oxurion increased by $0.9 million due to $0.5 million of additional research services performed in 2018 pursuant to an amendment to the collaboration agreement, as well as incremental revenue

related to the achievement of developmental milestones of $0.4 million for the advancement of the research by Oxurion into a Phase I clinical trial.

Research and Development Expenses

The table below summarizes our research and development expenses for the period:

	Nine Months Ended September 30,		
	2017	2018 (as restated)	Change
	(in thousands)		
BT1718 (MT1)	$ 2,102	$ 1,269	$ (833)
BT5528 (EphA2)	—	2,311	2,311
BT8009 (Nectin-4)	—	1,504	1,504
Other discovery and platform related expense	4,428	5,791	1,363
Employee and contractor related expenses	2,395	5,414	3,019
Facility expenses	400	1,090	690
Research and development incentives	(1,945)	(3,111)	(1,166)
Total research and development expenses	$ 7,380	$ 14,268	$ 6,888

Research and development expense increased by $6.9 million in the nine months ended September 30, 2018 compared to the nine months ended September 30, 2017, primarily due to increases of $2.3 million and $1.5 million in the BT5528 and BT8009 program spending, respectively, as we nominated candidates for these development programs in 2018, as well as an increase of $1.4 million in other unallocated discovery and platform related expense, an increase of $3.0 million in employee and contractor related expenses, and an increase of $0.7 million in facilities related expenses due to an increase in headcount as we expanded our operations in the United States and the United Kingdom. These expenses were offset by a decrease in program spending on BT1718 of $0.8 million due to the timing of clinical material manufacturing, as well as an increase in the research and development tax credit reimbursement of $1.2 million, due to the corresponding increase in research and development spending in the United Kingdom.

We begin to separately track program expenses at candidate nomination, at which point we will accumulate all costs to support that program to date. Through September 30, 2018, since the candidate nominations of BT1718, BT5528 and BT8009, we have incurred approximately $10.8 million, $2.3 million and $1.5 million of expenses for the development of these programs, respectively.

General and Administrative Expenses

General and administrative expenses were $6.0 million for the nine months ended September 30, 2018, compared to $3.9 million for the nine months ended September 30, 2017. The increase of $2.1 million primarily reflected increases of $1.2 million in personnel related costs, $0.1 million in facilities related costs, and $1.2 million in professional fees. These increases were due to the hiring of additional personnel in our general and administrative functions as we expanded our operations in the United States and the United Kingdom. These amounts were offset by an increase in gains from the effect of foreign exchange rates of $0.4 million during nine months ended September 30, 2018.

Other Expense, net

Other expense, net increased by $1.3 million during the nine months ended September 30, 2018, compared to nine months ended September 30, 2017, due to the re-measurement associated with changes in the fair value of the warrant liability associated with our outstanding warrants to subscribe for Series A and Series B1 convertible preferred shares. This was offset by an increase in interest income as a result of higher cash balances on hand following the closing of our Series B1 financing in May and October of 2017.

Liquidity and Capital Resources

From our inception through December 31, 2018, we have not generated any revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We do not expect to generate significant revenue from sales of any products for several years, if at all.

To date, we have financed our operations primarily with proceeds from the sale of convertible preferred shares, as well as proceeds received from upfront payments, payments for research and development services, and development milestone payments from our collaboration agreements with AstraZeneca, Oxurion and BioVerativ.

Through December 31, 2018, we have received gross proceeds of $126.4 million from the sale of convertible preferred shares, and $20.7 million of payments under our collaboration revenue arrangements including $4.1 million from Oxurion, $2.3 million from AstraZeneca and $14.3 million from BioVerativ. In January 2019, we received $1.6 million of proceeds from the sale of Series B2 convertible preferred shares as well as an additional $5.0 million that was paid to us by AstraZeneca.

Cash Flows

The following table summarizes our cash flows for each of the periods presented:

	Year Ended December 31,	
	2017	2018
	(as restated)	
	(in thousands)	
Net cash used in operating activities[(1)]	$ (1,415)	$ (26,078)
Net cash used in investing activities	(1,113)	(1,186)
Net cash provided by financing activities	57,876	25,430
Effect of exchange rate changes on cash	2,913	(2,449)
Net increase (decrease) in cash	$ 58,261	$ (4,283)

(1) The Company has also disclosed the impact of the restatement to the previously issued cash flow information for the nine month periods ended September 30, 2017 and 2018. See Note 1 to the audited consolidated financial statements included elsewhere in this prospectus.

Operating Activities

Net cash used in operating activities for the year ended December 31, 2017 included our net loss of $16.3 million, net cash provided by changes in our operating assets and liabilities of $13.1 million and net non-cash charges of $1.8 million, which included share-based compensation expense of $0.5 million and depreciation and amortization of $0.3 million, as well as a non-cash research and development expense of $0.9 million related to the issuance of warrants to purchase

Series A convertible preferred shares to certain of our early investors and founders. Net changes in our operating assets and liabilities for the year ended December 31, 2017 consisted primarily of an increase in deferred revenue of $14.1 million primarily due to upfront payments received from our BioVerativ collaboration arrangement, an increase of $1.4 million in research and development incentives receivable, an increase in other assets of $1.0 million and a $1.3 million increase in accrued expenses and other current liabilities.

Net cash used in operating activities for the year ended December 31, 2018 included our net loss of $21.8 million, net cash used by changes in our operating assets and liabilities of $6.6 million and net non-cash charges of $2.4 million, which included share-based compensation expense of $1.0 million and depreciation and amortization of $0.7 million, as well as a changes in the fair value of our warrant liability of $0.7 million. Net changes in our operating assets and liabilities for the year ended December 31, 2018 consisted primarily of an increase of $3.6 million in research and development incentives receivable, an increase in accounts receivable of $0.4 million, an increase in prepaid expenses and other assets of $1.6 million, as well as a decrease in accounts payable of $0.2 million and a decrease deferred revenue of $3.9 million due to the recognition of revenue related to the BioVerativ collaboration arrangement. These amounts were offset by an increase in accrued expenses and other current liabilities of $2.6 million.

Investing Activities

During the years ended December 31, 2017 and 2018, we used $1.1 million and $1.2 million, respectively, of cash in investing activities for purchases of property and equipment consisting primarily of laboratory equipment for new lease space obtained.

Financing Activities

During the year ended December 31, 2017, net cash provided by financing activities was $57.9 million, consisting of $51.3 million and $6.6 million of net proceeds from the sale of our Series B1 convertible preferred shares issued in May 2017 and October 2017, respectively.

During the year ended December 31, 2018, net cash provided by financing activities was $25.4 million, consisting of net proceeds from the sale of our Series B2 convertible preferred shares issued in December 2018 offset by payments of initial public offering costs of $0.6 million.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and as we:

- continue our development of our product candidates, including conducting future clinical trials of BT1718;
- progress the preclinical and clinical development for BT5528 and BT8009;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;

- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, commercial and scientific personnel;
- acquire or in-license other products and technologies;
- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and
- add operational, financial and management information systems and personnel, including personnel to support our research and development programs, any future commercialization efforts and our transition to operating as a public company following the completion of this offering.

In addition, if we obtain marketing approval for any product candidate that we identify and develop, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing, and distribution to the extent that such sales, marketing, and distribution are not the responsibility of our collaboration partners. Even if we are able to generate product sales, we may not become profitable. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce, or eliminate our research and development programs or future commercialization efforts.

We expect that the net proceeds from this offering, together with our existing cash, will enable us to fund our operating expenses through . We have based our estimates on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development of product candidates and programs, and because the extent to which we may enter into collaborations with third parties for development of our product candidates is unknown, we are unable to estimate the timing and amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our future capital requirements will depend on many factors, including:

- the scope, progress, results, and costs of drug discovery, preclinical development, laboratory testing, and clinical trials for the product candidates we may develop;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;

- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, and distribution, for any product candidates for which we receive marketing approval;
- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.
- the success of our collaborations with AstraZeneca, Oxurion and Bioverativ;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the costs of operating as a public company.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, monetization transactions, government contracts or other strategic transactions. To the extent that we raise additional capital through the sale of equity, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights shareholder of our ADSs. If we raise additional funds through collaboration agreements, strategic alliances, licensing arrangements, monetization transactions, or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2018 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

	Payments due by period				
	Total	Less than 1 year	1 to 3 years	4 to 5 years	More than 5 years
	(in thousands)				
Operating lease commitments[1]	$ 3,187	$ 888	$ 1,816	$ 483	$ —
Total	$ 3,187	$ 888	$ 1,816	$ 483	$ —

(1) Amounts reflect minimum payments due for our office and laboratory space leases. We have one office lease in Cambridge, U.K. under an operating lease that expires in December 2021. We lease laboratory space in Lexington, Massachusetts under operating leases that expires in December 2022.

We enter into various agreements with contract manufacturing organizations to provide clinical trial materials and with vendors for preclinical research studies, synthetic chemistry and other services for operating purposes. These payments are not included in the table of contractual obligations above since the contracts are generally cancelable at any time upon less than 90 days' prior written notice. We are not contractually able to terminate for convenience and avoid any and all future obligations to these vendors. Under such agreements, we are contractually obligated to make certain minimum payments to the vendors, with the payments in the event of a termination with less than 90 days' notice based on the timing of the termination and the exact terms of the agreement.

Legal Proceedings

From time to time, we may become involved in various legal proceedings and claims, either asserted or unasserted, which arise in the ordinary course of business.

In September 2016, we filed a complaint in the District Court of the Hague against Pepscan Systems B.V. ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement we entered into with Pepscan in 2009 and 2010. In response, Pepscan counterclaimed for injunctive relief and unquantified damages. We are vigorously prosecuting our claims and defending against those of Pepscan. We do not believe that a loss is probable or estimable at this time, and as such, we have not recorded a liability related to the Pepscan litigation as of December 31, 2017 and 2018. Should we not be successful in maintaining our rights to Pepscan's patent or in our alternative demand that the patent be invalidated, commercialization of our lead product could be delayed. As the Pepscan patent expires prior to the expected commercialization date of the product, we do not believe that the legal proceedings could have a material adverse effect on our business and operating results. We are unable to reasonably estimate a range of potential loss related to this matter at this time.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in greater detail in Note 2 to our consolidated financial statements appearing at the end of this prospectus, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Collaboration Revenues

Our revenues are generated primarily through collaborative arrangements and license agreements with pharmaceutical companies. The terms of these arrangements may include (i) performing research and development services using our bicyclic peptide screening platform with the goal of identifying compounds for further development and commercialization, (ii) options to obtain additional research and development services or licenses for additional targets, or to optimize product candidates, upon the payment of option fees, or (iii) the transfer of intellectual property rights (licenses).

The terms of these arrangements typically include payment to us of one or more of the following: non-refundable upfront license fees; payments for research and development services; fees upon the exercise of options to obtain additional services or licenses; payments based upon the achievement of defined collaboration objectives; future regulatory and sales-based milestone payments; and royalties on net sales of future products.

We adopted ASU 2014-09, Revenue from Contracts with Customers (Topic 606) ("ASC 606") and all subsequent amendments using the full retrospective transition method for all periods presented. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when, or as, we satisfy the performance obligations. We only apply the five-step model to contracts when it is probable that we will collect substantially all of the consideration we are entitled to in exchange for the goods or services it transfers to the customer. As part of the accounting for these arrangements, we must make significant judgments, including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each performance obligation.

Once a contract is determined to be within the scope of ASC 606, we assess the goods or services promised within the contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations.

Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer. The promised goods or services in our contracts with customers primarily consist of license rights to our intellectual property for research and development, research and development services, and options to acquire additional research and development services or options to obtain additional licenses, such as a commercialization license for a potential product candidate. Promised goods or services are considered distinct when: (i) the customer can benefit from the good or service on its own or together with other readily available resources, and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct, we consider factors such as the stage of development of the underlying intellectual property, the capabilities of the customer to develop the intellectual property on their own and whether the required expertise is readily available. In addition, we consider whether the collaboration partner can benefit from a promise for its intended purpose without the receipt of the remaining promises, whether the value of the promise is dependent on the unsatisfied promises, whether there are other vendors that could provide the remaining promises, and whether it is separately identifiable from the remaining promises.

We estimate the transaction price based on the amount of consideration we expect to receive for transferring the promised goods or services in the contract. The consideration may include both fixed consideration and variable consideration. At the inception of each arrangement that includes variable consideration, we evaluate the amount of the potential payments and the likelihood that the payments will be received. We utilize either the most likely amount method or expected value method to estimate variable consideration to include in the transaction price based on which method better predicts the amount of consideration expected to be received. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

After determining the transaction price, we allocate it to the identified performance obligations based on the estimated standalone selling prices. We must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the

contract. We utilize key assumptions to determine the standalone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction, probabilities of technical and regulatory success and the estimated costs. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amounts we would expect to receive for each performance obligation.

We then recognize as revenue in the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time based on the use of an output or input method.

Licenses of Intellectual Property: If a license to our intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, we recognize revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are combined with other promises, such as research and development services and a research license, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the research and development and licensing agreement.

Research and Development Services: The promises under our collaboration agreements may include research and development services to be performed by us on behalf of the partner. Payments or reimbursements resulting from our research and development efforts are recognized as the services are performed and presented on a gross basis because we are the principal for such efforts.

Customer Options: We evaluate customer options to obtain additional items (i.e. additional license rights) for material rights, or options to acquire additional goods or services for free or at a discount. Optional future services that reflect their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations and are accounted for as separate contracts. If optional future services reflect a significant or incremental discount, they are material rights, and are accounted for as performance obligations. We allocate the transaction price to material rights based on the relative standalone selling price, which is determined based on the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised or expires.

Milestone Payments: Our collaboration agreements may include development and regulatory milestones. We evaluate whether the milestones are considered probable of being reached and estimate the amounts to be included in the transaction price using the most likely amount method. We evaluate factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's control, such as marketing approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, we re-evaluate the probability of achievement of such milestones and any related constraint, and if necessary, adjusts the estimate of the overall

transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue and net loss in the period of adjustment.

Royalties: For sales-based royalties, including milestone payments based on the level of sales, we determine whether the sole or predominant item to which the royalties relate is a license. When the license is the sole or predominant item to which the sales-based royalty relates, we recognize revenue at the later of: (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, we have not recognized any sales-based royalty revenue resulting from our collaboration agreements.

We receive payments from customers based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until we perform our obligations under these arrangements. Amounts are recorded as accounts receivable when our right to consideration is unconditional, such as when we have a contractual right to payment per the terms of the contract.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- vendors in connection with performing research activities on our behalf and conducting preclinical studies and clinical trials on our behalf;
- CMOs in connection with the production of preclinical and clinical trial materials;
- CROs, investigative sites or other service providers in connection with clinical trials;
- vendors in connection with preclinical and clinical development activities; and
- vendors related to product manufacturing and development and distribution of preclinical and clinical supplies.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs, research institutions and vendors that supply, conduct and manage preclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and

actual results could differ from our estimates. Through December 31, 2018, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Share-Based Compensation

We are authorized to issue ordinary shares, as well as options and other securities exercisable for or convertible into ordinary shares, as incentives to our employees, consultants, and members of our board of directors. To the extent such incentives are in the form of share options, the options may have been granted pursuant bilateral EMI option award agreements in the form approved by the board of directors. Such agreements provide for the grant of potentially tax-favored Enterprise Management Incentive, or EMI, options, to our U.K. employees, directors and consultants. Options issued pursuant to such agreements have an exercise price of £0.01 per share. The exercise price for share options granted to U.S. employees have an exercise price that is not less than the fair value of ordinary shares as determined by the board of directors as of the date of grant. Exercise prices of our options to subscribe for ordinary shares and restricted share are in British Pound Sterling.

We measure share-based awards granted to employees and directors based on their fair value on the date of the grant and recognize compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. We record the expense for awards with only service-based vesting conditions using the straight-line method and account for forfeitures as they occur.

We have granted awards that include both a service condition, that vest over time, and a performance condition, that will accelerate vesting upon the achievement of a specified collaboration revenue threshold. For equity awards that contain both performance and service conditions, we recognize share-based compensation expense using an accelerated attribution model over the requisite service period when the achievement of a performance-based milestone is probable based on the relative satisfaction of the performance condition as of the reporting date.

For share-based awards granted to non-employee consultants, compensation expense is recognized over the period during which services are rendered by such consultants until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is remeasured using the then-current fair value of our ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model, as applicable.

The fair value of each restricted ordinary share award is based on the fair value of our ordinary shares, less any applicable purchase price.

The fair value of each share option is estimated using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the fair value of ordinary shares, the expected share price volatility, the expected term of the award, the risk-free interest rate, and expected dividends. See Note 9 to our consolidated financial statements appearing at the end of this prospectus for more information.

We classify share-based compensation expense in our consolidated statements of operations in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Determination of the Fair Value of Ordinary Shares

Given the absence of an active market for our ordinary shares, the board of directors determined the fair value of the ordinary shares based on input from management, which utilized an independent valuation of our enterprise value, determined utilizing an analytical valuation model. The third party valuation reports performed utilized various valuation methodologies in accordance

with the framework of the *American Institute of Certified Public Accountants' Technical Practice Aid, Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of our ordinary shares at each grant date, including the following factors:

- prices paid for our convertible preferred shares, which we had sold to outside investors in arm's-length transactions, and the rights, preferences, and privileges of our convertible preferred shares and ordinary shares;
- valuations performed by an independent valuation specialist;
- our stage of development and our business strategy,
- the progress of our research and development programs, including the status of preclinical studies and planned clinical trials for our product candidates;
- the fact that the grants of share-based awards involved illiquid securities in a private company;
- our financial position, including cash on hand, and our historical and forecasted performance and operating results
- the likelihood of achieving a liquidity event for the underlying ordinary shares; and
- external market conditions affecting the biotechnology industry, and trends within the biotechnology industry;

The analytical valuation models employed an Option Pricing Model, or OPM.

OPM

The OPM treats ordinary and convertible preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, securities such as ordinary shares have value only if the funds available for distribution to shareholders exceeded the value of the convertible preferred shares liquidation preferences at the time of the liquidity event, such as a strategic sale or a merger. The ordinary shares are modeled as a call option on the underlying equity value at a predetermined exercise price. In this model, the exercise price is based on a comparison with the total equity value rather than, as in the case of a regular call option, a comparison with a per share price. Thus, ordinary shares are considered to be a call option with a claim on the enterprise at an exercise price equal to the remaining value immediately after the convertible preferred share liquidation preference is paid.

The OPM uses the Black-Scholes option-pricing model to price the call options. This model defines the securities' fair values as functions of the current fair value of a company and uses assumptions, such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities. The aggregate value of the ordinary shares derived from the OPM is then divided by the number of ordinary shares outstanding to arrive at the per share value.

We used the OPM back-solve approach to estimate enterprise value under the OPM. The OPM back-solve approach uses the OPM to derive an implied equity value for one type of a company's equity securities from a contemporaneous sale transaction involving another type of the company's equity securities. For the OPM, we based our assumed volatility factor on the historical trading volatility of our publicly traded peer companies. At each valuation date, we determined the

appropriate volatility to be used, considering such factors as our expected time to a liquidity event and our stage of development.

To derive the fair value of our ordinary shares using the OPM, we calculated the proceeds to our ordinary shareholders based on the preferences and priorities of our convertible preferred shares and ordinary shares. We then applied a discount for lack of marketability to the ordinary shares to account for the lack of access to an active public market.

Valuations method

Our retrospective valuation of our ordinary shares as of September 30, 2017 were prepared using the OPM back-solve approach.

Our retrospective valuations of our ordinary shares as of May 31, 2018 and September 30, 2018, as well as our contemporaneous valuation on December 31, 2018 were prepared using the OPM method, which incorporated probability weighting of sale and IPO outcomes at December 31, 2018, because of an increase in the likelihood of an IPO.

These third-party valuations performed resulted in valuations of our ordinary shares of $3.71 per share as of September 30, 2017, $3.77 per share on May 31, 2018, $4.87 per share on September 30, 2018, and $6.87 per share on December 31, 2018.

The assumptions underlying these valuations represented our board of directors' best estimates at the time they were made, which involve inherent uncertainties and the application of the judgment of our board of directors. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our share-based compensation expense could be materially different.

Once a public trading market for our ordinary shares has been established in connection with the completion of this offering, it will no longer be necessary for our board of directors to estimate the fair value of our ordinary shares in connection with our accounting for granted share options and other such awards we may grant, as the fair value of our ordinary shares will be determined based on the quoted market price of our ordinary shares.

Options and Restricted Shares Granted

The following table sets forth, by grant date, the number of shares subject to options granted from January 1, 2018 through February 28, 2019, the per share exercise price of the options, the

fair value per ordinary share on each grant date, and the per share estimated fair value of the options:

Grant Date	Type of Award	Number of Shares	Purchase or Exercise Price Per Share[1][4]	Retrospective Fair Value Per Ordinary Share on Grant Date[2][4] (as restated)	Per Share Estimated Fair Value on Grant Date[2][3][4] (as restated)
February 1, 2018	Options	13,100	$ 2.53	$ 3.54	$ 2.53
February 8, 2018	Restricted Shares	6,825	$ 0.01	$ 3.54	$ 3.53
September 18, 2018	Options	36,500	$ 2.53	$ 3.62	$ 2.68
November 30, 2018	Options	16,000	$ 3.61	$ 4.76	$ 3.58
December 1, 2018	Options	3,500	$ 3.61	$ 4.76	$ 3.58
December 17, 2018	Options	16,798	$ 3.61	$ 6.87	$ 5.50
December 17, 2018	Options	112,140	$ 0.01	$ 6.87	$ 6.87
December 17, 2018	Restricted Shares	13,461	$ 0.01	$ 6.87	$ 6.86
January 31, 2019	Options	85,596	$ 4.95	$ 6.87	$ 5.20

(1) Represents the determination by our board of directors of the fair value of our ordinary shares on the date of grant, taking into consideration the various objective and subjective factors described below.

(2) The fair value of ordinary shares at the grant date was adjusted in connection with a retrospective fair value assessment for financial reporting purposes.

(3) For purposes of recording share-based compensation for grants of options to a non-employee, we measure the fair value of the award on the service completion date (vesting date). At the end of each reporting period prior to completion of the services, we remeasure the value of any unvested portion of the award based on the then-current fair value of the award and adjust the expense accordingly. The amount in this column reflects only the grant-date fair value of the award.

(4) The exercise prices per the respective share options and the subscription price of restricted shares are in pounds sterling. The amounts in this table are translated to U.S. Dollars at the rate of $1.2763 to £1.00, which was the noon buying rate of the Federal Reserve Bank of New York on December 31, 2018, the last business day of the year ended December 31, 2018.

On December 17, 2018, each of the U.K. employees that were holders of share options granted prior to December 2017, each with an exercise price of £0.01 per share, surrendered all of their issued share options that had not lapsed or been exercised. Thereafter, such persons: (a) subscribed for ordinary shares equal to such number of ordinary shares as were vested under their surrendered option agreement at a subscription price of £0.01 per ordinary share; and (b) were granted options to subscribe for ordinary shares equal to such number of ordinary shares as were unvested under their surrendered option agreement at a subscription price of £0.01 per ordinary share, and with identical vesting terms as the original awards. In conjunction with the surrender of 238,443 vested share options, we issued 238,443 ordinary shares. We evaluated the surrender of share options and issuance of vested ordinary shares and unvested share options as a modification in accordance with ASU 2017-09. The modification did not have any accounting impact as there were no changes in the fair value, vesting conditions, or the classification of the awards (as equity or liability) in conjunction with the surrender of share options and issuance of vested ordinary shares and unvested share options. As such, the grant of options to subscribe for ordinary shares equal to such number of ordinary shares as were unvested under their surrendered option agreement at a subscription price of £0.01 per ordinary share, and with identical vesting terms as the original awards is not reflected in the table above.

For the years ended December 31, 2017 and 2018, we recorded share-based compensation expense for share options and restricted shares granted of $0.5 million and $1.0 million, respectively. Expense for non-employee consultants was immaterial in all periods. As of December 31, 2018, total unrecognized compensation expense related to the unvested employee

and director share-based awards was $1.0 million, which is expected to be recognized over a weighted average period of 3.1 years. As of December 31, 2018, total unrecognized compensation cost related to the unvested employee and director restricted share awards was $0.2 million, which is expected to be recognized over a weighted average period of 1.9 years. We expect the impact of our share-based compensation expense for restricted shares and share options granted to employees and non-employees to increase in future periods due to the potential increases in the value of our ordinary shares and headcount.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. We assess the likelihood that our deferred tax assets will be recovered in the future and, to the extent we believe, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies. See Note 11 to our consolidated financial statements appearing at the end of this prospectus for additional information.

We are subject to corporate taxation in the United Kingdom and the United States. The calculation of our tax provision involves the application of both U.K. and U.S. tax law and requires judgement and estimates.

We account for uncertainty in income taxes in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed as the amount of benefit to recognize in the consolidated financial statements. The amount of benefits that may be used is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes included the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate, as well as the related net interest and penalties.

We receive reimbursements of certain research and development expenditures, through our subsidiaries in the United Kingdom, as part of a United Kingdom government's research and development tax reliefs program. Under the program, a percentage of qualifying research and development expenses incurred by the Company's subsidiaries in the United Kingdom are reimbursed up to 14.5% of the surrendable losses. We assess our research and development activities and expenditures to determine which activities and expenditures are likely to be eligible under the research and development incentive program described above. At each period end, we estimate the reimbursement available to the Company based on available information at the time.

We recognize income from the research and development incentives when the relevant expenditure has been incurred, the associated conditions have been satisfied and there is reasonable assurance that the reimbursement will be received. We record these research and development incentives as a reduction to research and development expenses in the statements of operations and comprehensive loss, as the research and development tax credits are not dependent on us generating future taxable income, our ongoing tax status, or tax position. The

refund is denominated in pounds sterling and, therefore, the receivable is remeasured into U.S. dollars as of each reporting date. The research and development incentives receivable represent an amount due in connection with the above program. We recorded a reduction to research and development expense of $2.9 million and $5.9 million during the years ended December 31, 2017 and 2018, respectively.

Quantitative and Qualitative Disclosures About Market Risks

Interest Rate Sensitivity

As of December 31, 2018, we had cash of $63.4 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in interest-bearing savings accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

As of December 31, 2018, we had no debt outstanding and are therefore not subject to interest rate risk related to debt.

Foreign Currency Exchange Risk

The functional currency of Bicycle Therapeutics Limited and its wholly owned non-U.S. subsidiaries, BicycleTx Limited and BicycleRD Limited, is the British Pound Sterling and the consolidated financial statements are presented in United States dollars, USD. The functional currency of Bicycle Therapeutics Inc. is the United States dollar. The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. The functional currency of the Company's subsidiaries is the same as the local currency.

Monetary assets and liabilities denominated in currencies other than the functional currency are remeasured into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. Adjustments that arise from exchange rate changes on transactions denominated in a currency other than the local currency are included in general and administrative expense in the consolidated statements of operations and comprehensive loss as incurred. We recorded a foreign exchange loss of $0.6 million and a foreign exchange gain of $0.3 million for the years ended December 31, 2017 and 2018, respectively. These foreign currency transaction gains and losses are included in other expense in our consolidated statements of operations and comprehensive loss.

For financial reporting purposes, our consolidated financial statements have been translated into U.S. dollars. We translate the assets and liabilities of Bicycle Therapeutics Limited, BicycleTx Limited and BicycleRD Limited into USD at the exchange rate in effect on the balance sheet date. Revenues and expenses are translated at the average exchange rate in effect during the period and shareholders' (deficit) equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net income (loss) but are included in our foreign exchange adjustment included in the consolidated statements of convertible preferred shares and shareholders' (deficit) equity as a component of accumulated other comprehensive income (loss).

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future.

Emerging Growth Company Status

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an "emerging growth company," or EGC, can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, or the Securities Act, for complying with new or revised accounting standards. Thus, an EGC can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

In addition, we intend to rely on the other exemptions and reduced reporting requirements provided by the JOBS Act. Subject to certain conditions set forth in the JOBS Act, we are entitled to rely on certain exemptions as an "emerging growth company," we are not required to, among other things, (i) provide an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b), (ii) provide all of the compensation disclosure that may be required of non-emerging growth public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements (auditor discussion and analysis), and (iv) disclose certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer's compensation to median employee compensation. These exemptions will apply for a period of five years following the completion of this offering or until we no longer meet the requirements of being an emerging growth company, whichever is earlier. We would cease to be an emerging growth company if we have more than $1.07 billion in annual revenue, we have more than $700.0 million in market value of our share held by non-affiliates (and we have been a public company for at least 12 months and have filed one annual report on Form 10-K), or we issue more than $1.0 billion of non-convertible debt securities over a three-year period.

Off-balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

BUSINESS

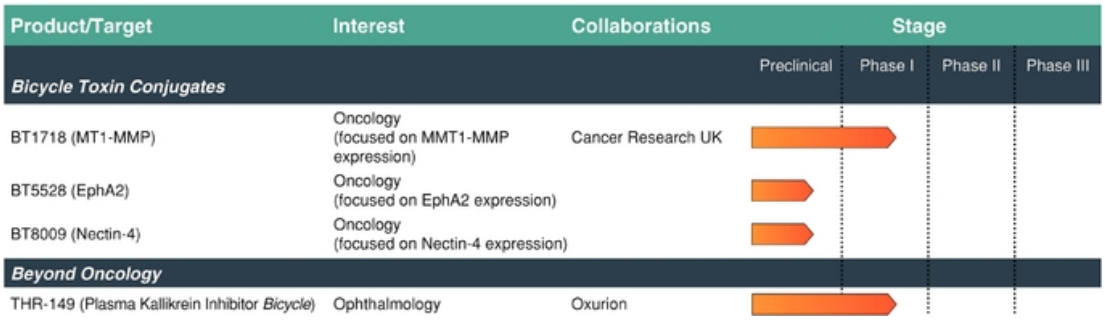
We are a clinical-stage biopharmaceutical company developing a novel class of medicines, which we refer to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained to form two loops which stabilize their structural geometry. This constraint is designed to confer high affinity and selectivity and the relatively large surface area presented by the molecule allows targets to be drugged that have historically been intractable to non-biological approaches. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic, or PK, properties of a small molecule. *Bicycles* are excreted by the kidney rather than the liver and have shown no signs of immunogenicity to date, which we believe together support a favorable toxicological profile.

We have a novel and proprietary phage display screening platform which we use to identify *Bicycles* in an efficient manner. The platform initially displays linear peptides on the surface of engineered bacteriophages, or phages, before "on-phage" cyclization with a range of small molecule scaffolds which can confer differentiated physicochemical and structural properties. Our platform encodes quadrillions of potential *Bicycles* which can be screened to identify molecules for optimization to potential product candidates. We have used this powerful screening technology to identify our current portfolio of candidates in oncology and intend to use it in conjunction with our collaborators to seek to develop additional future candidates across a range of other disease areas.

Our initial internal programs are focused on oncology indications with high unmet medical need. Our lead product candidate, BT1718, is a *Bicycle* Toxin Conjugate, or BTC. This *Bicycle* is being developed to target tumors that express Membrane Type 1 matrix metalloprotease, or MT1-MMP. The *Bicycle* is chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK, or CRUK. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019. We are also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2, or EphA2, and Nectin-4, respectively, for oncology indications. We are currently conducting Investigational New Drug application, or IND, -enabling activities for BT5528 and BT8009. Our discovery pipeline in oncology includes *Bicycle*-targeted innate immune activators as well as T-cell modulators.

Beyond oncology, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas where we believe our proprietary *Bicycle* screening platform can identify therapies to treat diseases with significant unmet medical need. Our partnered programs outside of oncology include collaborations for anti-bacterial, cardiovascular, hematology, ophthalmology and respiratory indications.

The following table summarizes key information about our programs:



We were founded in 2009 based on innovative science conducted by Sir Greg Winter and Professor Christian Heinis. Sir Greg Winter is a pioneer in monoclonal antibodies and, in 2018, was awarded a Nobel prize in chemistry for the invention of the technology underpinning our proprietary phage display screening platform that we use to identify *Bicycles*. Since our founding, we have generated substantial intellectual property, including three patent families directed to novel scaffolds, 11 patent families directed to our platform technology, 52 patent families directed to bicyclic peptides and related conjugates, and four patent families directed to clinical indications. The work we have conducted in developing *Bicycles* and our proprietary screening platform have created substantial know-how that we believe provides us with a competitive advantage.

Our management team includes veterans in drug development with executive experience at leading pharmaceutical companies including GlaxoSmithKline, Novartis and Pfizer. Our board of directors and scientific advisory board include industry experts and seasoned investors, with extensive experience in immuno-oncology. We are supported by prominent healthcare-focused investment funds, including Ahren Innovation Capital, Atlas Venture Fund, Cambridge Innovation Capital, Longwood Fund, Novartis Venture Fund, S.R. One, Limited, SV Life Sciences, Tybourne Capital (HK) Management Limited and Vertex HC Ventures.

Our Strategy

Our mission is to become a leading biopharmaceutical company by pioneering *Bicycles* as a novel therapeutic modality to treat diseases that are inadequately addressed with existing treatment modalities. Specifically, we seek to execute on the following strategy to maximize the value of our novel technology and pipeline:

- ***Advance our lead product candidate, BT1718, through clinical development.*** BT1718 is being investigated in an ongoing Phase I/IIa clinical trial sponsored by CRUK. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019. We intend to advance development of this candidate aggressively across oncology indications in which the target MT1-MMP is expressed.

- ***Advance our other Bicycle Toxin Conjugate programs into clinical development.*** We intend to progress our IND-enabling activities for BT5528 and BT8009 to advance these programs into clinical development for oncology indications. Based on promising observations from our preclinical models, we believe EphA2 and Nectin-4 are attractive targets for cytotoxin delivery and that *Bicycles* provide a promising delivery modality.

- ***Pursue clinical development of our discovery programs.*** We intend to continue our ongoing discovery activities to screen and select promising candidates for oncology indications. For example, our discovery pipeline includes T-cell modulators, from which we

expect to identify a development candidate. In addition, we are also developing *Bicycle*-targeted innate immune activators.

- ***Leverage our powerful proprietary screening platform and novel Bicycle modality to grow our pipeline.*** Our novel and proprietary phage display screening platform allows us to rapidly and efficiently identify potential candidates for development. We can incorporate a wide range of small molecule scaffolds into *Bicycles* to increase diversity and confer differentiated physicochemical and structural properties. We have used our powerful *Bicycle* screening platform to identify our current pipeline of promising BTCs, innate immune activators and T-cell modulators, and intend to use it to develop a broader pipeline of diverse product candidates.

- ***Collaborate strategically with leading organizations to access enabling technology and expertise in order to expand the application of our novel Bicycle modality to indications beyond oncology.*** We are collaborating with leading biopharmaceutical companies and organizations to apply our novel *Bicycle* modality to other disease areas, including anti-bacterial, cardiovascular, hematological, ophthalmological and respiratory indications. We may opportunistically enter into additional collaborations in the future to apply our technology to areas of unmet medical need.

- ***If approved, maximize the commercial potential of our product candidates by either establishing our own sales and marketing infrastructure or doing so through collaborations with others.*** Subject to receiving marketing approval, we intend to pursue the commercialization of our product candidates either by building internal sales and marketing capabilities or doing so through opportunistic collaborations with others.

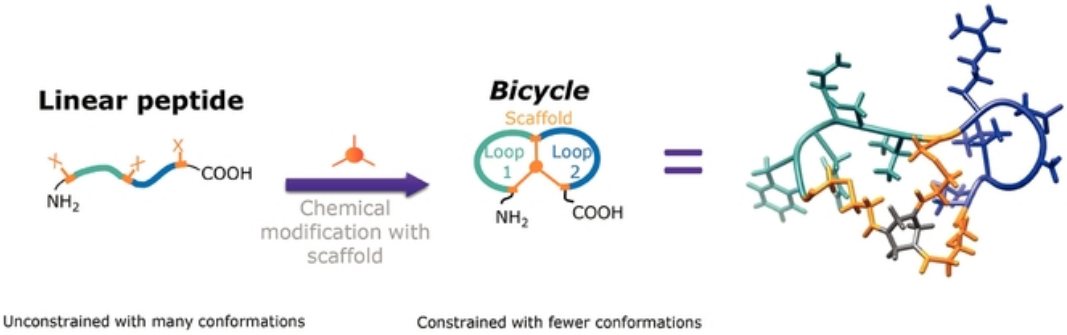
The *Bicycle* Opportunity

Introduction to Bicycles

Bicycles are fully synthetic, short peptides consisting of nine to 15 amino acids constrained to form two loops which stabilize the structural geometry of the peptide and facilitate target binding with high affinity and selectivity. *Bicycles* represent a unique therapeutic class, combining the pharmacological properties normally associated with a biologic with the manufacturing and PK advantages of a small molecule, with no signs of immunogenicity observed to date.

Drugs must bind to target proteins with high affinity and selectivity to achieve a therapeutic effect, while minimizing undesired effects on other proteins and physiological functions. Peptides exist in a number of folded states, only a few of which are able to bind to target proteins, and a key challenge for peptide therapeutics is designing structures that achieve these goals. We have designed our molecules to be highly constrained by linking a chemical connector compound, also known as a scaffold, to particular amino acids in the peptide chain. The resulting cyclized molecule, which we refer to as a *Bicycle*, is locked in the preferred state to bind to the target proteins.

Schematic of the Creation of a Cyclized Molecule Resulting in a Bicycle



We have expanded the diversity of the chemical space we can cover from approximately 10^{13} potential molecules in 2009 to 10^{17} today. We have applied our novel *Bicycle* modality to a growing range of targets, from a single target in 2009 to more than 90 today. We can create a wide range of *Bicycles* by varying four parameters:

- the number of amino acids in the two loops;
- the amino acid composition at each position;
- the symmetry of the two loops; and
- the small molecule scaffold used to cyclize the *Bicycle*.

Properties of Bicycles as Therapeutic Agents

Bicycles have a large surface area available for target binding, which is designed to allow for high affinity and selectivity to the designated target. As short sequences of amino acids, or peptides, they have a low molecular weight, typically ranging from 1.5 kDa to 2.0 kDa. *Bicycles* have a readily adjustable PK profile with good plasma stability and rapid distribution from the vasculature into the extracellular space. This PK profile enables rapid tissue penetration and a renal route of elimination that minimizes liver exposure. Toxicity issues are observed with small molecules that are metabolized and eliminated by the liver. *Bicycle* peptides, by contrast, are not subject to metabolism or elimination by the liver but are metabolized in the peripheral circulation or kidney with subsequent rapid excretion in the urine. Consequently, by increasing excretion in urine, the liver exposure is minimized and the risk of liver toxicity is reduced. The modular nature of *Bicycles* allows us to optimize therapeutic molecules for specific targets. To date, we have observed no signs of immunogenicity.

Compared to biologics, *Bicycles* have a lower cost of production and a simpler manufacturing process, and are recognized by regulatory authorities as small molecule new chemical entities. *Bicycles* can be readily identified to drug a wide spectrum of targets and target classes, including many that have so far been undruggable with small molecules, such as protein-protein interactions. Our novel and proprietary screening platform allows us to screen *Bicycles* against molecular targets rapidly and efficiently, affording potentially reduced timelines and costs compared to other high-throughput screening approaches. Leveraging our platform, we can rapidly and efficiently identify a compound for development in as few as six months with the historical average time being 12 months after a target has been selected.

Properties of Bicycles May Translate into Potential Therapeutic and Other Advantages

Bicycle Property	Importance	Strategic Potential
Bicyclic structure	• Conformational constraint to reduce rotational freedom	• High affinity to designated target • Increased selectivity to designated target
	• Stable 3D structure	• Ability to adopt structures found in native ligands • Ability to generate diverse libraries covering a wide chemical space • No immunogenicity observed to date • Novel structures suitable for patent protection
Small size	• Rapid and extensive extravascular permeability	• Rapid penetration into tissue (e.g. tumor) • Controllable systemic half-life allows the creation of short or long acting molecules
	• Renal elimination	• Bypass of liver metabolism/processing to reduce liver and gastrointestinal toxicity
	• High payload to *Bicycle* ratio	• Low tendency for aggregation • Ease of formulation • High toxin delivery
Large molecular footprint	• Ability to target and disrupt protein-protein interactions	• Ability to bind to target classes usually intractable to small molecule approaches • High selectivity • High affinity
Fully synthetic manufacturing	• Scalable and controllable manufacturing through well established procedures	• Reduced cost of goods compared to biologics • Defined product composition • Multiple suppliers for manufacturing
Ability to conjugate	• Versatility to easily combine with *Bicycles*/modalities without affecting properties • Potential to create multivalent molecules, e.g. bifunctionals, other trifunctionals	• Ability to quickly and efficiently generate a range of drug candidates from small number of *Bicycles*

Comparison of Bicycles to Other Common Classes of Therapeutics

	Bicycle	Antibody	ScFv (fragment)	Peptide	Small molecule
Molecular Weight (kDa)	~1.5-2	~150	~28	~1-5	~<0.8
Extracellular volume	Whole body	Low (vascular)	Intermediate	Whole body	Typically whole body
Half life	Minutes to hours (adjustable). Days possible*	Days to weeks	Minutes to days*	Minutes to hours	Hours (tunable)
Clearance	Renal	Hepatic	Renal, hepatic	Renal, hepatic	Renal, hepatic
Tumor penetrance	High	Low (outer rim only)	Low (poor exposure)	Medium to high	High
Target classes	All tested successful	Many, but can be restricted due to large size	Many, but can be restricted due to large size	Many	Limited
Selectivity	High	High	High	Medium	Poor
Modularity	High	Low	Low	High	Low
Synthesis	Simple	Complex biologic	Complex biologic	Simple	Simple
Immunogenicity	None detected to date	Possible	Frequent	Possible	None

*Requires use of extension technology

Our Proprietary *Bicycle* Screening Platform

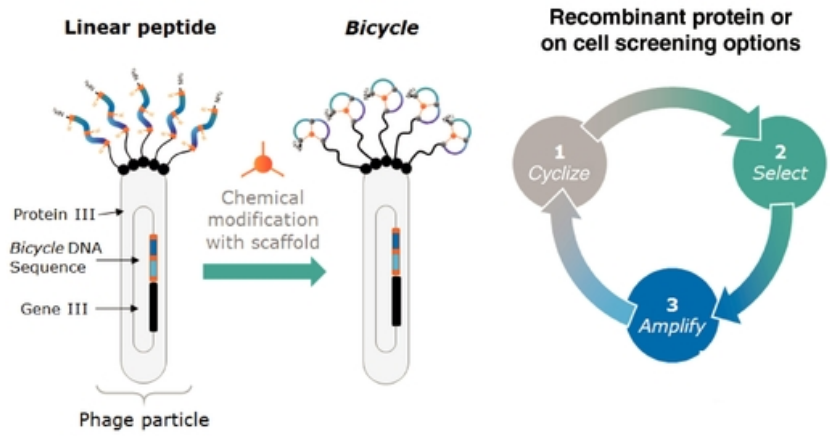
We utilize our novel and proprietary phage display screening platform to identify *Bicycles* that are potentially useful in medicine. We have used this technology to identify our current pipeline, and intend to leverage it to develop a broader portfolio of product candidates to address unmet medical needs across a wide range of diseases.

Phages are bacteria-infecting viruses consisting of genetic material wrapped in a protein coat. Phages can be harnessed to identify *Bicycles* by splicing DNA into the genome of a phage so that the linear peptides that encode *Bicycles* are presented on the surface of the phage. Our founder Sir Greg Winter, a pioneer in phage display, applied this technology and added a cyclization step that

forms *Bicycles* from these linear peptides. This technology underpins our novel and proprietary screening platform.

Our screening process self-selects for *Bicycles* that are amenable to attachment, commonly referred to as conjugation, to other molecular payloads such as cytotoxins, innate immune activators or other *Bicycles*. *Bicycles* can be linked together with synthetic ease to create complex molecules with combinatorial pharmacology. Alternatively, *Bicycles* in the form of multimers can also be used as standalone therapeutics, such as those that we are exploring in our T-cell modulator program. We believe that the flexibility of our *Bicycles* and our powerful screening platform allow new therapeutics to be rapidly conceived and reduced to practice to potentially serve diverse therapeutic applications across a wide range of indications.

Schematic of our Proprietary Bicycle Screening Process



We have optimized our proprietary *Bicycle* screening platform, enabling the technique to be applied to a diverse range of over 90 challenging targets to date, successfully identifying *Bicycles* for over 80% of these targets, some of which are intractable to small molecules. During these screens, *Bicycles* with diverse pharmacologies were identified, including enzyme inhibitors, receptor antagonists, agonists (partial, full and supra) and neutral site binders. Neutral site binders often bind to entirely novel sites on target proteins, previously undescribed in the scientific literature. These binders can be useful when conjugated with therapeutic payloads since they allow antigen-targeted payload delivery without impacting target function.

Our Product Candidates

Our portfolio of internal product candidates is directed to oncology applications where we believe they have the potential to treat a broad spectrum of cancers. We are collaborating with biopharmaceutical companies and organizations in other therapeutic areas, where we believe our proprietary *Bicycle* screening platform can identify therapies to treat diseases with significant unmet medical need.

Our Pipeline

The following table summarizes key information about our pipeline programs.

Program	Interest	Stage	Status
Oncology ***Bicycle* Toxin Conjugates**			
BT1718	• High MT1-MMP expressing tumors (e.g., breast cancer, lung cancer, sarcoma, gastric cancer, head and neck cancer, ovarian cancer, pancreatic cancer)	• Phase I/IIa	• Ongoing Phase I/IIa clinical trial in collaboration with CRUK. Preliminary clinical data from Phase I part of the trial expected in the second half of 2019
BT5528	• High EphA2 expressing tumors (e.g., lung cancer, breast cancer, bladder cancer, gastric cancer, ovarian cancer)	• Preclinical	• IND-enabling activities in process
BT8009	• High Nectin-4 expressing tumors (e.g. breast cancer, bladder cancer, pancreatic cancer, lung cancer)	• Preclinical	• IND-enabling activities in process
***Bicycle*-Targeted**			
Systemically-Delivered Activators	• Oncology	• Discovery	• Discovery activities in process
T-Cell Modulators			
CD137	• Oncology	• Discovery	• Discovery activities in process
Beyond Oncology			
THR-149 (Plasma Kallikrein Inhibitor)	• Ophthalmology	• Phase I	• Collaborating with Oxurion
Inhaled	• Respiratory	• Discovery	• Collaborating with AstraZeneca
Cardiovascular	• Cardiovascular	• Discovery	• Collaborating with AstraZeneca
Hematology	• Hemophilia and Sickle Cell	• Discovery	• Collaborating with Bioverativ
Novel anti-bacterials	• Anti-bacterials	• Discovery	• Collaborating with Innovate UK

Our Oncology Programs

We believe *Bicycles* are an ideal vehicle to deliver small molecule payloads to tumors, both as potent cytotoxins in the case of BTCs, as well as small molecule agonists of the immune system in the case of our *Bicycle*-targeted immune activators. We believe that *Bicycle* conjugates can offer improved performance as compared to antibody-mediated delivery.

In addition to their use as drug conjugates, *Bicycles* can also be configured for use as standalone therapeutics in the form of multimers. We have identified *Bicycles* that have been observed to directly interact with CD137, a key immune cell co-stimulatory molecule. We believe our CD137-targeting *Bicycles* may overcome limitations inherent in antibody-mediated approaches and have the potential to be converted into simple "bi-specific" immune cell-engaging *Bicycle* molecules.

Bicycle Toxin Conjugates

Within our BTC programs, we are developing BT1718 (carrying a DM1 cytotoxin payload), which is designed to target MT1-MMP expressing tumors. BT1718 is currently being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial that is being conducted in collaboration with CRUK. We expect to receive preliminary data from the Phase I part of this clinical trial in the second half of 2019. We are also conducting IND-enabling activities for BT5528 and BT8009 (carrying a monomethyl auristatin E, or MMAE cytotoxin payload), targeting EphA2 and Nectin-4, respectively. Studies have demonstrated that MT1-MMP, EphA2 and Nectin-4 are overexpressed in many cancer cell types, including lung cancer, pancreatic, colorectal, prostate, bladder, ovarian, esophageal and other cancers. Studies have also shown that tumor overexpression in each of these targets has been associated with poor prognosis in specific cancers. We therefore believe our BTC candidates may address a wide range of cancer types with significant unmet medical need.

Background

The discovery of monoclonal antibodies enabled the development of antibody drug conjugates, or ADCs. ADCs link antibodies that target tumor-associated antigens to potent cytotoxins through a process known as conjugation. ADCs are designed to selectively and potently destroy cancer cells by combining the targeting capability of antibodies with the cancer-killing ability of cytotoxins. Despite the growing use of ADCs in treating cancer and high interest in ADC development programs, we believe there are significant challenges to ADCs. The large molecular size of the antibody impairs the penetration of ADCs into tumors. ADCs are generally required to internalize into tumor cells after binding to internalizing tumor antigens to the surface. Finally, the relatively long systemic exposure and subsequent liver clearance generally associated with ADCs result in dose-limiting toxicities such as hematological, liver and gastrointestinal toxicities, and neuropathies.

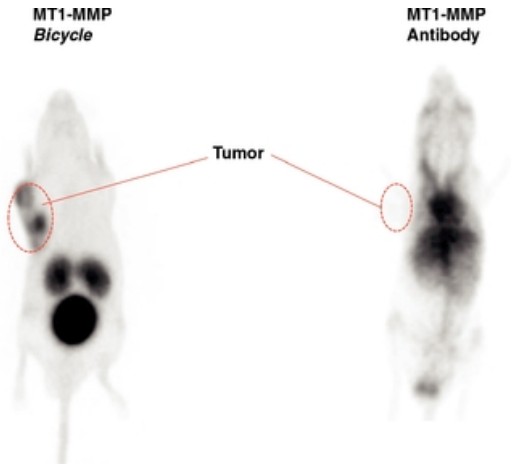
Properties of Bicycle Toxin Conjugates

We believe the properties of our BTCs may address the challenges associated with ADCs and therefore that our approach has the potential to offer substantial benefits, including:

- ***Extensive and rapid tumor penetration.*** *Bicycles* have been observed in our preclinical studies to penetrate tumors more rapidly and exhibited increased penetration to poorly perfused regions of the tumor when compared to a comparator antibody.
- ***Retention in tumors.*** In preclinical studies a tumor antigen targeting *Bicycle* was observed to be retained in the tumor for 24 hours after dosing.
- ***Short systemic half-life and renal elimination***. *Bicycles* have been observed in clinical and preclinical studies to have a short systemic half-life of approximately 20-30 minutes. Due to their small size, *Bicycles* are able to exit the tissue rapidly and are excreted through the kidneys rather than the liver, which we expect will support a favorable toxicity profile.
- ***No requirement for internalization.*** Unlike ADCs, which require cellular internalization for activity, BTCs do not require internalization into the cell, and therefore potentially can target a wider range of tumor antigens.
- ***Access to non-expressing tumor cells.*** The toxin in our BTCs is liberated in the extracellular space, enabling cell-killing adjacent cells that do not express the specific target through a toxin bystander effect. In our preclinical studies, we observed activity for BTCs even in tumors that were heterogeneous for target expression.
- ***Larger toxin payload.*** Despite the small size of *Bicycles*, they are able to carry a larger dose of toxin per unit mass than a comparator ADC. Therefore, we believe that *Bicycles* can deliver a higher concentration of the linked toxin to increase the probability of tumor killing.
- ***Manufacturing.*** The fully synthetic process by which *Bicycles* are manufactured facilitates ease and consistency of manufacturing and improved formulation compared to ADCs.

In order to compare the ability of a *Bicycle* conjugate and an antibody conjugate to penetrate a tumor, using positron emission tomography, or PET, imaging, we compared a radiolabeled *Bicycle* to an antibody directed at the same target in a preclinical rodent study. As shown in the figure below, we observed that 15% to 20% of the injected dose per gram was detected after administration of the *Bicycle* in the tumor at 40 to 60 minutes, with no antibody detectable in the tumor during this time. We also observed accumulation of the balance of the *Bicycles* in the bladder and kidneys, indicating rapid renal excretion. In contrast, the antibody was detected in the vasculature.

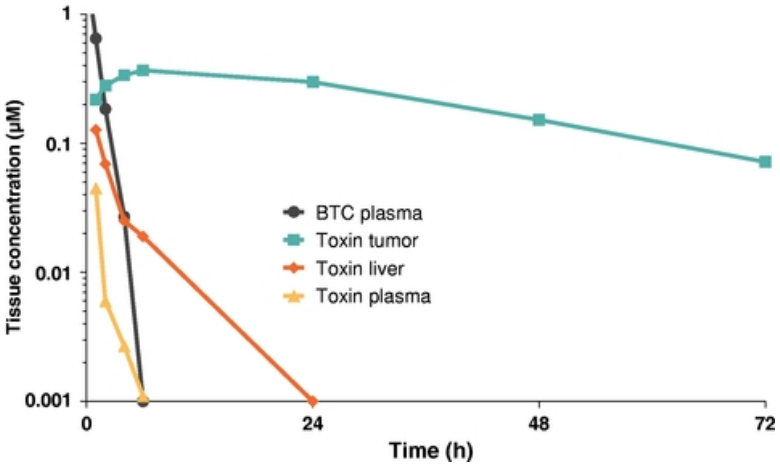
PET Imaging Revealing Payload Delivery in a Mouse Model



In addition, in a preclinical rodent study using photoacoustic imaging, we observed that *Bicycles* were retained in the tumor for 24 hours and at levels substantially in excess of those observed with a comparator antibody.

The figure below summarizes the results of a preclinical rodent xenograft model that investigated payload concentrations over time in different organ systems after administration of a BTC. In this model, we observed the toxin payload was retained in the target-expressing tumor over time, but was rapidly eliminated from other tissues.

Payload Concentrations Over Time in Different Organ Systems After Administration of a BTC

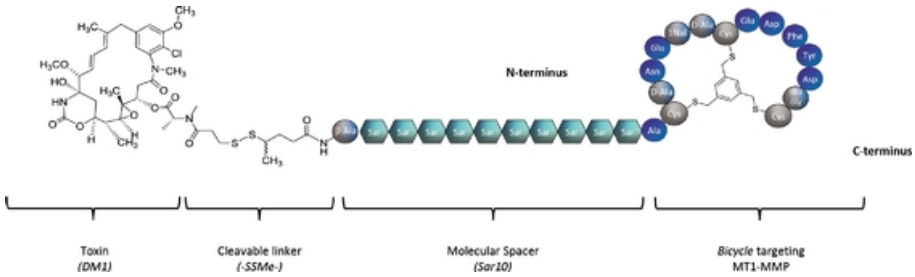


We believe these data demonstrate the potential of BTCs to have long-term sustained activity and to limit the toxicity that is associated with ADCs.

BT1718

Our lead product candidate, BT1718, is a BTC that we are developing for oncology indications. The molecule is comprised of our MT1-MMP targeting *Bicycle*, a hindered disulphide cleavable linker and a cytotoxin DM1 payload.

Schematic of BT1718



MT1-MMP is a matrix metalloprotease involved in tissue remodeling and is generally expressed at relatively low levels in normal adult tissues. MT1-MMP has an established role in cell invasion and metastasis, and we believe that MT1-MMP is an attractive target for cytotoxin delivery due to its high level of expression on stromal and tumor cell subsets in various cancers, including breast, lung, sarcoma, gastric, head and neck, ovarian and pancreatic cancers. We estimate that MT1-MMP is expressed in approximately 76% to 96% of the ovarian, bladder, endometrial and triple negative breast cancer samples we have tested, depending on cancer type.

In our preclinical studies, we observed that BT1718 was associated with the greatest anti-tumor effect when membrane staining for MT1-MMP was high. Tumors with lower levels of expression of MT1-MMP were observed to have reduced levels of response to BT1718. We are collaborating with leading cancer researchers to determine MT1-MMP expression levels across a panel of tumor types, which will help inform patient selection for further clinical development. One of the goals of our clinical trials is to better understand the relationship between the level of target expression and activity of BT1718.

We are not aware of any other cytotoxin conjugates in development that target MT1-MMP.

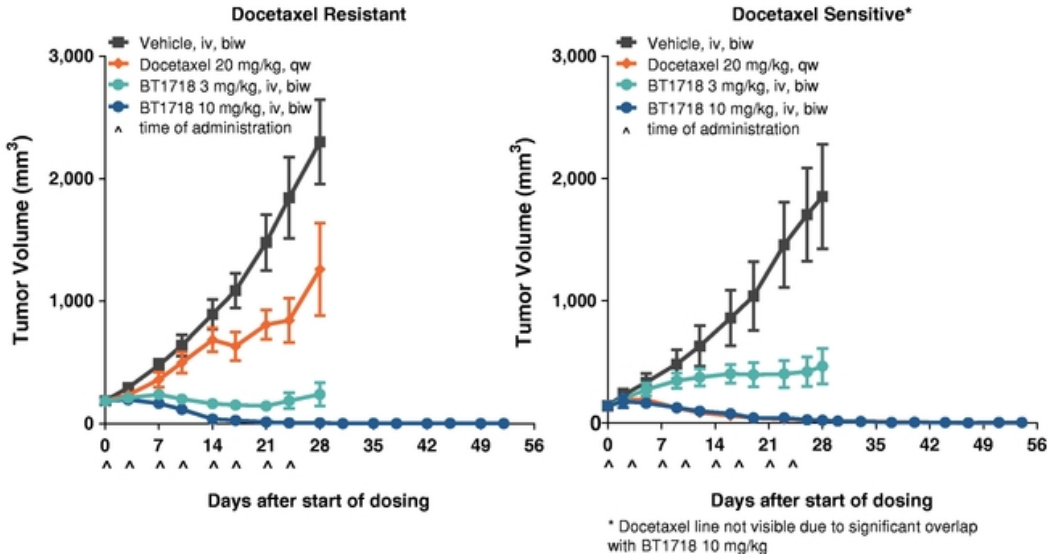
Preclinical Experience

BT1718 has been dosed in multiple species, including rodents and non-human primates. In *in vivo* preclinical studies, we observed dose-dependent anti-tumor activity following administration of BT1718 with disease stabilization or regression in multiple xenograft models across tumor types including lung, breast, gastric, head and neck, fibrosarcoma and colorectal. These models utilized an endpoint of tumor volume, as calculated from standard caliper measurements of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT1718. A 3 mg/kg dose of BT1718 administered biweekly was observed to be associated with stable disease or tumor regression in several models. Further, the highest dose of BT1718 tested, 10 mg/kg administered biweekly, was observed to be associated with complete regressions in the majority of MT1-MMP-expressing xenograft tumors tested, with most mice remaining tumor-free for up to 60 days after the last dose, following which the study ended.

BT1718 was also evaluated in two lung adenocarcinoma patient-derived xenograft models, one sensitive to, and one resistant to, docetaxel, a marketed chemotherapy medication. In both cases, we observed that BT1718 treatment at a dose of 3 mg/kg administered twice per week was

associated with a significant reduction of tumor volume. Further, a 10 mg/kg dose of BT1718 administered twice per week was associated with complete and durable regression of tumors. In the docetaxel resistant model, we observed that BT1718 at both doses tested was associated with statistically significant responses, whereas docetaxel, at its maximum-tolerated dose, was not. To determine whether data is statistically significant, we use a "p-value," which represents the probability that random chance could explain the results. Generally, a p-value less than 0.05 is considered statistically significant, and may be supportive of a finding of efficacy by regulatory authorities. However, regulatory authorities, including the FDA and EMA, do not rely on strict statistical significance thresholds as criteria for marketing approval and maintain the flexibility to evaluate the overall risks and benefits of a treatment. If not otherwise specified, we used a conventional 5% or lower p-value ($p < 0.05$) to define statistical significance for the clinical trials and studies and data presented in this prospectus. These models utilized an endpoint of tumor volume, as calculated from standard caliper measurments of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT1718.

Effect of BT1718 on Tumor Volume in Preclinical Patient-Derived Xenograft Models



We also evaluated the PK profile of BT1718 in several *in vivo* preclinical studies. In these studies, we observed that BT1718 exhibited a consistent PK profile across species, as well as behavior consistent with our expectations of a BTC, including a volume of distribution approximately equal to extracellular fluid, rapid clearance and a short systemic half-life. These studies utilized an endpoint of tumor volume, as calculated from standard caliper measurments of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT1718.

Pharmacokinetic Profile of BT1718

Preclinical Species	Clearance (CLp; mL/min/kg)	Volume of distribution (Vss; L/kg)	Terminal half-life ($t^1/2$; hours)
Mouse	8.4	0.20	0.3
Rat	9.4	0.29	0.6
Non-Human Primate	8.0	0.20	0.4

Clinical Development

Ongoing Phase I/IIa First in Human Clinical Trial

BT1718 is being investigated in an ongoing Phase I/IIa open label dose escalation and expansion clinical trial sponsored by CRUK. Up to 40 patients with advanced solid tumors are being enrolled in the ongoing Phase I part of this trial at three sites in the United Kingdom in which two dosing regimens are being evaluated.

The Phase I part of this clinical trial is evaluating the safety and tolerability of BT1718 and establishing a recommended Phase IIa dose using two dosing schedules, twice per week and once per week, each as one-hour intravenous infusions. The PK profile, preliminary efficacy and potential predictive pharmacodynamics, or PD, biomarkers of BT1718 activity are also being investigated. The endpoint for the Phase I part of this clinical trial is establishment of the recommended dose for the Phase II evaluation. This part of the trial is designed as a dose escalation trial without pre-selection for MT1-MMP status. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019.

Once a recommended Phase IIa dose has been determined, the Phase IIa part of the trial is expected to commence. In this part of the trial, patients with high expression of MT1-MMP will be prospectively selected, and we expect to determine tumor types for investigation in this part of the trial in conjunction with CRUK. Due to their high expression of MT1-MMP, tumor types of interest currently include breast, lung, sarcoma, gastric, head and neck, ovarian and pancreatic cancers.

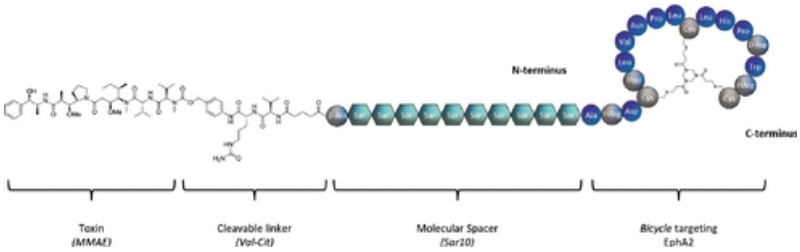
The Phase IIa part will be conducted at up to six sites in the United Kingdom. We plan to initially investigate the optimal dosing frequency in two cohorts, with up to 14 patients in each, in which BT1718 will be administered either once or twice weekly. Once the optimal dosing frequency is established, this schedule will be used to dose patients to investigate two different tumor types in two additional cohorts, with up to 16 patients per cohort. The endpoints for the Phase IIa part of this clinical trial are safety and preliminary efficacy in patients with two cancers expressing MT1-MMP.

The Phase I part of the clinical trial commenced in early 2018 and this part of the trial remains ongoing. As of March 1, 2019, six cohorts of patients have been dosed and evaluated on the twice-weekly schedule, with doses ranging from 0.6 mg/m^2 to 9.6 mg/m^2. Two cohorts in the once-weekly schedule have been completed, at doses of 9.6 mg/m2 and 15 mg/m2, and patients are currently being enrolled for a 20 mg/m2 dose cohort. We observed that the once-weekly dose of 15 mg/m2 was associated with stable disease observed in two out of three patients. We are expecting to establish the recommended dose and commence the Phase II part of the clinical trial in May 2019.

BT5528

BT5528 is a BTC designed to target EphA2. The molecule is comprised of our EphA2 targeting *Bicycle*, a valine-citrulline, or val-cit, cleavable linker and a cytotoxin MMAE payload.

Schematic of BT5528



EphA2 is a member of the Ephrin superfamily of receptor tyrosine kinases regulating cell migration, adhesion, proliferation and differentiation. EphA2 is expressed at relatively low levels in normal adult tissues, but is overexpressed in numerous difficult to treat tumors including lung, breast, bladder, gastric, ovarian, endometrial, cervical, melanoma and glioma. In both cell-derived and patient-derived preclinical models, we observed target-dependent anti-tumor activity signals following administration of our EphA2 toxin conjugates.

EphA2 has previously been pursued by other companies utilizing ADCs. However, significant safety concerns, including bleeding events and liver toxicity, were observed in preclinical studies and early clinical development, which resulted in the discontinuation of development. For example, in a Phase I clinical trial of MEDI-547, an EphA2-targeting ADC, an increase in the liver enzyme ALT and AST was observed in half of the dosed patients and bleeding events were observed in five out of six patients, in each case within two to eight days following a single dose. The bleeding events observed in humans from the clinical trial were consistent with findings from the preclinical studies in other species, including primates.

We believe EphA2 is an attractive target for our BTCs due to the potential of *Bicycles* to overcome the safety concerns observed with ADCs. In our preclinical PK and toxicokinetic studies, we observed a short half-life and volume of distribution similar to BT1718. We observed that the accumulation of MMAE in the tumor tissue led to mitotic arrest of tumor cells and tumor regression was evident within days of administration. Due to the shorter half-life, improved penetration into solid tumors and kidney elimination, we believe that BT5528 could address the challenges of ADCs. We plan to screen for specific tumor types that we may investigate with BT5528 using an approach similar to the one we are adopting for BT1718.

Our IND-enabling preclinical studies for BT5528 are currently ongoing.

Preclinical Experience

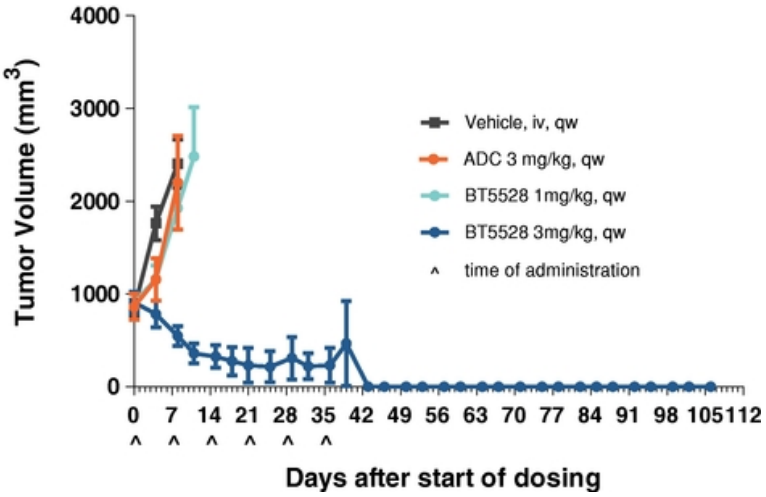
BT5528 has been evaluated in preclinical studies in multiple species, including rodents and non-human primates. In our preclinical studies, BT5528 was not observed to have a significant effect on clotting parameters and did not exhibit abnormal liver function at tolerated doses. We also observed no bleeding events in primates at toxin equivalent doses over 100-fold higher than the clinical dose of MEDI-547 used in patients. These studies utilized an endpoint of tumor volume, as calculated from standard caliper measurements of subcutaneous tumor, measured through course of experiment and at experiment end to evaluate the activity of BT5528.

In *in vivo* preclinical studies, we observed dose-dependent anti-tumor activity following administration of BT5528 with disease stabilization or regression in multiple xenograft models representing tumor types including lung, breast, gastric, fibrosarcoma, prostate, ovarian and oesophageal, with activity correlating with EphA2 expression. We observed that a dose of 1 mg/kg of BT5528 administered weekly was associated with stable disease or tumor regression in several models. Complete regressions were observed in the majority of EphA2-expressing xenograft tumors

in mice administered 2 mg/kg or 3 mg/kg of BT5528 weekly, with most mice remaining tumor-free for more than 60 days after dose cessation, following which the study was ended. These studies utilized an endpoint of tumor volume, as calculated from standard caliper measurements of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT5528.

As shown in the figure below, we observed that BT5528 displayed superior activity to an EphA2 targeting ADC in a mouse patient-derived xenograft model. In this model, the tumors were large (approximately 1,000 mm^3) at the commencement of dosing. The tumor was derived from a docetaxel resistant non-small cell lung cancer from a 74 year-old male smoker with moderate EphA2 expression. BT5528 was dosed once weekly.

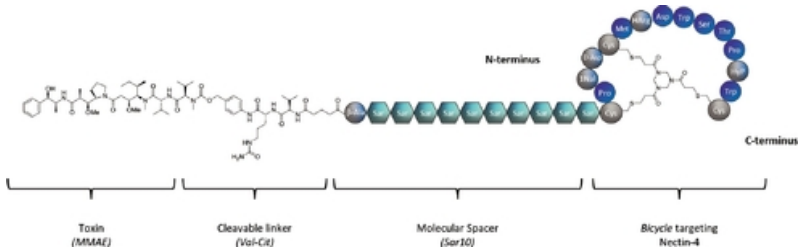
Effect of BT5528 on Tumor Volume in a Preclinical Patient-Derived Xenograft Model



BT8009

BT8009 is a BTC designed to target Nectin-4. The molecule is comprised of our Nectin-4 targeting *Bicycle*, a val-cit cleavable linker, and a cytotoxin MMAE payload.

Schematic of BT8009



Nectin-4 (also known as PVRL4) is a cell adhesion molecule from the Nectin and Nectin-like family, members of which are integral to the formation of the homotypic and heterotypic cell junctions. Nectin-4 has been shown to be overexpressed in tumor cells and is believed to play a role in tumor cell growth and proliferation. High in normal embryonic and fetal tissue, Nectin-4

declines in adulthood, showing a limited distribution in healthy tissues. However, Nectin-4 is expressed on tumor cells in numerous cancer types including bladder, breast, gastric, lung and ovarian. In addition, we believe the favorable characteristics of BTC-targeted therapies may address some of the challenges in treating pancreatic cancer.

We have observed that BT8009 efficiently delivered MMAE to the tumor and had a broad spectrum of activity, including decreasing Nectin-4 expression.

We are aware of one Nectin-4 ADC program in development, which is being jointly conducted by Seattle Genetics and Astellas, and is currently in Phase II clinical development. We plan to screen for specific tumor types that we may investigate with BT8009 using an approach similar to the one that we are adopting for BT1718 and BT5528.

Our IND-enabling preclinical studies for BT8009 are currently ongoing.

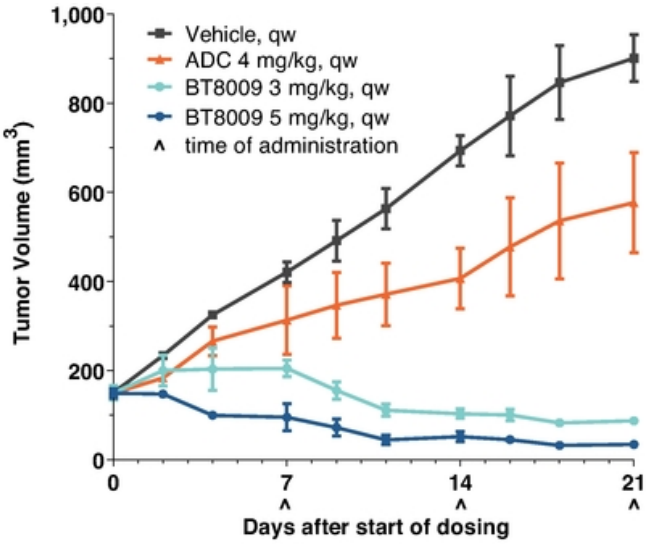
Preclinical Experience

In *in vivo* preclinical studies, we observed that BT8009 was associated with dose-dependent anti-tumor activity with disease stabilization or regression in multiple xenograft models representing tumor types including lung, breast, and esophageal cancers. We observed that BT8009 activity was correlated with either Nectin-4 protein or mRNA expression. We observed that a dose of 3 mg/kg of BT8009 administered weekly was associated with complete regression in multiple models. In two models, there was no observed tumor regrowth at 59 days after the last administration, following which the study was ended. These studies utilized an endpoint of tumor volume, as calculated from standard caliper measurements of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT8009.

In head to head preclinical studies comparing BT8009 to enfortumab vedotin, an ADC in clinical development that we replicated, BT8009 displayed comparable or superior activity to the ADC in three cell-derived xenograft studies and five patient-derived xenograft models. These studies utilized an endpoint of tumor volume, as calculated from standard caliper measurements of subcutaneous tumor and measured through the course of the preclinical study and at the end of the preclinical study to evaluate the activity of BT8009.

The figure below illustrates results from a preclinical non-small cell lung cancer cell-derived xenograft. In that model, we observed that BT8009 showed superior activity at early timepoints compared to high dose administrations of enfortumab vedotin, docetaxel and doxorubucin. We also observed that administration of BT8009 was associated with complete regression of the tumor.

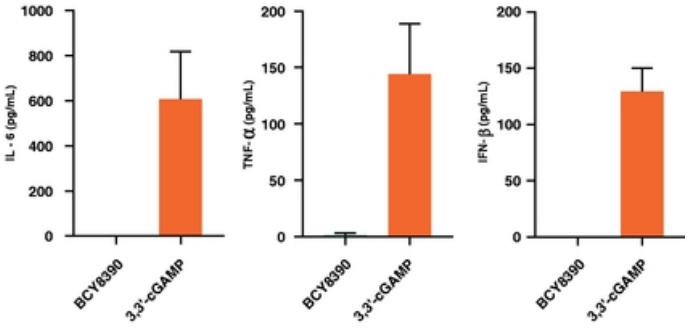
Effect of BT8009 on Tumor Volume in a Preclinical Non-Small Cell Lung Cancer-Derived Xenograft Model



Bicycle Targeted Innate Immune Activators

Local activation of the innate immune system within tumors is a promising area for cancer drug discovery. Many of the current clinical programs require direct injection of molecules activating the innate immune system into tumors to avoid excessive systemic activation of the immune system and associated toxicity. Based on our experience with BTCs, we believe that *Bicycles* can systemically deliver activators of the innate immune system to tumors without activating the immune system in normal tissues. We believe that this approach has the potential to avoid the need for direct tumor injection and to allow inaccessible tumors to be reached, while enabling rapid systemic elimination of excess payloads in an inactive form.

We are currently advancing this approach through the development of systemically-delivered *Bicycle* STING agonists, targeted to both novel and validated tumor targets. As shown in the figure below, in a preclinical study, a *Bicycle* conjugated to a cyclic dinucleotide STING agonist (BCY8390) delivered systemically in mice was observed to result in significantly lower serum inflammatory cytokine release, as measured by levels of IL-6, TNF-a and IFN-b as compared to the unconjugated STING agonist (3,3'-cGAMP). We believe these results support the potential for *Bicycle* innate immune activators to be systemically administered.



Bicycle T-Cell Modulators

We are developing cytotoxic T-cell activators, designed to trigger an immune response to tumors. We have identified potent *Bicycle* activators of CD137, a tumor necrosis factor receptor, or TNFR, family member and we believe we are currently the only company that has fully chemically synthetic CD137 agonists. We believe that *Bicycles* represent a differentiated approach to target CD137 that may confer several advantages over existing modalities due to the multivalency and PK characteristics of *Bicycles*. Our *Bicycle* T-cell modulators are designed to circumvent the limitations of antibody and biologic therapies, such as liver toxicity and limited efficacy, and to better enable combination therapy.

We are also exploring CD137 in a bi-specific format linked to *Bicycles* that bind tumor antigens, inhibit checkpoint proteins or otherwise activate the immune system. We believe we are currently the only company that has fully chemically synthetic bi-specific CD137 agonist.

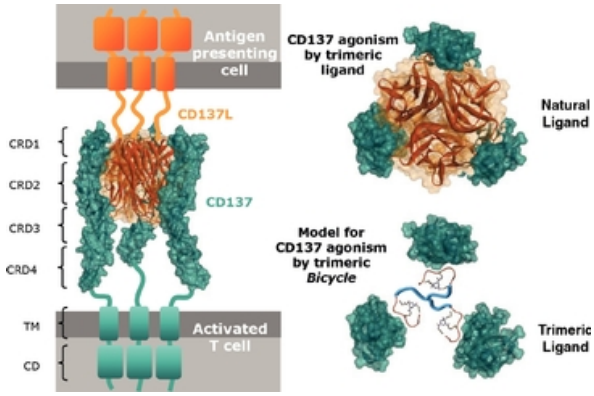
Approaches that activate cytotoxic T-cells, a type of cell used in a body's immune response, have been observed to improve outcomes in cancer. However, prolonged immune activation can be toxic and lead to T-cell exhaustion, which is a challenge amplified by the long half-life of antibodies and biologics that are often used in these treatment approaches. We believe the differentiated properties of *Bicycles* may allow us to develop molecules with a pharmacodynamically distinct and improved profile over existing therapies.

We are aware of anti-CD137 antibodies undergoing clinical testing, including urelumab being developed by Bristol-Myers Squibb, which produced single agent responses but also severe liver toxicity, and utomilumab being developed by Pfizer, which exhibited minimal clinical activity with less toxicity.

Properties of Bicycle T-Cell Modulators

In order to activate the CD137 receptor, cross-linking of a trimeric receptor is required. As a result, we are developing trimeric and tetrameric molecules that cross-link the receptor into an active form as shown in the image below.

Schematic of a Proposed Trimeric CD137 Bicycle Agonist



These *Bicycle* multimers feature the following favorable pharmacological characteristics for immuno-oncology therapeutics. We believe these characteristics have the potential to overcome the limitations of antibodies and fusion proteins.

- ***Simplicity and small size.*** Our trimeric and tetrameric *Bicycles* are chemically synthesized and are very small in comparison to other molecules targeting the CD137 receptor. For example, the approximate molecular weight of urelumab is 146 kDa. In contrast, the molecular weight of our tri- and tetrameric *Bicycles* are in the range of approximately 9 kDa to 15 kDa, which is designed to facilitate the rapid penetration of the therapeutic into tumor tissue.

- ***Tunable PK.*** *Bicycles* are amenable to chemical modifications that allow the PK of the multimers to be fine-tuned. We believe this enables the development of molecules with the optimal balance of prolonged CD137 agonism, but with rapid enough elimination from systemic circulation to avoid the undesired toxicities of CD137, as has been observed with urelumab. In addition, this tunable half-life is expected to enable different sequences of therapeutics to be evaluated in the clinic potentially reducing the risk of overlapping toxicities.

- ***Renal elimination.*** Rapid renal elimination may avoid liver toxicity observed with other CD137 agonists in development.

- ***Modular.*** The modular nature of *Bicycles* permits the presentation of CD137 binders in various orientations allowing us to design molecules with a range of activities. We believe that we can select the optimal activity profile to avoid the weak efficacy seen with the utomilumab molecule or the overstimulation of CD137 by urelumab that resulted in systemic toxicity.

Comparison of the Features of our Bicycle T-Cell Modulators to Biological T-Cell Modulators

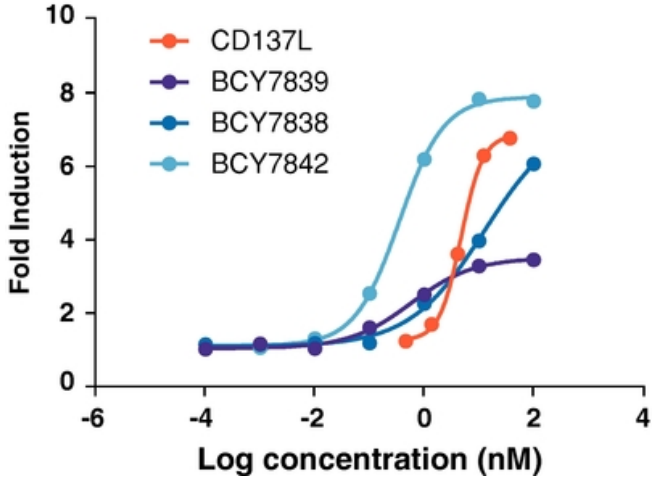
Limitations of multivalent and bi-specific biologics	*Bicycles* potentially overcome these limitations
Pharmacology	
• Very large molecules: (~150-350 kDa) for multimeric; ~40-200 kDa for bi-specific • Limits on presentation of binding domain to the target results in fixed orientation • Difficult to make a molecule bind to more than two targets • High chance for immunogenicity as the size and complexity increase	• Very small: (~9-15 kDa) for multimeric; ~3.5-5 kDa for bi-specific • Linkage through various sites of attachment allows presentation of binder in various orientations • Easy to make tri- and tetrameric molecules • Immunogenicity unlikely—multimeric molecules are still smaller than smallest monovalent antibody
Manufacturing	

• Low yield (even for research scale ~10 mg)
  • Requires another optimization of the molecule even if the parent molecules are fully optimized
• Increase in heterogeneity
  • Requires more controls and stringent potency assays
	• Simple chemical synthesis
	• Chemically defined, new chemical entity

Preclinical Experience

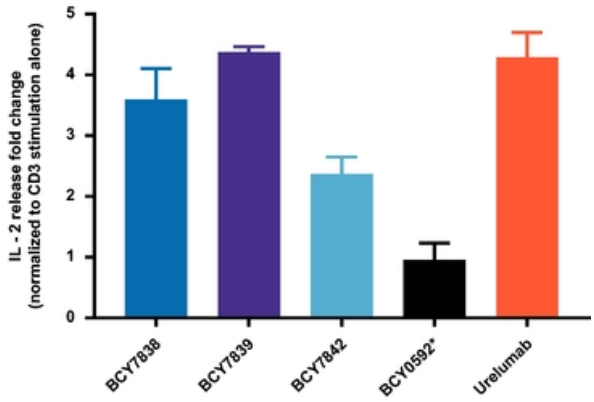
We observed that simple multivalent *Bicycle* CD137 agonists (BCY7839, BCY7838 and BCY7842) displayed potent activity in preclinical cell-based assays. As shown in the figure below, several *Bicycle* CD137 agonists displayed comparable or higher fold induction compared to the natural ligand (CD137L) in an engineered reporter cell assay.

Activity of Bicycle CD137 Agonist Compared to the Natural Ligand



As shown in the figure below, we also observed *Bicycles* stimulated the release of the cytokine IL-2, a marker of immune response, from primary human T-cells to a comparable degree as urelumab, which we believe provides meaningful evidence of activity.

Activity of CD137 Bicycles on Immune Response



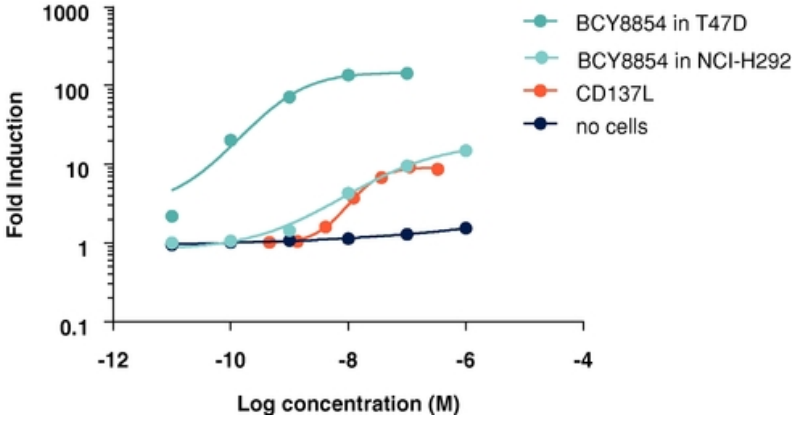
* Negative control non-agonist *Bicycle*

In additional *in vivo* studies, we observed that CD137 *Bicycles* increased the cytotoxic T-cell infiltration in tumor tissue. The *Bicycles* did not significantly change the expression of CD137 on tumoral T-cells while urelumab led to a decrease in the target cell population. We believe this increased cytotoxic T-cell infiltration correlates with the anti-tumor activity of the *Bicycle* CD137 agonists.

Bi-Specific Approach

In preclinical studies, we have also linked CD137 binding *Bicycles* to tumor antigen targeting *Bicycles*. We constructed multiple bi-specific molecules and observed that these bi-specific molecules agonize the CD137 receptor only in the presence of cells that express the appropriate tumor antigen.

As shown in the figure below, we observed that a bi-specific Nectin-4-CD137 agonist (BCY8854) demonstrated activity only when tumor cells presenting Nectin-4 were present, with the fold induction dependent on the degree of Nectin-4 expression. With a high expressing cell line (T47D), the activation of CD137 by the bi-specific molecule was observed to be significantly higher than the natural ligand (CD137L) and when a low expressing cell line (NCI-H292) was tested, activation was lower.



We believe that our ability to rapidly generate and test bi-specific molecules and their simple molecular format may form the basis of additional programs in the future. In addition to the immune cell and tumor targets that we have already investigated, we are also planning to screen, or have started to screen, *Bicycles* that target FcgRIIIA and NKp46 as well as DLL3, GCC and Trop2.

Beyond Oncology

We have entered into several collaborations outside of our internal focus in oncology to leverage the broad applicability of *Bicycles*. Our strategic collaborations are based on the ability of *Bicycles* to address a wide variety of targets and we are working with collaborators with deep therapeutic expertise outside of oncology to enable us to more efficiently develop novel medicines for patients.

AstraZeneca. In November 2016, we entered into a research collaboration agreement with AstraZeneca AB, or AstraZeneca, with a focus on targets within respiratory, cardiovascular and metabolic disease.

Bioverativ. In August 2017, we entered into a collaboration agreement with Bioverativ, Inc., or Bioverativ, focused on hemophilia and sickle cell disease.

Oxurion. In August 2013, we entered into a research collaboration and license agreement with Oxurion NV (formerly ThromboGenics NV), or Oxurion, focused on ophthalmology. The lead molecule of the partnership is THR-149, a novel plasma kallikrein inhibitor, for the treatment of diabetic macular edema. A Phase I clinical trial of THR-149 is currently ongoing. The Phase I clinical trial, which is being conducted by Oxurion, is an open-label, multi-center, dose escalation trial to evaluate the safety of a single intravitreal injection of THR-149 for the treatment of diabetic macular edema, or DME. The study will enroll up to 12 patients to investigate three dose levels of THR-149 with the primary endpoint being the incidence of dose-limiting toxicities up to the Day 14 visit.

Our Collaborations

Cancer Research UK

In December 2016, we entered into a clinical trial and license agreement with the Cancer Research Technology Limited and CRUK. Pursuant to the agreement, as amended in March 2017 and June 2018, CRUK's Centre for Drug Development will sponsor and fund a Phase I/IIa clinical trial of our lead product candidate, BT1718, in patients with advanced solid tumors.

CRUK is responsible for designing, preparing, carrying out and sponsoring the clinical trial at its cost. We are responsible for supplying agreed quantities of GMP materials for the study, the supply of which has been completed. In the event that additional quantities are needed, we will provide CRUK with all reasonable assistance to complete the arrangements necessary for the generation and supply of such additional GMP materials but CRUK will be responsible for supplying and paying for such additional quantities of GMP materials.

We granted to CRUK a license to our intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial. We retain the right to continue the development of BT1718 during the clinical trial. Upon the completion of the Phase I/IIa clinical study, we have the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and we decide to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, we will assign or grant to Cancer Research Technology Limited an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case we will receive tiered royalties of 70% to 90% of the net revenue depending on the stage of development when the license is granted) less certain

costs, as defined by the agreement. The CRUK agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a single digit percentage on net sales of products developed.

The CRUK agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity generates its revenue from the sale of tobacco products). CRUK may terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met, in which case, if the study is terminated by CRUK prior to the completion of the Phase Ia dose escalation part of the study for such reasons or if CRUK refuses release of any additional quantities of GMP materials or if the parties cannot agree upon a plan to supply the additional quantities of GMP materials, we will be obligated to refund 50% of the costs and expenses incurred or committed by CRUK to perform the clinical trial. If the study is terminated by CRUK for an insolvency event, a material breach by us, or if we are acquired by an entity that generates its revenue from the sale of tobacco products, we will reimburse CRUK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case where we are acquired by an entity that generates its revenue from the sale of tobacco products, CRUK will not be obliged to grant a license to us in respect of the results of the clinical trial and we will assign or grant to Cancer Research Technology Limited an exclusive license to develop and commercialize the product without Cancer Research Technology Limited being required to make any payment to us.

Our Other Collaborators

Bioverativ

In August 2017, we entered into a research collaboration agreement with Bioverativ Inc. (acquired by Sanofi), or Bioverativ, in the field of non-malignant hematology. Under the Bioverativ collaboration agreement, we are active in two disease areas: sickle cell disease and hemophilia with an unspecified option which was to be determined. We use our Bicycle screening platform to perform research and development services for the programs and Bioverativ can select, under one or more license collaborations, products for each program.

Under the Bioverativ agreement, we are obligated to perform research activities on the initial two named collaboration programs, under mutually agreed upon research plans. The research and development services for each program (including for clarity the third, optional program) consist of two stages. The first is an initial stage of screening and optimization to identify high affinity Bicycle binders and optimization of early drug like properties and is led by Bicycle. If lead compounds are identified, the second stage includes chemical optimization and testing of these compounds in disease relevant biological assays, conducted jointly by us and Bioverativ, in preparation for lead collaboration product nomination. Each collaboration program has a maximum initial period of three years, unless a program is abandoned or extended for up to one year by Bioverativ. Bioverativ may, at its sole discretion, approve any compound to be progressed into drug development and upon the selection of a collaboration product for each collaboration program, must pay a $5.0 million payment (or $7.0 million if such product includes certain additional enabling intellectual property developed by us in the course of the collaboration) in order to obtain worldwide development and exploitation rights for that collaboration product. Bioverativ will lead preclinical and clinical development, as well as subsequent marketing and commercialization.

Under the terms of the Bioverativ collaboration agreement, we granted to Bioverativ, for each collaboration program, a non-exclusive, sublicensable (through multiple tiers), worldwide license under certain of our intellectual property to conduct the activities assigned to Bioverativ in the applicable research plan for the duration of the applicable research term, but for no other purpose

and we have agreed not to, directly or indirectly, by ourselves or in collaboration with others, screen the Bicycle platform for compounds that bind to a target that is the subject of the Bioverativ collaboration or otherwise perform any work related to or disclose such a target until the earliest of the filing acceptance for the first regulatory approval in a major market with respect to the collaboration program, termination or abandonment of such collaboration program or the seventh anniversary of the first date of the research term for the collaboration program.

Under the terms of the Bioverativ collaboration agreement, we received a $10.0 million up front cash payment. Additionally, prior to the initiation of the research plan for each of the first two collaboration programs, Bioverativ made a non-refundable payment of $1.4 million for the sickle cell program and $2.8 million for the hemophilia program as payment for our services during the respective Bicycle Research Term for each program. During the Joint Research Term, Bioverativ is obligated to fund our services at a minimum of $0.7 million and fund certain external costs incurred by us of up to $1.0 million per year. In addition, Bioverativ is required to make certain other milestone payments to us upon the achievement of specified development, regulatory and commercial milestones. More specifically, for each collaboration program, we are eligible to receive, inclusive of the $5.0 to $7.0 million milestone payment described above, between $47.5 million and $67.0 million in development milestone payments. We are also eligible to receive up to $104.0 million in regulatory milestone payments for each collaboration product. In addition, we are eligible to receive up to $55.0 million in commercial milestone payments, on a collaboration program by collaboration program basis. In addition, to the extent any of the collaboration products covered by the licenses granted to Bioverativ are commercialized, we would be entitled to receive tiered royalty payments of mid-single digits to low-teen digits based on a percentage of net sales. Royalty payments are subject to certain reductions, including for instances where Bioverativ faces generic competition in certain countries.

Either party may terminate the agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. Either party may terminate the agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. In the event of a breach, the collaboration agreement may be terminated by either party in its entirety, or, if the breach is limited to a country or countries, with respect to the country or countries to which the breach applies. Bioverativ may terminate the agreement, entirely or on a program by program, licensed product by licensed product or country by country basis, for convenience.

Bioverativ was also provided with an option to obtain screening services on the additional program upon making an option fee payment in addition to a non-refundable payment as payment for our services during the respective Bicycle Research Term. The option expired unexercised in November 2018.

AstraZeneca

In November 2016, we entered into a research collaboration agreement with AstraZeneca AB. The collaboration is focused on the research and development of Bicycle peptides that bind to an undisclosed number of biological targets for the treatment of respiratory, cardiovascular and metabolic diseases. After discovery and initial optimization of such Bicycle peptides, AstraZeneca will be responsible for all research and development, including lead optimization and drug candidate selection. AstraZeneca receives development, commercialization and manufacturing license rights with regard to any selected drug candidate(s).

Under the AstraZeneca collaboration agreement, Bicycle is obligated to use commercially reasonable efforts to perform research activities, under mutually agreed upon research plans. The research plans includes two discrete parts, on a research program by research program basis:

(i) the Bicycle Research Term, which is focused on the generation of Bicycle peptide libraries using our peptide drug discovery platform, to be screened against selected biological targets, with the goal of identifying compounds that meet agreed criteria set by the parties, and (ii) the AZ Research Term, during which AstraZeneca may continue research activities with the goal of identifying compounds that satisfy the relevant pharmacological and pharmaceutical criteria for clinical testing. AstraZeneca may, at its sole discretion, approve any compound to be progressed into drug development and, upon the selection of each drug candidate, AstraZeneca is to pay a milestone of $8 million.

Each research program is to continue for an initial period of three years, referred to as the research term, including one year for the Bicycle Research Term and two for the AZ Research Term. AstraZeneca may extend the research term for each research program by twelve months (or fifteen months, if needed to complete certain toxicology studies). The research term for a specific program can be shorter if it is ceased due to a screening failure, a futility determination, or abandonment by AstraZeneca. AstraZeneca has certain substitution rights should a screening failure or futility determination be reached. but is obligated to fund these additional efforts related to substitution.

Under the terms of the AstraZeneca collaboration agreement, we granted to AstraZeneca the right and license (with the right to sublicense) to certain background, foreground and platform intellectual property, for the duration of the agreement, to the extent reasonably necessary or useful for AstraZeneca to conduct the activities that are assigned to it in the applicable research plan or that are reasonably necessary or useful or the purpose of researching, developing or exploiting resulting compounds and products. We have agreed not to, directly or indirectly, by ourselves or in collaboration with others, screen the Bicycle platform for compounds that bind to a target that is the subject of the AstraZeneca collaboration or otherwise perform any work related to or disclose such a target until the earlier of the tenth anniversary of the date on which such target was selected or the dosing of the first patient in the first Phase III clinical trial for a product that modulates such collaboration target.

The activities under the AstraZeneca collaboration agreement are governed by a joint steering committee and joint project team each formed by an equal number of representatives from our company and AstraZeneca. The joint steering committee oversees and reviews each research program and the activities of the joint program team. Among other responsibilities, the joint steering committee monitors the research progress and ensures open and frequent exchange between the parties regarding research program activities.

AstraZeneca receives development and commercialization licenses associated with each designated drug candidate, and owes a milestone fee of $8 million for the first drug candidate selected from each research program. In addition, AstraZeneca is required to make certain other milestone payments to us upon the achievement of specified development, regulatory and commercial milestones. More specifically, for each research program, we are eligible to receive, in addition to the milestone fee described above, up to $162 million development, regulatory and commercial milestones on a research program by research program basis. In addition, to the extent any of the drug candidates covered by the licenses conveyed to AstraZeneca are commercialized, we would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Royalty payments are subject to certain reductions, including in certain countries where AstraZeneca faces generic competition. In total, we could receive more than $1 billion in milestone payments and royalties under the collaboration agreement.

Either party may terminate the AstraZeneca collaboration agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. In the event of a breach, the collaboration agreement may be terminated in its entirety, or, if the breach is limited to a country or countries, with respect to the country or countries to which the breach applies. Either party may

terminate the AstraZeneca collaboration agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. AstraZeneca may terminate the AstraZeneca collaboration agreement, entirely or on a licensed product by licensed product or country by country basis, for convenience.

Under the AstraZeneca collaboration agreement, AstraZeneca was granted an option to nominate additional targets on the same contractual terms as the initial targets. In May 2018, AstraZeneca made an irrevocable election to exercise the additional target option, giving AstraZeneca the option to designate additional targets, for $5.0 million to be paid by AstraZeneca to us no later than January 31, 2019.

Oxurion (formerly ThromboGenics)

In August 2013, we entered into a research collaboration and license agreement with Oxurion NV (formerly ThromboGenics NV), or Oxurion. Under the Oxurion collaboration agreement, we are responsible for identifying Bicycle peptides related to the collaboration target, human plasma kallikrein, for use in various ophthalmic indications. Oxurion is responsible for further development and product commercialization after the defined research screening is performed by us.

The collaboration includes two stages. During Stage I, which has been completed, we were obligated to perform specific research activities in accordance with the research plan focused on screening the target using our Bicycle platform to identify compounds that meet the criteria set by the parties. During Stage II, which is ongoing, Oxurion has continued research activities on selected Bicycle peptides with the goal of identifying compounds for further development and commercialization. We are not obligated or expected to perform any research services during Stage II of the research plan. THR-149 has been selected as a development compound under the Oxurion collaboration agreement.

We granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein.

The Oxurion collaboration agreement provided an upfront payment of €1.0 million and potential additional research and development funding, at an agreed upon FTE rate, should the research effort require more than one FTE or the research plan be amended or extended by Oxurion. In addition, Oxurion is required to make certain milestone payments to us upon the achievement of specified research, development, regulatory and commercial milestones. More specifically, for each collaboration compound, we are eligible to receive up to €8.3 million in research and development milestone payments, from which we have received €1.8 million as of December 31, 2018, in connection with the development of THR-149, and up to €16.5 million in regulatory milestone payments. In addition, to the extent any of the collaboration products covered by the licenses granted to Oxurion are commercialized, we would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Royalty payments are subject to certain reductions. Also, if Oxurion grants a sublicense to a third party for rights to the program for non-ophthalmic use prior to the filing of an IND, we would be entitled to receive payments in the double digits (no higher than first quartile) based on a percentage of non-royalty sublicensing income. If Oxurion grants a sublicense to a third party for rights to the program for non-opthalmic use after the filing of an IND, we would be entitled to receive payments of mid-single digits to low teen-digits.

Either party may terminate the Oxurion collaboration agreement if the other party has breached any of its material obligations and such breach continues after the specified cure period. Either party may terminate the Oxurion collaboration agreement in the event of the commencement

of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party. Oxurion may terminate the Oxurion collaboration agreement for convenience. We may terminate the Oxurion collaboration agreement if Oxurion challenges the validity of any licensed patents or opposes the grant of a licensed patent.

In November 2017, we entered into an amendment to the Oxurion collaboration agreement. This amendment provides for additional research services to be performed by us related to the identification of additional Bicycles binding to the target for Oxurion, in its discretion, to select as development compounds. We were obligated to perform the work in accordance with an amended research plan under Stage I of the collaboration and were funded at a specified FTE rate, plus any direct out of pocket expenses, and Oxurion will be responsible for Stage II research and any development after the selection of a development compound. As of December 1, 2018, we had completed Stage I of the research plan. Additional milestones were added for the potential additional licensed compounds, consistent with those of the initial Oxurion collaboration agreement. Additionally, the tiered royalty rates for all licensed compounds other than THR-149 was increased by one percentage point. We are not obligated or expected to perform any research services during Stage II of the collaboration.

Founder Royalty Arrangements

We have entered into two royalty agreements with our founders, Christian Heinis, John Tite, and Sir Gregory Winter, and our initial investors, Atlas Venture Fund VIII LP, Novartis Bioventures LTD. Pursuant to the first royalty agreement, we are obligated to pay an aggregate royalty percentage in the low single digits on net sales arising from products licensed under the Oxurion collaboration agreement. Pursuant to the second royalty agreement, we are obligated to pay an aggregate royalty percentage in the low single digits on net sales arising from products licensed under the AstraZeneca collaboration agreement.

Intellectual Property

Overview

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including our *Bicycle* platform. This includes seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties, which are directed to the use of our Bicycle platform and composition of matter involved in the platform, composition of matter and use of product candidates, and other inventions that are important to our business. We have three patent families directed to novel scaffolds, and 11 patent families directed to our platform technology, including the composition of matter of Bicycle® binders and method of treatment of related indications, including cancer. For example, a patent family directed to the composition of matter of Bicycle® binders and method of treatment of related indications, including cancer, was issued in the United States and Europe, and is pending in several other jurisdictions. The issued patents from this family, and the pending patent applications if issued, are expected to expire in 2034, before patent term extensions, if any. We have 52 patent families directed to the composition of matter of bicyclic peptides and related conjugates, and four patent families directed to methods of using bicyclic peptide conjugates for treating various indications. For example, two patent families directed to the composition of matter of one of our product candidates, BT1718, and methods of use for treating cancer are pending in certain jurisdictions, which if issued, would expire in 2035 and 2037, respectively. We also rely on trade secrets and know-how that may be important for the development of our business. This includes aspects of our proprietary technology platform and our continuing technological innovation to develop, maintain, and strengthen our position in the field of peptide, peptidomimetic, and small

molecule-based therapeutics. We additionally may rely on regulatory protection afforded through data exclusivity, market exclusivity and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for our product candidates, technology and know-how, defend and enforce our patents; prevent others from infringing our proprietary rights, preserve the confidentiality of our trade secrets, and to operate without infringing the proprietary rights of others.

Our ability to stop third parties from making, having made, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable licenses, patents or trade secrets that cover these activities. In some cases, these rights may need to be enforced by third party licensors. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same. For more information, please see "Risk Factors — Risks Related to Our Intellectual Property."

We seek to protect our proprietary position in a variety of ways, including by pursuing patent protection in certain jurisdictions where it is available. For example, we file U.S. and certain foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets and that may be used to identify and develop novel products. We seek protection, in part, through confidentiality and proprietary information agreements. We are a party to various other license agreements that give us rights to use specific technologies in our research and development.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application related to the patent. A U.S. patent also may be accorded a patent term adjustment, or PTA, under certain circumstances to compensate for delays in obtaining the patent caused by the United States Patent and Trademark Office. In some instances, such a PTA may result in a U.S. patent term extending beyond 20 years from the earliest date of filing a non-provisional patent application related to the U.S. patent. In addition, in the United States, the term of a U.S. patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions.

Company-Owned Intellectual Property

Our portfolio includes three patent families covering novel scaffolds, 11 patent families directed to our platform technology, 52 patent families covering bicyclic peptides and related conjugates, and four patent families directed to clinical indications. In total, we own 40 patents in the U.S. and in Australia, Canada, China, Europe, Japan, New Zealand, Russia and Singapore, with terms expiring at various dates in February 2029 to October 2034 exclusive of potential patent term adjustment and/or patent term extension.

In addition, we have 139 patent applications pending in the U.S. and Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, South Korea, New Zealand, Russia and Singapore, and any patents that may be issued from these patent applications are generally expected to have terms that will expire at various dates in February 2029 to October 2039 subject to possible patent term extensions and/or patent term adjustments.

Trade Secret Protection

Finally, we may rely, in some circumstances, on trade secrets to protect our technology. We anticipate relying on trade secrets to protect the know-how behind our *Bicycle* platform. However, trade secrets can be difficult to protect. We seek to protect our technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For further information, please see "Risk Factors — Risks Related to Our Intellectual Property."

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a number of currently marketed products and product candidates in preclinical research and clinical development by third parties for the various oncology applications that we are targeting. For example, a number of multinational companies as well as large biotechnology companies, including Astellas Pharma, Inc., Seattle Genetics, Inc., AstraZeneca, GlaxoSmithKline plc and Merrimack Pharmaceuticals, Inc., are developing programs for the targets that we are exploring for our BTC programs. Furthermore, Agenus Inc., Bristol-Myers Squibb Company, Pfizer Inc., and Roche Holding AG, or Roche, have or are developing programs for CD137, and Amgen Inc., Pieris Pharmaceuticals, Inc. and Roche are developing bi-specifics. In addition, we are aware that technologies for drug discovery, including peptide-based medicines, continue to advance rapidly, which may compete with our own screening technology or render it obsolete.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in discovering product candidates, obtaining approval for drugs and achieving widespread market acceptance. Our competitors' drugs may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

Sales and Marketing

Subject to receiving marketing approval, we intend to pursue the commercialization of our product candidates either by building internal sales and marketing capabilities or through opportunistic collaborations with others.

We plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Manufacturing

Each of our *Bicycles* is entirely synthetic. We believe the synthetic nature of our product candidates allow for a more cost effective and scalable manufacturing process compared to biologics. In addition, this property of *Bicycles* allows for the manufacturing of product candidates of consistent pharmaceutical quality with favorable stability characteristics. Based on our experience, we believe that the manufacturing of *Bicycles* can be made to be well controlled, reproducible and scalable.

We operate an outsourced model for the manufacture of our product candidates, and contract with good manufacturing practice, or GMP, licensed pharmaceutical contract development and manufacturing organizations, both for the synthesis of each drug substance component, and the formulation and packaging of the finished drug product. We selected these organizations based on their experience, capability, capacity and regulatory status. We do not own or operate GMP manufacturing facilities, nor do we currently plan to build our own GMP manufacturing capabilities for the production of candidates for clinical or commercial use.

We currently engage five third-party manufacturers to provide clinical supplies of our product candidates, three third-party manufacturers to provide non-clinical supplies of our product candidates and three third-party manufacturers to provide fill-finish services. Projects are managed by a specialist team of our internal staff, which is designed to promote compliance with the technical aspects and regulatory requirements of the manufacturing process.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs and devices under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities. In addition, an applicant may need to recall a product.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of nonclinical, or preclinical, laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent IRB representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of a new drug application, or NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an

IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA can place an IND on full or partial clinical hold at any point in development, and depending upon the scope of the hold, clinical trial(s) may not restart until resolution of the outstanding concerns to the FDA's satisfaction.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- ***Phase I.*** The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- ***Phase II.*** The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- ***Phase III.*** The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

- ***Phase IV.*** Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase I,

Phase II and Phase III clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the applicant must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to substantial user fees, and the sponsor of an approved NDA is also subject to annual program user fees. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected

benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are Fast Track designation, Breakthrough Therapy designation and priority review designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a

condition, elimination or substantial reduction of a treatment-limiting adverse reaction, documented enhancement of patient compliance that is expected to lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase IV or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally

outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase IV clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the NDA holder and any third-party manufacturers that the NDA holder may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or voluntary product recalls;
- fines, warning letters or holds on post-approval clinical trials;

- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs generally may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Companion Diagnostics

We may employ companion diagnostics to help us to more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics can identify patients who are most likely to benefit from a particular therapeutic product; identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness. Companion diagnostics are regulated as medical devices by the FDA and, as such, require either clearance or approval prior to commercialization. The level of risk combined with available controls to mitigate risk determines whether a companion diagnostic device requires Premarket Approval Application, or PMA, approval or is cleared through the 510(k) premarket notification process. For a novel therapeutic product for which a companion diagnostic device is essential for the safe and effective use of the product, the companion diagnostic device should be developed and approved or 510(k)-cleared contemporaneously with the therapeutic. The use of the companion diagnostic device will be stipulated in the labeling of the therapeutic product.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug."

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, which states the proposed generic drug will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. An applicant who submits a section 505(b)(2) NDA, which is for new or improved formulations or new uses of previously approved drug products and where at least one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, also must certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will be receiving orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information

submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Europe/Rest of World Regulation

In addition to regulations in the United States, a manufacturer is subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of products, if approved. Even if a manufacturer obtains FDA approval of a product, it must still obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial application must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the clinical trial application is approved in accordance with a country's requirements, clinical trial development may proceed. To obtain regulatory approval of an investigational drug under EU regulatory systems, a manufacturer must submit a marketing authorization application. More concretely, in the EEA (which is comprised of the 28 Member States

of the EU plus Norway, Liechtenstein and Iceland, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

- The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, and which is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

- National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

In Europe, the period of orphan drug exclusivity is ten years, although it may be reduced to six years if, at the end of the fifth year, it is established that the criteria for orphan drug designation are no longer met, in other words, when it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product approval, pricing and reimbursement vary from country to country. In all cases, the clinical trials are to be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical

necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, no uniform policy for coverage and reimbursement exists in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. Therefore one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for our product candidates will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Other Healthcare Laws and Regulations

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse

and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Such restrictions under applicable federal and state healthcare laws and regulations, include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security, price reporting and physician sunshine laws. Some of our pre-commercial activities are subject to some of these laws.

The federal Health Care Program Anti-Kickback Statute, or Anti-Kickback Statute, prohibits any person or entity, including a prescription drug manufacturer or a party acting on its behalf, from, among other things, knowingly and willfully, directly or indirectly, soliciting, receiving, offering, or providing any remuneration that is intended to induce the referral of business, including the purchase, order or recommendation or arranging of, any good or service for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the Anti-Kickback Statute has been violated. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Moreover, a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

The federal civil False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, for payment to, or approval by, federal programs, including Medicare and Medicaid, claims for items or services, including drugs, that are false or fraudulent or not provided as claimed. Persons and entities can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, any of our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and other third-party payor reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for federal civil False Claims Act violations may include up to three times the actual damages sustained by the government, plus significant mandatory civil penalties for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, False Claims Act violations may also implicate various federal criminal statutes.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or

services. Like the Anti-Kickback Statute a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Also, many states have similar fraud and abuse statutes or regulations that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, to the extent that any of our product candidates, if approved, are sold in a foreign country, we may be subject to similar foreign laws.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, including the final omnibus rule published on January 25, 2013, mandates, among other things, the adoption of uniform standards for the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy and security of individually identifiable health information, which require the adoption of administrative, physical and technical safeguards to protect such information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, defined as independent contractors or agents of certain healthcare providers, healthcare clearinghouses and health plans, known as covered entities, that create, receive or obtain protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities and business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, certain state and foreign laws govern the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The U.S. federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, ACA, , including the provision commonly referred to as the Physician Payments Sunshine Act imposed, among other things, new annual reporting requirements for covered manufacturers for certain payments and other transfers of value provided to physicians and teaching hospitals, as well as certain ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, covered manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. Failure to submit timely, accurately and completely the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties of up to an aggregate of over $169,000 per year and up to an aggregate of over $1.1 million per year for "knowing failures." Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices or require the tracking and reporting of gifts, compensation or other remuneration to physicians.

Because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs, we intend to develop a comprehensive compliance program that establishes internal control to facilitate adherence to the rules and program requirements to which we will or may become subject. Although the development and implementation of compliance programs designed to establish internal control and facilitate compliance can mitigate the risk of investigation, prosecution, and penalties assessed for violations of these laws, the risks cannot be entirely eliminated.

If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our

operations, exclusion from participation in federal and state healthcare programs, including Medicare and Medicaid, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Healthcare Reform

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress passed the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expansion of the types of entities eligible for the 340B drug discount program;
- establishment of the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Some of the provisions of the ACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health

insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing or delaying penalties, starting January 1, 2019, for not complying with the Affordable Care Act's individual mandate to carry health insurance, delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Also, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. For example, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. For example, in November 2018, CMS issued a proposed rule for comment that would, among other things, provide Medicare prescription drug plans under Part D more transparency in pricing and greater flexibility to negotiate discounts for, and in certain circumstances exclude, drugs in the six "protected" formulary classes and allow Medicare Advantage plans to use certain drug management tools such as step therapy for physician-administered drugs. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

Employees

As of March 1, 2019, we had 60 full-time or part-time employees, including 28 with M.D. or Ph.D. degrees. Of these employees, 48 employees are engaged in research and development activities and nine employees are engaged in general and administrative activities. None of our

employees are represented by labor unions or covered by collective bargaining agreements. We consider the relationship with our employees to be good.

Facilities

We occupy approximately 13,500 rentable square feet of office and laboratory space in Cambridge, United Kingdom under a lease that expires in December 2021, with a five-year extension option, and an additional 11,000 rental square feet of office and laboratory space in Lexington, Massachusetts under a lease that expires in December 2022, with a five-year extension option. We believe that our office and laboratory spaces are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Legal Proceedings

Other than as described below, we are not currently subject to any material legal proceedings.

License Litigation

In 2009, we entered into a non-exclusive patent license agreement with Pepscan Systems B.V., or Pepscan, pursuant to which we licensed rights related to the scaffold used for *Bicycles* contained in certain of our product candidates, including our lead product candidate, BT1718. The agreement required us to enter into a framework services agreement with Pepscan for Pepscan to provide certain *Bicycles* not produced by us. In 2010, we entered into such a framework services agreement. In 2014, we terminated the framework services agreement in accordance with its terms. Subsequently, in 2016, Pepscan terminated the patent license agreement.

We instituted proceedings in the District Court of The Hague to contest the right of Pepscan to terminate the patent license agreement. In response, Pepscan claimed, among other things, that the termination of the framework services agreement and alleged breaches by us of confidentiality obligations constituted grounds for the termination of the patent license agreement. In a preliminary judgement delivered in April 2018, the District Court of the Hague rejected Pepscan's claim that it was entitled to terminate the patent license agreement on the basis of a breach of a purported exclusive supply obligation. The District Court of the Hague reserved for further proceedings the question of whether Pepscan was entitled to terminate the patent license agreement on the basis of allegations that we had breached our confidentiality obligations. The District Court of the Hague gave us an opportunity to submit proof to the contrary through written evidence and further hearings.

In July 2018, Pepscan appealed the decision of the District Court of the Hague and the proceedings before the District Court of the Hague have been stayed pending a decision in the appeal brought by Pepscan. We intend to defend the appeal and any further proceedings before the District Court of the Hague.

The patent that is the subject of these proceedings expires in 2024.

European Patent Opposition Proceedings

In January 2013, Pepscan filed a notice of opposition in respect of European patent 2 257 624, which is a foundational patent that covers our technology platform. In June 2015, the European Patent Office issued a decision to maintain this patent as granted and rejecting Pepscan's opposition. Pepscan subsequently filed a notice of appeal to revoke the patent in its entirety, along with supporting materials. We filed a reply requesting that the appeal be dismissed. As of the date of this prospectus, no decision has been issued by the European Patent Office in respect of this appeal.

In April 2015, Pepscan filed a notice of opposition in respect of European patent 2 474 613, which is a divisional patent that covers extensions of our technology platform. In February 2017, the European Patent Office issued a decision to maintain this patent in its amended form, which upheld this patent. Pepscan subsequently filed a notice of appeal to revoke the patent in its entirety, along with supporting materials. We also filed a Notice of Appeal contesting the amendments to the patent required by the decision of the Opposition Division along with supporting materials. As of the date of this prospectus, no decision has been issued by the European Patent Office in respect of these appeals.

MANAGEMENT

Executive Officers and Directors

Our executive officers and directors and their respective ages and positions as of March 21, 2019:

Name	Age	Position(s)
Executive Officers:		
Kevin Lee, Ph.D., MBA	50	Chief Executive Officer and Director
Lee Kalowski, MBA	38	President and Chief Financial Officer
Peter Leone, MBA	62	Chief Business Officer
Michael Skynner, Ph.D.	50	Chief Operating Officer
Maria Koehler, M.D., Ph.D.	62	Chief Medical Officer
Nick Keen, Ph.D.	51	Chief Scientific Officer
Non-Employee Directors		
Pierre Legault, MBA, CPA	64	Director and Non-Executive Chairman of the Board of Directors
Michael Anstey, DPhil	38	Director
Kate Bingham, MBA	53	Director
Deborah Harland, Ph.D., MBA	58	Director
Anja König, Ph.D.	48	Director
Eashwar Krishnan	42	Director
Carolyn Ng, Ph.D.	35	Director
Jason Rhodes, MBA	49	Director
Sir Greg Winter, FRS	67	Director

(1) Member of the Audit Committee.

(2) Member of the Compensation Committee.

(3) Member of the Nominating and Corporate Governance Committee.

The following is a biographical summary of the experience of our executive officers and directors. There are no family relationships among any of our executive officers or directors.

Executive Officers

Kevin Lee, Ph.D., MBA has served as our Chief Executive Officer and a member of our board of directors since September 2015. From April 2012 to September 2015, Dr. Lee served as Senior Vice President and Chief Scientific Officer of the Rare Disease Research Unit at Pfizer Inc., a pharmaceutical company. From November 2004 to April 2012, Dr. Lee worked at GlaxoSmithKline plc, where in addition to leading the formation of multiple strategic commercial and academic partnerships, he led epigenetics research and was responsible for the creation of the EpiNova Discovery Performance Unit. Before joining GlaxoSmithKline, Dr. Lee was a lecturer at Warwick University Medical School and founded Cambridge Biotechnology Ltd, which specialized in developing small molecule and peptide therapeutics for inflammation and metabolic diseases before its trade sale to Biovitrum in 2005 and Neurosolutions (now Oncosil Medical Ltd ASX). Dr. Lee received a BPharm from Nottingham University and a Ph.D. in pharmacology from Cambridge University. Dr. Lee has an MBA from Warwick Business School and currently serves as a non-executive director for Nodthera Ltd, a position he has held since October 2018, and as a director at Wilbraham Consulting Ltd., a position he has held since December 2017.

We believe that Dr. Lee is qualified to serve on our board of directors based on his extensive leadership, executive, managerial, business and pharmaceutical and biotechnology company

experience, along with his years of industry experience in the development and commercialization of pharmaceutical products.

Lee Kalowski, MBA has served as our Chief Financial Officer since July 2017 and as our President since February 2019. Prior to joining us, from September 2014 until September 2016, Mr. Kalowski served as the Chief Financial Officer and from September 2016 until July 2017, served as the consulting Chief Financial/Business Officer of Tokai Pharmaceuticals, Inc. (NASDAQ: TKAI), a biopharmaceutical company. Prior to Tokai, from June 2010 to September 2014, Mr. Kalowski served in global biotechnology equity research at Credit Suisse, where he covered companies in the biopharmaceutical industry as a Senior Analyst from May 2011 until September 2014 and as an Associate from June 2010 until May 2011. Mr. Kalowski received a B.A. in biology and economics from Union College and an MBA from The Wharton School of the University of Pennsylvania.

Peter Leone, MBA has served as our Chief Business Officer since February 2019. Prior to joining us, from April 2016 to January 2019, Mr. Leone served as Vice President of Strategic Business Initiatives at Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR), a biopharmaceutical company. Prior to Arrowhead, from 2010 to 2012, Mr. Leone was Chief Operating Officer at Alvos Therapeutics, Inc., a biopharmaceutical company, which now operates as a subsidiary of Arrowhead. Before Alvos, Mr. Leone was the founding Chief Executive Officer or Chief Operating Officer at three different venture backed companies, including Mersana Therapeutics, Inc. (NASDAQ: MRSN), a biopharmaceutical company. Mr. Leone received a B.A. in engineering science with pre-med studies from Dartmouth College and an MBA from the Stanford University Graduate School of Business.

Michael Skynner, Ph.D. has served as our Chief Operating Officer since January 2018 and prior to this, served as our Vice President of Operations since January 2016. Prior to joining us, Dr. Skynner worked at Pfizer Inc., a pharmaceutical company, from September 2013 to January 2016, where he was Head of Rare Disease Alliances, led rare disease efforts in Europe and founded and ran the Pfizer Rare Disease Consortium. Prior to Pfizer, from May 2008 to September 2013, Dr. Skynner worked at GlaxoSmithKline plc, where he focused on developing therapeutics targeting inflammatory kinases. Prior to GlaxoSmithKline, in 2001, Dr. Skynner co-founded Cambridge Biotechnology Ltd, which specialized in developing small molecule and peptide therapeutics for inflammation and metabolic diseases before its trade sale to Biovitrum in 2005. Dr. Skynner obtained his Ph.D. in biochemistry from Imperial College.

Maria Koehler, M.D, Ph.D. has served as our Chief Medical Officer since September 2017. Prior to joining us, from March 2009 to September 2017, Dr. Koehler was the Vice President of Strategy, Innovation and Collaborations for the Oncology Business Unit at Pfizer Inc., a pharmaceutical company. Prior to joining Pfizer, Dr. Koehler was the group leader for the Medicine Development Center of GlaxoSmithKline Oncology. Prior to that, Dr. Koehler was a Senior Medical Director for oncology research and development at AstraZeneca plc. Dr. Koehler has also served as the Clinical Director of Bone Marrow Transplantation at University Hospital in Pittsburgh and the Director of the Bone Marrow Transplant Program and Associate Professor at St. Christopher's Hospital in Philadelphia. Dr. Koehler is a board-certified hematology/oncology physician. Dr. Koehler received her M.D. and Ph.D. from Silesian School of Medicine in Katowice, Poland.

Nicholas Keen, Ph.D. has served as our Chief Scientific Officer since January 2017. Prior to joining us, from April 2011 until December 2016, Dr. Keen was the Head of Oncology Drug Discovery at the Cambridge (US) office of the Novartis Institutes for Biomedical Research (NIBR), a subsidiary of Novartis AG, a pharmaceutical company. Prior to Novartis, from August 2005 to March 2011, Dr. Keen led the early lead generation group for oncology at AstraZeneca plc's US research site in Waltham, MA, and before this, from January 1997 to July 2005 worked in AstraZeneca's UK oncology research group. Dr. Keen completed his undergraduate studies at the University of

Cambridge, his graduate studies at the Imperial Cancer Research Fund in Cambridge and his post-doctoral studies at the Laboratory of Molecular Biology in Cambridge.

Non-Employee Directors

Pierre Legault has served as our chairman and a member of our board of directors since March 2019. Mr. Legault has served on the board of directors of Urovant Sciences Ltd. since July 2018 and has also served on the board of directors of Poxel SA since January 2016 and has been chairman of such board since March 2016. Since February 2018, Mr. Legault has served on the board of directors and as chairman of the board of Artios Pharma Limited. Mr. Legault has also served as a director of Clementia Pharmaceuticals Inc. since January 2018 and Syndax Pharmaceuticals Inc. since January 2017. Mr. Legault has also previously served as a member of the boards of directors at Forest Laboratories, Inc., Tobira Therapeutics, Inc., NPS Pharmaceuticals, Inc., Regado Biosciences, Inc., ARMO Biosciences, Inc., Iroko Pharmaceuticals LLC, Cyclacel Pharmaceuticals Inc., Eckerd Pharmacy and NephroGenex, Inc., where he also served as the Chairman and Chief Executive Officer from 2012 to 2016. From 2010 to 2012, Mr. Legault served as the Chief Executive Officer of Prosidion Ltd., a subsidiary of Astellas Pharma Inc., and from 2009 to 2010, he served as the Chief Financial Officer and Treasurer of OSI Pharmaceuticals, Inc. Mr. Legault also previously served as the Chief Executive Officer of Eckerd Pharmacy and Senior Executive Vice President and Chief Accounting Officer of the Rite Aid Corporation. Between 1989 and 2005, Mr. Legault held various global roles such as President, Chief Executive Officer and Chief Financial Officer at legacy companies of the Sanofi-Aventis group. Mr. Legault earned a B.B.A. in Business & International Finance from HEC Montreal, an MBA. in Marketing from McGill University and holds C.A. and C.P.A. diplomas. He also studied at Harvard Business School in their Graduate Executive MBA program.

We believe that Mr. Legault's is qualified to serve on our board of directors based on his experience leading and managing a number of biopharmaceutical companies.

Michael Anstey, DPhil has served as a member of our board of directors since June 2017. Dr. Anstey is an Investment Director at Cambridge Innovation Capital plc. Prior to this role, from January 2010 to January 2017, Dr. Anstey was a Principal in the Healthcare Practice Area of the Boston Consulting Group. Prior to Boston Consulting Group, Inc., from January 2008 to December 2009, Dr. Anstey was on the investment team at Oxford Capital Partners LLP. Dr. Anstey currently serves on the board of directors of Congenica Ltd. and Storm Therapeutics Ltd. Dr. Anstey graduated with a first class honors degree in biology from Queen's University, Canada and earned a DPhil in zoology in the field of neurobiology from Oxford University.

We believe that Dr. Anstey is qualified to serve on our board of directors based on his knowledge of the healthcare sector and his experience as a seasoned investor.

Kate Bingham, MBA has served as a member of our board of directors since October 2014. Ms. Bingham joined SV Health Investors LLP (then Schroder Ventures), a venture capital fund, in 1991. Ms. Bingham currently serves on the boards of directors of Autifony Therapeutics Limited, Calchan Holdings Limited, Karus Therapeutics Limited, Ervaxx Limited, TRex Bio, Zarodex Therapeutics Limited, Pulmocide Limited and Sitryx Therapeutics Limited. She is Deputy Chairman of St. Paul's Girls' School, London, and sits on the Investment Committee of Oxford University Spin-out Equity Management (OSEM). Ms. Bingham holds a B.A. in biochemistry from Oxford University and graduated from Harvard Business School with an MBA.

We believe that Ms. Bingham is qualified to serve on our board of directors based on her knowledge of the healthcare sector across international markets.

Deborah Harland, Ph.D., MBA has served as a member of our board of directors since December 2009. Since 2005, Dr. Harland has been a Partner at S.R. One, Limited, the corporate venture capital arm of GlaxoSmithKline plc. Dr. Harland is currently a member of the boards of directors of Asceneuron SA, F-star, MISSION Therapeutics Ltd., and VHsquared Ltd. and is an independent Director on the Board of Cancer Research Technology, the specialist commercialisation and development arm of Cancer Research UK, the world's largest cancer research charity. Dr. Harland holds a BSc. (with honors) in pharmacology from the University of Bath, a Ph.D. in pharmacology from the University of London and an MBA from Henley Management College.

We believe that Dr. Harland is qualified to serve on our board of directors based on her knowledge of the healthcare sector across international markets, her extensive operational, drug development and licensing experience.

Anja König, Ph.D. has served as a member of our board of directors since 2009. Dr. König is the global head of the Novartis Venture Fund in Basel, Switzerland. Dr. König currently serves on the board of directors of Forendo Pharma, Ltd. Prior to joining Novartis in 2006, she was an Associate Partner at McKinsey & Company, where she was a leader in McKinsey's North American Pharmaceutical Practice. Dr. König holds a Ph.D. in physics from Cornell University.

We believe Dr. König's extensive knowledge of the healthcare sector qualifies her to serve on our board of directors. Dr. König has notified us that she will resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. Dr. König's resignation is not due to any disagreement with the company or any matters relating to our operations, policies or practices.

Eashwar Krishnan has served as a member of our board of directors since 2019. Mr. Krishnan is the Managing Partner of Tybourne Capital Management, a Hong Kong based global equity investment management firm founded in 2012. Prior to founding Tybourne, Mr Krishnan was a senior analyst at Lone Pine Capital for over 11 years. Mr Krishnan joined Lone Pine Capital in 2000 as a Managing Director with responsibility for the firm's global technology investments. Prior to joining Lone Pine Capital, Mr Krishnan spent two years as an analyst in the Principal Investment Area at Goldman Sachs in London (1998-2000) and worked as a summer research fellow at the Jet Propulsion Laboratory in Pasadena, California (1997). Mr Krishnan holds a first class degree in Physics from Trinity College, Cambridge University, U.K. and St. Stephen's College, Delhi University, India. Mr. Krishnan also serves on the Campaign Board of Cambridge University.

We believe Mr. Krishnan is qualified to sit on our board of directors based on his extensive investment experience, including in the life sciences.

Carolyn Ng, Ph.D. has served as a member of our board of directors since 2018. Dr. Ng is a principal of Vertex Ventures HC, a global venture capital firm. Dr. Ng currently serves on the Board of Obsidian Therapeutics, Inc. and Twentyeight-Seven Therapeutics, Inc. Prior to joining Vertex, from 2012 to 2014, Dr. Ng was a Pharma Strategy Consultant at Deallus Consulting, a specialized life sciences consulting firm. Dr. Ng started her career in the oncology pharmacy department of the National University Cancer Institute of Singapore, where she worked in 2006. Dr. Ng holds a Ph.D. in Cancer Molecular Biology from the National University of Singapore Graduate School for Integrative Sciences and Technology and a B.S. degree in pharmacy with first class honours from the National University of Singapore.

We believe that Dr. Ng is qualified to serve on our board of directors based on her extensive experience in life sciences investing and knowledge of the healthcare sector.

Jason Rhodes, MBA has served as a member of our board of directors since 2015. Mr. Rhodes is a partner at Atlas Venture LP, a venture capital firm, since 2014. He has been a

Founder and Chairman of Generation Bio, Co. since 2016 and a Founder, Chairman and currently acting Chief Executive Officer of Disarm Therapeutics, Inc. since 2016, both of which are biotechnology companies. He has been a member of the boards of directors of Replimune Group, Inc. (NASDAQ: REPL) since 2015, Gemini Therapeutics, Inc. since 2016 and Accent Therapeutics, Inc. since 2017. From 2010 to 2014, Mr. Rhodes was at Epizyme, Inc. (NASDAQ: EPZM), where he most recently served as President and Chief Financial Officer. He led business development at Alnylam (NASDAQ: ALNY) from 2007 to 2010. Mr. Rhodes obtained a B.A. from Yale University in 1991 and an M.B.A. from the Wharton School of the University of Pennsylvania in 1996.

We believe that Mr. Rhodes is qualified to serve on our board of directors based on his experience as a life sciences investor, including serving on other boards of directors. Mr. Rhodes has notified us that he will resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. Mr. Rhodes' resignation is not due to any disagreement with the company or any matters relating to our operations, policies or practices.

Sir Greg Winter, FRS is our Co-Founder and has served on of our board of directors since our inception. Sir Greg was a member of staff of the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge, U.K from 1981 to 2012, serving as both Deputy and Acting Director. He is currently Master of Trinity College, Cambridge. Sir Greg is a Fellow of the Royal Society and was knighted in 2004 for services to science. In 2018, Sir Greg was awarded a Nobel Prize in Chemistry for his work in developing phage display for the directed evolution of antibodies and peptides to produce new medicines. He has been the Acting Chairman of Biosceptre International Limited from 2016 to 2018. Sir Greg was a founder and non-Executive Director of Cambridge Antibody Technology and Domantis.

We believe that Sir Greg is qualified to serve on our board of directors based on his extensive research experience, knowledge of antibody medicines and academic achievements, combined with his experience in the biotechnology industry.

Composition of Our Board of Directors

Our board of directors currently consists of ten members, all of whom were elected pursuant to the board composition provisions of in our articles of association and investment agreement, which is described under "Certain Relationships and Related Party Transactions—Agreements with Our Shareholders" in this prospectus. These board composition provisions will terminate upon the closing of this offering as the articles of association adopted by us immediately prior to closing of this offering will not include such provisions and the investment agreement relating to the group will terminate immediately prior to closing. Upon the termination of these provisions, there will be no further contractual obligations regarding the election of our directors. Our nominating and governance committee and board of directors may therefore consider a broad range of factors relating to the qualifications and background of nominees, which may include diversity and is not limited to race, gender or national origin. We have no formal policy regarding board diversity. Our nominating and governance committee's and board of directors' priority in selecting board members is identification of persons who will further the interests of our shareholders through his or her established record of professional accomplishment, the ability to contribute positively to the collaborative culture among board members, knowledge of our business, understanding of the competitive landscape and professional and personal experiences and expertise relevant to our growth strategy. Our directors hold office until their successors have been elected and qualified or until the earlier of their resignation or removal.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution. See "Description of Share Capital and Articles of Association—Post-IPO Articles of Association—Board of Directors."

Our board of directors has determined that all members of the board of directors, except are independent, as determined in accordance with the rules of Nasdaq. In making such independence determination, our board of directors considered the relationships that each such non-employee director has with us and all other facts and circumstances that the board of directors deemed relevant in determining their independence. Upon the effectiveness of the registration statement of which this prospectus forms a part, we expect that the composition and functioning of our board of directors and each of our committees will comply with all applicable requirements of Nasdaq and the rules and regulations of the SEC.

Staggered Board

Our articles of association to be effective upon completion of this offering provide that our board of directors will be divided into three classes, Class I, Class II and Class III, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

- Our Class I directors will be , and ;
- Our Class II directors will be , and ; and
- Our Class III directors will be , and .

Our articles of association to be effective upon completion of this offering provide that the authorized number of directors may be changed only by ordinary resolution of the shareholders. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class shall consist of one third of the board of directors.

The division of our board of directors into three classes with staggered three-year terms may delay or prevent shareholder efforts to effect a change of our management or a change in control.

Board's Role in Risk Oversight

Our board of directors oversees the management of risks inherent in the operation of our business and the implementation of our business strategies. Our board of directors performs this oversight role by using several different levels of review. In connection with its reviews of our operations and corporate functions, our board of directors addresses the primary risks associated with those operations and corporate functions. In addition, our board of directors reviews the risks associated with our business strategies periodically throughout the year as part of its consideration of undertaking any such business strategies.

Each of our board committees also oversees the management of our risk that falls within the committee's areas of responsibility.

In performing this function, each committee has full access to management, as well as the ability to engage advisors. Our Chief Financial Officer reports to the audit committee and is responsible for identifying, evaluating and implementing risk management controls and methodologies to address any identified risks. In connection with its risk management role, our

audit committee meets privately with representatives from our independent registered public accounting firm and our Chief Financial Officer. The audit committee oversees the operation of our risk management program, including the identification of the primary risks associated with our business and periodic updates to such risks, and reports to our board of directors regarding these activities.

Board Committees

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee, each of which operates pursuant to a separate charter adopted by our board of directors. The composition and functioning of all of our committees will comply with all applicable requirements of the Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, Nasdaq and SEC rules and regulations.

Audit Committee

Upon the effectiveness of the registration statement of which this prospectus forms a part, , and will serve on the audit committee, which will be chaired by . Our board of directors has determined that each member of the audit committee is "independent" for audit committee purposes as that term is defined in the rules of the SEC and the applicable rules of Nasdaq. Our board of directors has designated as an "audit committee financial expert," as defined under the applicable rules of the SEC. The audit committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our independent registered public accounting firm
- approving auditing and permissible non-audit services, and the terms of such services, to be provided by our independent registered public accounting firm;
- reviewing the internal audit plan with the independent registered public accounting firm and members of management responsible for preparing our financial statements;
- reviewing and discussing with management and the independent registered public accounting firm our annual and quarterly financial statements and related disclosures as well as critical accounting policies and practices used by us;
- reviewing the adequacy of our internal control over financial reporting;
- establishing policies and procedures for the receipt and retention of accounting-related complaints and concerns;
- recommending, based upon the audit committee's review and discussions with management and the independent registered public accounting firm, whether our audited financial statements shall be included in our Annual Report on Form 10-K;
- monitoring the integrity of our financial statements and our compliance with legal and regulatory requirements as they relate to our financial statements and accounting matters;
- preparing the audit committee report required by the SEC rules to be included in our annual proxy statement;
- reviewing all related party transactions for potential conflict of interest situations and approving all such transactions; and
- reviewing earnings releases.

Compensation Committee

Upon the effectiveness of the registration statement of which this prospectus forms a part, , and will serve on the compensation committee, which will be chaired by . Our board of directors has determined that each member of the compensation committee is "independent" as that term is defined in the applicable rules of Nasdaq. The compensation committee's responsibilities include:

- annually reviewing and approving corporate goals and objectives relevant to the compensation of our Chief Executive Officer and Chief Financial Officer;
- evaluating the performance of our Chief Executive Officer and Chief Financial Officer in light of such corporate goals and objectives and recommending or determining the compensation of our Chief Executive Officer;
- reviewing and recommending or determining the compensation of our other executive officers;
- reviewing and establishing our overall management compensation, philosophy and policy;
- overseeing and administering our compensation and similar plans;
- evaluating and assessing potential current compensation advisors in accordance with the independence standards identified in the applicable rules of the Nasdaq Stock Market;
- retaining and approving the compensation of any compensation advisors;
- reviewing and approving our policies and procedures for the grant of equity-based awards;
- reviewing and making recommendations to the board of directors with respect to director compensation;
- preparing the compensation committee report required by the SEC rules to be included in our annual proxy statement;
- reviewing and discussing with management the compensation discussion and analysis to be included in our annual proxy statement or Annual Report on Form 10-K; and
- reviewing and discussing with the board of directors corporate succession plans for the Chief Executive Officer and other key officers.

Nominating and Corporate Governance Committee

Upon the effectiveness of the registration statement of which this prospectus forms a part, , and will serve on the nominating and corporate governance committee, which will be chaired by . Our board of directors has determined that each member of the nominating and corporate governance committee is "independent" as that term is defined in the applicable rules of Nasdaq. The nominating and corporate governance committee's responsibilities include:

- developing and recommending to the board of directors criteria for board and committee membership;
- establishing procedures for identifying and evaluating board of director candidates, including nominees recommended by shareholders;
- identifying individuals qualified to become members of the board of directors;
- recommending to the board of directors the persons to be nominated for election as directors and to each of the board's committees;

- developing and recommending to the board of directors a set of corporate governance guidelines; and
- overseeing the evaluation of the board of directors and management.

Our board of directors may establish other committees from time to time.

Compensation Committee Interlocks and Insider Participation

None of the members of our compensation committee has at any time during the prior three years been one of our officers or employees. None of our executive officers currently serves, or in the past fiscal year has served, as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving on our board of directors or compensation committee.

Corporate Governance

We intend to adopt, effective upon the effectiveness of the registration statement of which this prospectus forms a part, a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. Following the completion of this offering, a current copy of the code will be posted on the Corporate Governance section of our website, which is located at *www.bicycletherapeutics.com*. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for any officer, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

EXECUTIVE COMPENSATION

Executive Compensation Overview

Historically, our executive compensation program has reflected our growth and development-oriented corporate culture. To date, the compensation of the other executive officers identified in the summary compensation table below, who we refer to as the named executive officers, has consisted of a combination of base salary, bonuses and long-term incentive compensation in the form of share options or restricted shares. Our executive officers and all salaried employees are also eligible to receive health and welfare benefits.

As we transition from a private company to a publicly-traded company, we will evaluate our compensation values and philosophy and compensation plans and arrangements as circumstances require. At a minimum, we expect to review executive compensation annually with input from a compensation consultant if and when determined appropriate by the compensation committee. As part of this review process, we expect the board of directors and the compensation committee to apply our values and philosophy, while considering the compensation levels needed to ensure our executive compensation program remains competitive. We will also review whether we are meeting our retention objectives and the potential cost of replacing a key employee.

Summary Compensation Table — 2018

The following table presents information regarding the total compensation awarded to, earned by, and paid to our principal executive officer and the two most highly-compensated executive officers (other than the principal executive officer) who were serving as our executive officers at the end of the last completed fiscal year for services rendered in all capacities to us. We refer to these individuals as our named executive officers. Our named executive officers for 2018 are:

- Kevin Lee, our Chief Executive Officer;
- Lee Kalowski, our Chief Financial Officer and President; and
- Maria Koehler, our Chief Medical Officer.

The following table provides information regarding the total compensation, for services rendered in all capacities, that was earned by our named executive officers during the year ended December 31, 2018.

Name and Principal Position	Year	Salary ($)	Bonus ($)	Non-Equity Incentive Plan Compensation ($)	All Other Compensation ($)	Total ($)
Kevin Lee, Ph.D., MBA *Chief Executive Officer*	2018[1]	385,549[2]	127,630[3]	267,904[4]	36,811[5]	817,894
Lee Kalowski, MBA *Chief Financial Officer and President*	2018	349,520[6]	60,000[7]	110,536[4]	—	520,056
Maria Koehler, M.D., Ph.D. *Chief Medical Officer*	2018	385,500[8]	—	127,215[4]	—	512,715

(1) The amounts reported for Dr. Lee have been converted from GBP to USD using an exchange rate of $1.2763 to £1.00 as of December 31, 2018. In December 2018, Dr. Lee surrendered his vested share options in exchange for ordinary shares at a subscription price of £0.01 per ordinary share and surrendered his unvested share options in exchange for a new option grant on the same terms and vesting schedule as the unvested surrendered options. There was no value attributed to either action based on Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 718 and accordingly, there is no amount reported in this table in connection with such award. The assumptions used in calculating the grant date fair value of the shares are set forth in the Notes to our Consolidated Financial Statements included elsewhere in this prospectus.

(2) In 2018, Dr. Lee's base salary was $375,000 and increased in August 2018 to $429,597.

(3) The amount reported reflects a retention bonus paid to Dr. Lee in 2018 that is repayable in full to us if Dr. Lee gives notice prior to August 1, 2020.

(4) The amount reported represents the named executive officer's respective 2018 target bonus that was paid in February 2019, based on achievement of personal and Company goals. With respect to Dr. Lee, the amount also includes a stock grant awarded to Dr. Lee in lieu of cash with a grant date fair value of $24,042 in connection with entering into the Bioverativ collaboration arrangement.

(5) The amounts reported represent relocation reimbursements and $34,937 provided to Dr. Lee for pension benefits.

(6) At the beginning of 2018, Mr. Kalowski's base salary was $340,000 and increased in mid-January 2018 to $349,520.

(7) The amount reported represents a relocation bonus in the amount of $30,000 provided to Mr. Kalowski in 2018 and a discretionary cash bonus in the amount of $30,000 earned by Mr. Kalowski in 2018.

(8) At the beginning of 2018, Dr. Koehler's base salary was $375,000 and increased in mid-January 2018 to $385,500.

Employment Agreements with Our Named Executive Officers

Kevin Lee, Ph.D. MBA. On August 1, 2018, we entered into an employment agreement with Dr. Lee for the position of Chief Executive Officer. Dr. Lee currently receives a base salary of $429,597, which is subject to review and adjustment in accordance with our policy. Dr. Lee was granted a retention bonus of $127,630, which must be repaid if Dr. Lee notifies us that he has terminated his employment with us any time prior to August 1, 2020. Dr. Lee is eligible for an annual merit bonus of up to fifty percent (50%) of his salary, which may be paid in cash, in whole or in part, or options to purchase our shares, based on the achievement of certain performance goals, including corporate objectives, strategic initiatives and regulatory and clinical milestones, as determined by our remuneration committee. Dr. Lee is eligible for a shareholder value realization, or SVR, bonus, in which Dr. Lee, at the discretion of the remuneration committee, is eligible for a cash bonus in the event of a "Sale Event" (as defined in his employment agreement) on or before the fourth anniversary of his employment agreement. In the event of a "Sale Event" with proceeds of $587.39 million or less, Dr. Lee is entitled to a SVR bonus of 0.5% of the "Sales Event Proceeds" (as defined in his Employment Agreement). In the event of a "Sale Event" with proceeds between $583 million and $1.305 billion, Dr. Lee is entitled to a SVR bonus of 0.75% of the "Sales Event Proceeds". In the event of a "Sale Event" with proceeds of $1.305 billion or more, Dr. Lee is entitled to a SVR bonus of 1.0% of the "Sales Event Proceeds". Dr. Lee is eligible to participate in our employee benefit plans generally available to our executive employees, subject to the terms of those plans. Dr. Lee's employment has no specified term, but can be terminated at will by either party. Dr. Lee may be terminated, immediately and without notice, pursuant to the conditions specified in his employment agreement, in which event he would then be entitled to certain accrued obligations. We may also terminate Dr. Lee by providing twelve weeks advance written notice, in which event he would then be entitled to certain accrued obligations. Dr. Lee may terminate his employment with twelve weeks written notice and would then be entitled to certain accrued obligations.

Lee Kalowski, MBA. Under an employment agreement that became effective on July 31, 2017, Mr. Kalowski serves as our Chief Financial Officer and President. Mr. Kalowski currently receives a salary of $349,520 which is subject to review and adjustment in accordance with our policy. Mr. Kalowski is eligible to receive an annual discretionary cash bonus of up to 25% of his base salary, based on the achievement of certain performance goals, including corporate objectives, strategic initiatives and regulatory and clinical milestones, established our board of directors. Mr. Kalowski was also granted an option to purchase 97,813 ordinary shares, of which eighty percent (80%) vest over four (4) years, and twenty percent (20%) of which vest on the earlier of: (i) four years from the date of the option grant or (ii) the date on which our board of directors determines that we have received income of $22.19 million in respect of our collaborations with AstraZeneca, Oxurion and any future collaboration partners. Mr. Kalowski is eligible to participate in our employee benefit plans generally available to our executive employees, subject to the terms of

those plans. Mr. Kalowski's employment has no specified term, but can be terminated at will by either party. Mr. Kalowski can be terminated with cause, at any time, pursuant to us providing him with written notice, in which event he would be entitled to certain accrued obligations. Mr. Kalowski can also be terminated without cause, and if so, he would receive his base salary and other benefits including health insurance payments for three months after his termination date along with other accrued obligations. The termination benefits would be contingent upon Mr. Kalowski signing a general release of claims upon his termination. Mr. Kalowski may terminate his employment with 60 days written notice to us and would then be entitled to certain accrued obligations.

Maria Koehler, M.D., Ph.D. Under an employment agreement that became effective on September 18, 2017, Dr. Koehler became our Chief Medical Officer. Dr. Koehler currently receives a salary of $385,500, which is subject to review and positive adjustment in accordance with our policy. Dr. Koehler was granted a sign-on award of $60,000, which must be repaid if Dr. Koehler leaves our company within 24 months of the effective date of her employment. Dr. Koehler is eligible to receive an annual discretionary cash bonus of up to 30% of her base salary, based on the achievement of certain performance goals, including corporate objectives, strategic initiatives and regulatory and clinical milestones, established by our board of directors. Dr. Koehler was also granted an option to purchase 75,241 ordinary shares, of which eighty percent (80%) vest over four years, and twenty percent (20%) of which vest on the earlier of: (i) four years from the date of the option grant or (ii) the date on which our board of directors determines that we have received income of $22.2 million in respect of our collaborations with AstraZeneca, Oxurion and collaboration partners. Dr. Koehler is eligible to participate in our employee benefit plans generally available to our executive employees, subject to the terms of those plans. Dr. Koehler's employment has no specified term, but may be terminated at will by us or Dr. Koehler. Dr. Koehler can be terminated with cause, at any time, pursuant to us providing her written notice, in which case she would be entitled to certain accrued obligations. Dr. Koehler can also be terminated without cause, and if so, she would receive her base salary and other benefits including health insurance payments for three months after her termination date along with other accrued obligations. The termination benefits would be contingent upon Dr. Koehler signing a general release of claims upon her termination. Dr. Koehler may terminate her employment with 60 days written notice and would then be entitled to certain accrued obligations.

Outstanding Equity Awards at Fiscal Year-End — 2018

The following table summarizes, for each of our named executive officers, the number of ordinary shares underlying outstanding share options and share awards held as of December 31, 2018.

	Option Awards[1]				
Name	Grant Date	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)[3]	Option Expiration Date
Kevin Lee, Ph.D., MBA	12/17/2018[1]	—	115,287	$ 0.01	12/13/2029
Lee Kalowski, MBA	7/24/2017[2]	47,276	50,537	$ 2.12	7/23/2027
Maria Koehler, M.D., Ph.D.	9/18/2017[2]	33,858	41,383	$ 2.53	1/30/2028

(1) Commencing as of January 23, 2019, 5,579.6 of the shares subject to the option will vest every month through September 23, 2019; commencing as of October 23, 2019, 3,942.1 of the shares subject to the option will vest every month through March 23, 2020; commencing as of April 23, 2020, 3,155.1 of the shares subject to the option will vest every month through October 23, 2010; and commencing November 23, 2020, 2,761.7 of the shares subject to the option will vest every month through May 23, 2021, in each case provided that the named executive officer remains continuously employed with us through each applicable vesting date. The shares subject to the option are not early exercisable.

(2) 20% of the shares subject to the option will vest on the first anniversary of the grant date, 60% of the shares subject to the option will vest each month thereafter in 36 equal monthly installments, and the remaining 20% of the shares subject to the option will vest on the earlier of (i) the fourth anniversary of the grant date and (ii) the date in which our board of directors determines that we have received income of $22.2 million with respect to our collaborations with AstraZeneca, Oxurion, and any certain other collaborations, in all cases provided that the named executive officer remains continuously employed with us through each applicable vesting date.

(3) The amounts reported have been converted from GBP to USD using an exchange rate of $1.2763 to £1.00 as of December 31, 2018.

Equity Incentive Plans and Option Agreements

Option Agreements

On December 17, 2018, our board of directors approved the form of the unapproved bilateral option agreement for U.K. employees pursuant to which options to subscribe for ordinary shares can be granted to our employees and executive directors.

We have reserved 1,611,226 ordinary shares for the employee share option pool (amount to 16% of our issued share capital on a fully diluted basis) of which 520,797 ordinary shares have been issued, options for over 604,444 ordinary shares have been granted and 485,985 ordinary shares remain unallocated in the employee share option pool. Our board may act to increase the number of ordinary shares available for issuance.

In connection with certain corporate transactions, including a subdivision or consolidation or any other event that may affect the value of the options, the compensation committee has discretion to take action to prevent the dilution or enlargement of intended benefits, or to facilitate the transaction or event. In addition, in the event of a change in control, the compensation committee may accelerate the vesting and exercisability of any option in its discretion.

Our board of directors may amend the option agreement for future issuances of options at any time. However, no amendment may affect an award which has already been granted without the consent of the affected grantee.

2019 Share Option and Incentive Plan

Our 2019 Plan was adopted by our board of directors on , 2019 and approved by our shareholders on , 2019 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The 2019 Plan will be utilized for all future share incentive awards following the closing of our initial public offering. The 2019 Plan allows the compensation committee to make equity-based and cash-based incentive awards to our officers, employees, directors and other key persons (including consultants). Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares.

We have initially reserved ordinary shares, or the Initial Limit, for the issuance of awards under the 2019 Plan. The 2019 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2020, by % of the outstanding number of ordinary shares on the immediately preceding December 31, or such lesser number of shares as determined by our compensation committee, or the Annual Increase. This number is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

The shares we issue under the 2019 Plan will be authorized but unissued shares or shares that we reacquire. The ordinary shares underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by us prior to vesting, satisfied without any issuance of shares, expire or are otherwise

terminated (other than by exercise) under the 2019 Plan and or the awards that we granted prior to this offering will be added back to the ordinary shares available for issuance under the 2019 Plan.

Share options and share appreciation rights with respect to no more than ordinary shares may be granted to any one individual in any one calendar year. The maximum aggregate number of shares that may be issued in the form of incentive share options shall not exceed the Initial Limit cumulatively increased on January 1, 2020 and on each January 1 thereafter by the lesser of the Annual Increase for such year or ordinary shares.

The 2019 Plan will be administered by our compensation committee. Our compensation committee has full power to select, from among the individuals eligible for awards, the individuals to whom awards will be granted, to make any combination of awards to participants, and to determine the specific terms and conditions of each award, subject to the provisions of the 2019 Plan. Persons eligible to participate in the 2019 Plan will be those full or part-time officers, employees, non-employee directors and other key persons (including consultants) as selected from time to time by our compensation committee in its discretion.

The 2019 Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under Section 422 of the Code, and options that do not so qualify. The option exercise price of each option will be determined by our compensation committee but may not be less than 100% of the fair market value of our ordinary shares on the date of grant. The term of each option will be fixed by our compensation committee and may not exceed 10 years from the date of grant. Our compensation committee will determine at what time or times each option may be exercised.

Our compensation committee may award share appreciation rights subject to such conditions and restrictions as it may determine. Share appreciation rights entitle the recipient to ordinary shares, or cash, equal to the value of the appreciation in our share price over the exercise price. The exercise price of each share appreciation right may not be less than 100% of the fair market value of the ordinary shares on the date of grant.

Our compensation committee may award restricted shares and restricted share units to participants subject to such conditions and restrictions as it may determine. These conditions and restrictions may include the achievement of certain performance goals and/or continued employment with us through a specified vesting period. Our compensation committee may also grant ordinary shares that are free from any restrictions under the 2019 Plan. Unrestricted shares may be granted to participants in recognition of past services or other valid consideration and may be issued in lieu of cash compensation due to such participant. Our compensation committee may grant cash bonuses under the 2019 Plan to participants, subject to the achievement of certain performance goals.

The 2019 Plan provides that in the case of, and subject to, the consummation of a "sale event" as defined in the 2019 Plan, all outstanding awards may be assumed, substituted or otherwise continued by the successor entity. To the extent that the successor entity does not assume, substitute or otherwise continue such awards, then (i) all share options and share appreciation rights will automatically become fully exercisable and the restrictions and conditions on all other awards with time-based conditions will automatically be deemed waived, and awards with conditions and restrictions relating to the attainment of performance goals may become vested and non-forfeitable in connection with a sale event in the compensation committee's discretion and (ii) upon the effectiveness of the sale event, the 2019 Plan and all awards will automatically terminate. In the event of such termination, (i) individuals holding options and share appreciation rights will be permitted to exercise such options and share appreciation rights (to the extent exercisable) prior to the sale event; or (ii) we may make or provide for a cash payment to participants holding options and share appreciation rights equal to the difference between the per

share cash consideration payable to shareholders in the sale event and the exercise price of the options or share appreciation rights (to the extent then exercisable).

Our board of directors may amend or discontinue the 2019 Plan and our compensation committee may amend the exercise price of options and amend or cancel outstanding awards for purposes of satisfying changes in law or any other lawful purpose but no such action may adversely affect rights under an award without the holder's consent. Certain amendments to the 2019 Plan require the approval of our shareholders. No awards may be granted under the 2019 Plan after the date that is 10 years from the date of shareholder approval. No awards under the 2019 Plan have been made prior to the date of this prospectus.

2019 Employee Share Purchase Plan

Our 2019 Employee Share Purchase Plan, or the ESPP, was adopted by our board of directors on , 2019 and approved by our shareholders on , 2019 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The ESPP is intended to qualify as an "employee share purchase plan" within the meaning of Section 423(b) of the Code. Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares. The ESPP initially reserves and authorizes the issuance of up to a total of ordinary shares to participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2020 and each January 1 thereafter through January 1, 2029, by the least of (i) % of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) shares or (iii) such number of shares as determined by the ESPP administrator. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

All employees who have completed at least days of employment and whose customary employment is for more than hours per week are eligible to participate in the ESPP. However, any employee who owns 5% or more of the total combined voting power or value of all classes of shares is not eligible to purchase shares under the ESPP.

We will make one or more offerings each year to our employees to purchase shares under the ESPP. Unless otherwise determined by our compensation committee, offerings will usually begin on each January 1 and July 1 and will continue for six-month periods, referred to as offering periods. Each eligible employee may elect to participate in any offering by submitting an enrollment form at least 15 business days before the relevant offering date.

Each employee who is a participant in the ESPP may purchase shares by authorizing payroll deductions of up to % of his or her base compensation during an offering period. Unless the participating employee has previously withdrawn from the offering, his or her accumulated payroll deductions will be used to purchase shares on the last business day of the offering period at a price equal to 85% of the fair market value of the shares on the first business day or the last business day of the offering period, whichever is lower. Under applicable U.S. tax rules, an employee may purchase no more than $ worth of ordinary shares, valued at the start of the purchase period, under the ESPP in any calendar year.

The accumulated payroll deductions of any employee who is not a participant on the last day of an offering period will be refunded. An employee's rights under the ESPP terminate upon voluntary withdrawal from the plan or when the employee ceases employment with us for any reason.

The ESPP may be terminated or amended by our board of directors at any time. An amendment that increases the number of ordinary shares authorized under the ESPP and certain other amendments require the approval of our shareholders.

Pension Plan

We currently maintain a personal pension plan provided by Scottish Widows Group where we make contributions to our U.K. eligible employee's personal pension plan as selected by the Company. Each participant may make additional contributions at his or her discretion.

401(k) Plan

We maintain a tax-qualified retirement plan that provides eligible U.S. employees with an opportunity to save for retirement on a tax-advantaged basis. Plan participants are able to defer eligible compensation subject to applicable annual Code limits. We have the ability to make discretionary contributions to the 401(k) plan and currently match each participant's contribution up to a maximum of 4% of their eligible compensation The 401(k) plan is intended to be qualified under Section 401(a) of the Code with the 401(k) plan's related trust intended to be tax exempt under Section 501(a) of the Code. As a tax-qualified retirement plan, contributions to the 401(k) plan and earnings on those contributions are not taxable to the employees until distributed from the 401(k) plan.

Senior Executive Cash Incentive Bonus Plan

In 2019, our board of directors adopted the Senior Executive Cash Incentive Bonus Plan, or the Bonus Plan. The Bonus Plan provides for cash bonus payments based upon the attainment of performance targets established by our compensation committee. The payment targets will be related to financial and operational measures or objectives with respect to our company, or corporate performance goals, as well as individual performance objectives.

Our compensation committee may select corporate performance goals from among the following: achievement of cash flow (including, but not limited to, operating cash flow and free cash flow); research and development, publication, clinical and/or regulatory milestones; earnings before interest, taxes, depreciation and amortization; net income (loss) (either before or after interest, taxes, depreciation and/or amortization); changes in the market price of our ADSs; economic value-added; acquisitions or strategic transactions, including licenses, collaborations, joint ventures or promotion arrangements; operating income (loss); return on capital, assets, equity, or investment; total shareholder returns; coverage decisions; productivity; expense efficiency; margins; operating efficiency; working capital; earnings (loss) per share of our ADSs; sales or market shares; number of prescriptions or prescribing physicians; revenue; corporate revenue; operating income and/or net annual recurring revenue, any of which may be (A) measured in absolute terms or compared to any incremental increase, (B) measured in terms of growth, (C) compared to another company or companies or to results of a peer group, (D) measured against the market as a whole and/or as compared to applicable market indices and/or (E) measured on a pre-tax or post-tax basis (if applicable).

Each executive officer who is selected to participate in the Bonus Plan will have a target bonus opportunity set for each performance period. The bonus formulas will be adopted in each performance period by the compensation committee and communicated to each executive. The corporate performance goals will be measured at the end of each performance period after our financial reports have been published or such other appropriate time as the compensation committee determines. If the corporate performance goals and individual performance objectives are met, payments will be made as soon as practicable following the end of each performance

period. Subject to the rights contained in any agreement between the executive officer and us, an executive officer must be employed by us on the bonus payment date to be eligible to receive a bonus payment. The Bonus Plan also permits the compensation committee to approve additional bonuses to executive officers in its sole discretion and provides the compensation committee with discretion to adjust the size of the award as it deems appropriate to account for unforeseen factors beyond management's control that affected corporate performance.

Insurance and Indemnification

To the extent permitted by the Companies Act, we are empowered to indemnify our directors against any liability they incur by reason of their directorship. We maintain directors' and officers' insurance to insure such persons against certain liabilities. We expect to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering.

In addition to such indemnification, we provide our directors and executive officers with directors' and officers' liability insurance.

Insofar as indemnification of liabilities arising under the Securities Act may be permitted to our board of directors, executive officers, or persons controlling us pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

NON-EMPLOYEE DIRECTOR COMPENSATION

Other than as set forth in the table and described more fully below, we did not pay any compensation or make any equity awards or non-equity awards to any of our non-employee directors during the year ended December 31, 2018. Directors may be reimbursed for travel and other expenses directly related to their activities as directors. Directors who also serve as employees receive no additional compensation for their service as directors. During the year ended December 31, 2018, Dr. Lee, our Chief Executive Officer, was a member of our board of directors, as well as an employee, and thus received no additional compensation for his services as a director. See the section titled "Executive Compensation" for more information about Dr. Lee's compensation for the year ended December 31, 2018. The following table presents the total compensation for each person who served as a non-employee director during the year ended December 31, 2018.

Name	Fees Earned or Paid in Cash ($)	Total ($)
Stephen Hoffman, M.D., Ph.D.[1]	9,000	9,000
Michael Anstey, DPhil[2]	—	—
Kate Bingham, MBA[2]	—	—
Deborah Harland, Ph.D., MBA[2]	—	—
Anja König, Ph.D.[2]	—	—
Eashwar Krishnan[2]	—	—
James Lee[2]	—	—
Carolyn Ng, Ph.D.[2]	—	—
Jason Rhodes, MBA[2]	—	—
Sir Greg Winter, FRS[2]	—	—

(1) As of December 31, 2018, Dr. Hoffman held restricted share awards for 56,430 ordinary shares. Dr. Hoffman departed from the board of directors on March 18, 2019.

(2) Each of Michael Anstey, Kate Bingham, Deborah Harland, Anja König, James Lee, Carolyn Ng, Jason Rhodes and Sir Greg Winter did not receive any compensation for the year ended December 31, 2018, and none of them held any outstanding equity awards as of December 31, 2018. James Lee resigned from the board of directors on July 12, 2018. Eashwar Krishnan joined the board of directors on December 22, 2018.

Prior to this offering, we did not have a formal policy to compensate our non-employee directors. Immediately prior to the completion of this offering, we intend to implement a formal policy pursuant to which our non-employee directors will be eligible to receive the following cash retainers and equity awards:

Annual Retainer for Board Membership	
Annual service on the board of directors (other than chair)	$
Additional Annual Retainer for Committee Membership	
Annual service as member of the audit committee (other than chair)	$
Annual service as chair of the audit committee	$
Annual service as member of the compensation committee (other than chair)	$
Annual service as chair of the compensation committee	$
Annual service as member of the nominating and corporate governance committee (other than chair)	$
Annual service as chair of the nominating and corporate governance committee	$

Our policy will provide that, upon initial election to our board of directors, each non-employee director will be granted an equity award having a fair market value of $, or the Initial Grant. In addition, on the date of each of our annual meeting of shareholders following the completion of

this offering, each non-employee director who will continue as a non-employee director following such meeting will be granted an annual equity award having a fair market value of $, or the Annual Grant. If a new non-employee director joins our board of directors on a date other than the date of our annual meeting of shareholders, such non-employee director will be granted a pro-rata portion of the Annual Grant, based on the time between his or her appointment and our next annual meeting of shareholders. The Initial Grant will vest in equal annual installments over three years, subject to continued service as a director through the applicable vesting dates. The Annual Grant will vest in full on the earlier of (i) the first anniversary of the grant date or (ii) our next annual meeting of shareholders, subject to continued service as a director through the applicable vesting date. Such awards are subject to full accelerated vesting upon the sale of our company.

Employee directors will receive no additional compensation for their service as a director.

We will reimburse all reasonable out-of-pocket expenses incurred by directors for their attendance at meetings of our board of directors or any committee thereof.

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Within this section, we have calculated the dollar amounts using the historical exchange rate as of the closing date of each transaction. Other than compensation arrangements, we describe below transactions and series of similar transactions, since January 1, 2015, to which we were a party or will be a party, in which:

- the amounts involved exceeded or will exceed $120,000 or 1% of our total assets at year end for the last two completed fiscal years; and
- any of our directors, executive officers or holders of more than 5% of our share capital, or any member of the immediate family of the foregoing persons, had or will have a direct or indirect material interest.

Compensation arrangements for our directors and named executive officers are described elsewhere in this prospectus.

Preferred Share Financings

Series A Financing

On October 6, 2014, we entered into a Series A Investment Agreement relating to BicycleRD Limited, pursuant to which we agreed to issue, and the subscribers agreed to subscribe for, up to 2,030,001 Series A convertible preferred shares at price of £10.00 per Series A preferred share in three tranches. We issued 811,998 Series A convertible preferred shares for an aggregate cash subscription price of $13.0 million on October 6, 2014. The Series A Investment Agreement provided for second and third closings based on the achievement of defined performance milestones. Subsequently, we and the subscribers (amongst others) amended the Series A Investment Agreement to increase the Series A convertible preferred shares issued in the second closing and reduce the Series A convertible preferred shares issued in the third closing. We issued 812,002 Series A convertible preferred shares for an aggregate cash subscription price of $11.5 million on March 11, 2016, and 406,001 Series A convertible preferred shares for an aggregate cash subscription price of $5.3 million on October 3, 2016.

The following table summarizes the participation in the Series A financing across all three tranches by any of our directors, executive officers, holders of more than 5% of our share capital, or any member of the immediate family of the foregoing persons.

Name	Series A Preferred Shares		Aggregate Purchase Price Paid
Sir Greg Winter[1]	30,000	£	300,000
Atlas Venture Fund VII LP[2]	451,299	£	4,512,990
Novartis Bioventures Ltd[2]	451,299	£	4,512,990
S.R. One, Limited	451,299	£	4,512,990
SVLS[3]	451,299	£	4,512,990

(1) Sir Greg Winter is a member of our board of directors.

(2) This entity holds, in the aggregate, more than 5% of our share capital.

(3) Consists of (i) 441,959 Series A convertible preferred shares held by SVLS Fund V LP and (ii) 9,340 Series A convertible preferred shares held by SVLS Fund V Strategic Partners LP. These entities together hold, in the aggregate, more than 5% of our share capital.

On May 26, 2017, we issued warrants to subscribe for 200,000 Series A convertible preferred shares (or equivalent ordinary shares if exercised prior to the consummation of an initial public offering) to certain existing shareholders of BicycleRD Limited.

The following table summarizes the issuance of warrants to subscribe for Series A convertible preferred shares to any of our directors, executive officers, holders of more than 5% of our share capital, or any member of the immediate family of the foregoing persons.

Name	Series A Preferred Share Warrants		Aggregate Exercise Price
Atlas Venture Fund VIII LP[(1)]	50,000	£	500
Novartis Bioventures Ltd[(1)]	50,000	£	500
Sir Greg Winter[(2)]	50,000	£	500

(1) This entity holds, in the aggregate, more than 5% of our share capital.

(2) Sir Greg Winter is a member of our board of directors.

Series B Financing

On May 26, 2017, we entered into a Series B Investment Agreement pursuant to which we agreed to issue, and the subscribers agreed to subscribe for 3,562,583 Series B convertible preferred shares (then called Series B convertible preferred shares) at a price per Series B1 convertible preferred share of £11.2278 in a single tranche for an aggregate cash subscription price of $51.9 million. In conjunction with the issue of the Series B1 convertible preferred shares, we also issued warrants to subscribe for up to 627,903 Series B1 convertible preferred shares to the subscribers of the Series B1 convertible preferred shares.

In addition, on October 27, 2017, we entered into an Amended and Restated Series B Investment Agreement relating to BicycleRD Limited, pursuant to which an unaffiliated investor subscribed for a further 384,615 Series B1 convertible preferred shares at a Series B1 convertible preferred shares per Series B1 convertible preferred shares of £13.00, in a single tranche for an aggregate cash subscription price of $6.6 million. In conjunction with this financing, we also issued warrants to subscribe for 115,384 Series B1 convertible preferred shares to the subscriber of the Series B1 convertible preferred shares.

The following table summarizes the participation in the Series B1 financing (on May 26, 2017 and October 27, 2017) by any of our directors, executive officers, holders of more than 5% of our share capital or any member of the immediate family of the foregoing persons.

Name	Series B1 Preferred Shares		Aggregate Purchase Price Paid
Atlas Venture Fund VIII LP[(1)]	133,596	£	1,499,989
Novartis Bioventures Ltd[(1)]	445,323	£	4,999,998
S.R. One, Limited[(1)]	445,323	£	4,999,998
SVLS[(2)]	445,323	£	4,999,998
Vertex Global Healthcare Fund I PTE. Ltd[(1)]	890,646	£	9,999,995
Cambridge Innovation Capital (Jersey) Limited[(1)]	757,049	£	8,499,995
Longwood Fund IV, L.P.[(1)]	445,323	£	4,999,998
Ahren Innovation Capital Holding Limited[(1)]	384,615	£	4,999,995

(1) This entity holds, in the aggregate, more than 5% of our share capital.

(2) Consists of (i) 436,107 Series B1 convertible preferred shares held by SVLS Fund V LP and (ii) 9,216 Series B1 convertible preferred shares held by SVLS Fund V Strategic Partners LP. These entities together hold, in the aggregate, more than 5% of our share capital.

The following table summarizes the issuance of warrants to subscribe for Series B1 convertible preferred shares (or equivalent ordinary shares if exercised prior to the consummation of an initial public offering) to any of our directors, executive officers, holders of more than 5% of our share capital, or any member of the immediate family of the foregoing persons.

Name	Series B1 Preferred Share Warrants	Aggregate Exercise Price
Vertex Global Healthcare Fund I PTE. Ltd[1]	267,193	£ 2,672
Cambridge Innovation Capital (Jersey) Limited[1]	227,114	£ 2,271
Longwood Fund IV, L.P.[1]	133,596	£ 1,336
Ahren Innovation Capital Holding Limited[1]	115,384	£ 1,154

(1) This entity holds, in the aggregate, more than 5% of our share capital.

Series B2 Financing

In December 2018, we entered into an investment agreement relating to Bicycle Therapeutics Limited pursuant to which we agreed to issue, and the subscribers agreed to subscribe for 1,403,633 Series B2 convertible preferred shares at a price per Series B2 preferred share of £15.55, for an aggregate cash subscription price of $27.4 million (such amount is translated into dollars from pounds sterling based on an exchange rate of $1.00 to £1.2570 as of December 14, 2018). In December 2018 (and in conjunction with the Series B2 financing), the existing holders of warrants to subscribe for Series B1 convertible preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 convertible preferred shares (or equivalent ordinary shares if exercised prior to the consummation of an initial public offering) in the proportions set out below and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 convertible preferred shares (or equivalent ordinary shares if exercised prior to the consummation of an initial public offering) to Aquila Investments IV, an entity affiliated with Tybourne Capital Management (HK) Limited, at an aggregate exercise price of £1,949.

Name	No. of Series B1 Warrants Surrendered
Vertex Global HC Fund I Pte. Ltd.[1]	68,918
Cambridge Innovation Capital (Jersey) Limited[1]	51,345
Longwood Fund IV, LP[1]	48,314
Entities associated with Ahren Innovation Capital Holding Limited[1]	26,334

(1) This entity holds or will hold, after giving effect to the Series B2 financing, in the aggregate, more than 5% of our share capital.

The following table summarizes the participation in the Series B2 financing by any of our directors, executive officers, holders of more than 5% of our share capital, or any member of the immediate family of the foregoing persons.

Name	Series B2 Preferred Shares	Aggregate Purchase Price Paid
An entity affiliated with Tybourne Capital Management (HK) Limited[(1)]	1,017,783	£15,826,526
Cambridge Innovation Capital (Jersey) Limited[(1)]	160,771	£2,499,989
Vertex Global Healthcare Fund I PTE. Ltd[(1)]	144,694	£2,249,992
Entities associated with Ahren Innovation Capital Holdings Limited[(1)]	80,385	£1,249,987

(1) This entity holds or will hold, after giving effect to the Series B2 financing, in the aggregate, more than 5% of our share capital.

Consulting Agreement

In March 2019, we entered into a consultancy agreement with Stone Sunny Isles, Inc., or Stone Sunny Isles, pursuant to which Stone Sunny Isles has agreed to make available Pierre Legault to provide advisory services to us as requested by our board of directors or our chief executive officer. In consideration for the provision of the advisory services, we pay Stone Sunny Isles a monthly retainer of £10,416, which is billed in U.S. Dollars. Pierre Legault is the President, Treasurer and Director of Stone Sunny Isles.

Consulting Agreement

In April 2016, we entered into a consulting agreement with 10X Capital, Inc., or 10X Capital, pursuant to which 10X Capital agreed to make available Stephen Hoffman to provide advisory services to us as requested by the board of directors or by our chief executive officer. In consideration for the provision of the advisory services, we paid 10X Capital a monthly fee of $5,912. We have served notice to terminate this agreement in accordance with its terms in conjunction with Mr. Hoffman's departure from the board of directors in March 2019.

Founder Royalty Arrangements

We have entered into two royalty agreements with our founders, Christian Heinis, John Tite, and Sir Gregory Winter, and our initial investors, Atlas Venture Fund VIII LP, Novartis Bioventures LTD. Pursuant to the first royalty agreement, we are obligated to pay a royalty percentage in the low single digits on net sales arising from products licensed under the Oxurion collaboration agreement. Pursuant to the second royalty agreement, we are obligated to pay a royalty percentage in the low single digits on net sales arising from products licensed under the AstraZeneca collaboration agreement.

Agreements with Our Executive Officers and Directors

We have entered into employment agreements with certain of our executive officers and service agreements with our non-executive directors. These agreements contain customary provisions and representations, including confidentiality, non-competition, non-solicitation and inventions assignment undertakings by the executive officers. However, the enforceability of the non-competition provisions may be limited under applicable law.

Indemnification Agreements

We intend to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering. These agreements and our articles of association to be effective upon the completion of this offering require us to indemnify our directors and executive officers to the fullest extent permitted by law.

In addition, we have previously entered into and intend to enter into new agreements to indemnify our directors and executive officers. These agreements will, among other things, indemnify our directors and executive officers against certain liabilities and expenses incurred by such persons in connection with claims made by reason of their being such a director or executive officer.

Agreements With Our Shareholders

In connection with the preferred share financings, we entered into subscription and shareholder agreements containing registration rights and information rights, among other things, with certain holders of our convertible preferred shares. These shareholder agreements will terminate upon the closing of this offering, except for the registration rights granted under our investors' rights agreement, as more fully described in "Description of Share Capital and Articles of Association—Registration Rights."

Related Person Transaction Policy

In connection with this offering, we have adopted a written related party transactions policy that such transactions must be approved by our audit committee. This policy will become effective on the date on which the registration statement of which this prospectus is part is declared effective by the SEC. Pursuant to this policy, the audit committee has the primary responsibility for reviewing and approving or disapproving "related person transactions," which are transactions between us and related persons in which the related person has a direct or indirect material interest. For purposes of this policy, a related person will be defined as a director, executive officer, nominee for director, or greater than 5% beneficial owner of any class of our voting securities, and their immediate family members.

PRINCIPAL SHAREHOLDERS

The following table sets forth certain information known to us regarding beneficial ownership of our share capital as of March 21, 2019 by:

- each person, or group of affiliated persons, known by us to be the beneficial owner of more than 5% of our voting securities;
- each of our named executive officers and other executive officers;
- each of our directors; and
- all of our executive officers and directors as a group.

Beneficial ownership is determined in accordance with the rules of the SEC and generally includes voting or investment power with respect to securities. Except as noted by footnote, and subject to community property laws where applicable, we believe based on the information provided to us that the persons and entities named in the table below have sole voting and investment power with respect to all securities shown as beneficially owned by them. The information is not necessarily indicative of beneficial ownership for any other purpose.

Beneficial ownership is determined in accordance with the rules of the SEC. These rules generally attribute beneficial ownership of securities to persons who possess sole or shared voting power or investment power with respect to those securities and include ordinary shares that can be acquired within 60 days of March 21, 2019. Ordinary shares underlying convertible securities that can be acquired within 60 days of March 21, 2019 are deemed to be beneficially owned by the persons holding these securities for the purpose of computing percentage ownership of that person, but are not treated as outstanding for the purpose of computing any other person's ownership percentage.

Percentage ownership calculations are based on shares (which includes of unvested restricted shares subject to repurchase by us) outstanding as of March 21, 2019, and gives effect to the conversion of all of the outstanding convertible preferred shares, into an aggregate of ordinary shares upon the completion of this offering. The percentage of shares beneficially owned after completion of this offering is based on ordinary shares outstanding after this offering, including ordinary shares in the form of ADSs issued in connection with this offering.

Except as otherwise indicated in the table below, addresses of the directors, executive officers and named beneficial owners are care of Bicycle Therapeutics Limited, Building 900 Babraham Research Campus, Babraham, Cambridge CB22 3AT, United Kingdom.

Name and Address of Beneficial Owner	Number of Ordinary Shares Beneficially Owned Prior to this Offering	Percentage of Ordinary Shares Beneficially Owned	
		Prior to this Offering	After this Offering
5% or Greater Shareholders			
Atlas Venture Fund VIII LP[1]		%	%
Novartis Bioventures Ltd[2]		%	%
S.R. One, Limited[3]		%	%
SVLS[4]		%	%
Vertex Global Healthcare Fund I PTE. Ltd[5]		%	%
Cambridge Innovation Capital (Jersey) Limited[6]		%	%
Longwood Fund IV, L.P.[7]		%	%
Ahren Innovation Capital Holding Limited[8]		%	%
Directors, Named Executive Officers and Other Executive Officers			
Kevin Lee, Ph.D., MBA[9]		%	%
Lee Kalowski, MBA[11]		%	%
Peter Leone, MBA			
Michael Skynner, Ph.D.[12]		%	%
Maria Koehler, M.D., Ph.D.[13]		%	%
Nick Keen, Ph.D.[14]		%	%
Pierre Legault, MBA, CPA[15]		%	%
Michael Anstey, DPhil[16]		%	%
Kate Bingham, MBA[17]		%	%
Deborah Harland, Ph.D., MBA[18]		%	%
Eashwar Krishnan[19]			
Anja König, Ph.D.[20]		%	%
Carolyn Ng, Ph.D.[21]		%	%
Jason Rhodes, MBA[22]		%	%
Sir Greg Winter, FRS[23]		%	%
All Directors and Executive Officers as a Group (15 people)		%	%

* Represents beneficial ownership of less than one percent.

DESCRIPTION OF SHARE CAPITAL AND ARTICLES OF ASSOCIATION

The following describes our issued share capital, summarizes the material provisions of our articles of association and highlights certain differences in corporate law in the United Kingdom and the United States. Please note that this summary is not intended to be exhaustive. For further information, please refer to the full version of our articles of association, which are included as an exhibit to the registration statement of which this prospectus is a part.

We were incorporated pursuant to the laws of England and Wales as Bicycle Therapeutics Limited on October 27, 2017.We are registered with the Registrar of Companies in England and Wales under number 11036004, and our registered office is at Building 900 Babraham Research Campus, Babraham, Cambridge CB22 3AT, United Kingdom.

Certain resolutions will be required to be passed by our shareholders prior to the completion of this offering. These will include resolutions for the:

- adoption of new articles of association that will become effective upon the completion of this offering. See "—Post-IPO Articles of Association" below;
- general authorization of our directors for purposes of Section 551 of the Companies Act to issue shares in the company and grant rights to subscribe for or convert any securities into shares in the company up to a maximum aggregate nominal amount of £ for a period of years; and
- empowering of our directors pursuant to Section 570 of Companies Act to issue equity securities for cash pursuant to the Section 551 authority referred to above as if the statutory preemption rights under Section 561(1) of the Companies Act did not apply to such allotments.

Issued Share Capital

As of December 31, 2018, the issued share capital of Bicycle Therapeutics Limited was 628,902 ordinary shares which includes 58,746 of unvested restricted shares subject to repurchase, 2,800,001 Series A convertible preferred shares, 3,947,198 Series B1 convertible preferred shares and 1,323,248 Series B2 convertible preferred shares. The nominal value of our ordinary shares, Series A convertible preferred shares, Series B1 convertible preferred shares and Series B2 convertible preferred shares is £0.01 per share and each issued ordinary share, Series A convertible preferred share, Series B1 convertible preferred share and Series B2 convertible preferred share is fully paid (or deemed paid up).

Ordinary Shares

In accordance with our articles of association to be in effect upon the completion of this offering, the following summarizes the rights of holders of our ordinary shares:

- each holder of our ordinary shares is entitled to one vote per ordinary share on all matters to be voted on by shareholders generally;
- the holders of the ordinary shares shall be entitled to receive notice of, attend, speak and vote at our general meetings; and
- holders of our ordinary shares are entitled to receive such dividends as are recommended by our directors and declared by our shareholders.

Registered Shares

We are required by the Companies Act to keep a register of our shareholders. Under English law, the ordinary shares are deemed to be issued when the name of the shareholder is entered in our share register. The share register therefore is prima facie evidence of the identity of our shareholders, and the shares that they hold. The share register generally provides limited, or no, information regarding the ultimate beneficial owners of our ordinary shares. Our share register is maintained by our registrar.

Holders of our ADSs will not be treated as one of our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see "Description of American Depositary Shares" in this prospectus.

Under the Companies Act, we must enter an allotment of shares in our share register as soon as practicable and in any event within two months of the allotment. We will perform all procedures necessary to update the share register to reflect the ordinary shares being sold in this offering, including updating the share register with the number of ordinary shares to be issued to the depositary upon the closing of this offering. We also are required by the Companies Act to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

We, any of our shareholders or any other affected person may apply to the court for rectification of the share register if:

- the name of any person, without sufficient cause, is wrongly entered in or omitted from our register of members; or
- there is a default or unnecessary delay in entering on the register the fact of any person having ceased to be a member or on which we have a lien, provided that such delay does not prevent dealings in the shares taking place on an open and proper basis.

Preemptive Rights

English law generally provides shareholders with preemptive rights when new shares are issued for cash; however, it is possible for the articles of association, or shareholders in general meeting, to exclude preemptive rights. Such an exclusion of preemptive rights may be for a maximum period of up to five years from the date of adoption of the articles of association, if the exclusion is contained in the articles of association, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). On , our shareholders approved the exclusion of preemptive rights for a period of five years from the date of approval, which exclusion will need to be renewed upon expiration (i.e., at least every five years) to remain effective, but may be sought more frequently for additional five-year terms (or any shorter period). On , our shareholders approved the exclusion of preemptive rights for the allotment of ordinary shares in connection with this offering.

Distributions and Dividends

Under the Companies Act, before a company can lawfully make a distribution or dividend, it must ensure that it has sufficient distributable reserves, as determined on a non-consolidated basis. The basic rule is that a company's profits available for the purpose of making a distribution are its accumulated, realized profits, so far as not previously utilized by distribution or capitalization, less

its accumulated, realized losses, so far as not previously written off in a reduction or reorganization of capital duly made. The requirement to have sufficient distributable reserves before a distribution or dividend can be paid applies to us and to each of our subsidiaries that has been incorporated under English law.

Once we are a public company, it will not be sufficient that we have made a distributable profit for the purpose of making a distribution. An additional capital maintenance requirement will be imposed on us to ensure that the net worth of the company is at least equal to the amount of its capital. A public company can only make a distribution:

- if, at the time that the distribution is made, the amount of its net assets (that is, the total excess of assets over liabilities) is not less than the total of its called up share capital and undistributable reserves; and
- if, and to the extent that, the distribution itself, at the time that it is made, does not reduce the amount of its net assets to less than that total.

Disclosure of Interest in Shares

Pursuant to Part 22 of the Companies Act, a company is empowered by notice in writing to require any person whom the company knows to be, or has reasonable cause to believe to be, interested in the company's shares or at any time during the three years immediately preceding the date on which the notice is issued to have been so interested, within a reasonable time to disclose to the company details of that person's interest and (so far as is within such person's knowledge) details of any other interest that subsists or subsisted in those shares.

If a shareholder defaults in supplying the company with the required details in relation to the shares in question, or the Default Shares, the shareholder shall not be entitled to vote or exercise any other right conferred by membership in relation to general meetings. Where the Default Shares represent 0.25% or more of the issued shares of the class in question, the directors may direct that:

- any dividend or other money payable in respect of the Default Shares shall be retained by the company without any liability to pay interest on it when such dividend or other money is finally paid to the shareholder; and/or
- no transfer by the relevant shareholder of shares (other than a transfer approved in accordance with the provisions of the company's articles of association) may be registered (unless such shareholder is not in default and the transfer does not relate to default shares).

Purchase of Own Shares

English law permits a public limited company to purchase its own shares out of the distributable profits of the company or the proceeds of a fresh issue of shares made for the purpose of financing the purchase, subject to complying with procedural requirements under the Companies Act and provided that its articles of association do not prohibit it from doing so. Our articles of association, a summary of which is provided above, do not prohibit us from purchasing our own shares. A public limited company must not purchase its own shares if, as a result of the purchase, there would no longer be any issued shares of the company other than redeemable shares or shares held as treasury shares.

Any such purchase will be either a "market purchase" or "off market purchase," each as defined in the Companies Act. A "market purchase" is a purchase made on a "recognized investment exchange (other than an overseas exchange) as defined in the UK Financial Services and Markets Act 2000, or FSMA. An "off market purchase" is a purchase that is not made on a "recognized investment exchange." Both "market purchases" and "off market purchases" require

prior shareholder approval by way of an ordinary resolution. In the case of an "off market purchase," a company's shareholders, other than the shareholders from whom the company is purchasing shares, must approve the terms of the contract to purchase shares and in the case of a "market purchase," the shareholders must approve the maximum number of shares that can be purchased and the maximum and minimum prices to be paid by the company.

Nasdaq is an "overseas exchange" for the purposes of the Companies Act and does not fall within the definition of a "recognized investment exchange" for the purposes of FSMA and any purchase made by us would need to comply with the procedural requirements under the Companies Act that regulate "off market purchases."

A share buy back by a company of its shares will give rise to U.K. stamp duty reserve tax and stamp duty at the rate of 0.5% of the amount or value of the consideration payable by the company (rounded up to the next £5.00), and such stamp duty reserve tax or duty will be paid by the company. The charge to stamp duty reserve tax will be canceled or, if already paid, repaid (generally with interest), where a transfer instrument for stamp duty purposes has been duly stamped within six years of the charge arising (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

Our articles of association do not have conditions governing changes to our capital which are more stringent that those required by law.

Shareholder Rights

Certain rights granted under the Companies Act, including the right to requisition a general meeting or require a resolution to be put to shareholders at the annual general meeting, are only available to our members. For English law purposes, our members are the persons who are registered as the owners of the legal title to the shares and whose names are recorded in our register of members. In the case of shares held in a settlement system operated by the Depository Trust Company, or DTC, the registered member will be DTC's nominee, Cede & Co. If a person who holds their ADSs in DTC wishes to exercise certain of the rights granted under the Companies Act, they may be required to first take steps to withdraw their ADSs from the settlement system operated by DTC and become the registered holder of the shares in our register of members. A withdrawal of shares from DTC may have tax implications, for additional information on the potential tax implications of withdrawing your shares from the settlement system operated by DTC, see "Material Tax Considerations—United Kingdom Taxation."

Registration Rights

Upon the completion of this offering, the holders of shares of our ordinary shares issuable upon the conversion of our convertible preferred shares plus the ordinary shares issued as bonus shares to holders of convertible preferred shares and the ordinary shares issued on exercise of the warrants held by the holders of convertible preferred shares, will be entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of a registration rights agreement between us and holders of the holders of the convertible preferred shares. The registration rights agreement includes demand registration rights, short-form registration rights and piggyback registration rights.

Demand Registration Rights

Beginning 180 days after the effective date of the registration statement of which this prospectus forms a part, the holders of shares of our ordinary shares issuable upon the conversion of convertible preferred shares upon closing of this offering are entitled to demand registration rights. Under the terms of the registration rights agreement, we will be required, upon

the written request of holders of a majority of these securities to file a registration statement and use best efforts to effect the registration of all or a portion of these shares for public resale. We are required to effect only two registrations pursuant to this provision of the investment and shareholders' agreement.

Short-Form Registration Rights

Pursuant to the registration rights agreement, if we are eligible to file a registration statement on Form F-3 or Form S-3, upon the written request a holder of securities at an aggregate offer price of at least $10 million, we will be required to effect a registration of such shares. We are required to effect only two registrations in any twelve month period pursuant to this provision of the registration rights agreement. The right to have such shares registered on Form F-3 or Form S-3 is further subject to other specified conditions and limitations.

Piggyback Registration Rights

Pursuant to the registration rights agreement, if we register any of our securities either for our own account or for the account of other security holders, other than in connection with our initial public offering or a registration for any employee benefit plan, corporate reorganization, or the offer or sale of debt securities, the holders of the relevant shares (for so long as they are a party to the registration rights agreement) are entitled to include their shares in the registration. Subject to certain exceptions contained in the registration rights agreement, we and the underwriters may limit the number of shares included in the underwritten offering to the number of shares which we and the underwriters determine in our sole discretion will not jeopardize the success of the offering.

Indemnification

Our registration rights agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of Registration Rights

The registration rights granted under the registration rights agreement will terminate on the earliest of (i) in respect of any holder, at such time as the holder holds less than 1% of the Company's outstanding ordinary shares; (ii) the three anniversary of the completion of this offering and (iii) such time as the Company has completion the offering and all relevant ordinary shares may be sold pursuant to rule 144 during a 90 day period without registration.

Post-IPO Articles of Association

Our Articles of Association, or the Articles, were approved by our shareholders on and were adopted with effect from the completion of the offering. A summary of the terms of the Articles is set out below. The summary below is not a complete copy of the terms of the Articles.

The Articles contain no specific restrictions on our purpose and therefore, by virtue of section 31(1) of the Companies Act, our purpose is unrestricted.

The Articles contain, among other things, provisions to the following effect:

Share Capital

Our share capital will consist of ordinary shares. We may issue shares with such rights or restrictions as may be determined by ordinary resolution, including shares which are to be redeemed, or are liable to be redeemed at our option or the holder of such shares.

Voting

The shareholders have the right to receive notice of, and to vote at, our general meetings. Each shareholder who is present in person (or, being a corporation, by representative) at a general meeting on a show of hands has one vote and, on a poll, every such holder who is present in person (or, being a corporation, by representative) or by proxy has one vote in respect of every share held by him.

Variation of Rights

Whenever our share capital is divided into different classes of shares, the special rights attached to any class may be varied or abrogated either with the consent in writing of the holders of three-fourths in nominal value of the issued shares of that class or with the sanction of a special resolution passed at a general meeting of the holders of the shares of that class and may be so varied and abrogated whilst the company is a going concern.

Dividends

We may, subject to the provisions of the Companies Act and the Articles, by ordinary resolution from time to time declare dividends to be paid to shareholders not exceeding the amount recommended by our board of directors. Subject to the provisions of the Companies Act, in so far as, in the board of directors' opinions, our profits justify such payments, the board of directors may pay interim dividends on any class of our shares.

Any dividend unclaimed after a period of 12 years from the date such dividend was declared or became payable shall, if the board of directors resolve, be forfeited and shall revert to us. No dividend or other moneys payable on or in respect of a share shall bear interest as against us.

Liquidation Preference

On a distribution of assets on a liquidation, the surplus assets remaining after payment of liabilities shall be distributed among the holders of ordinary shares pro rata to the number of ordinary shares held.

Transfer of Ordinary Shares

Each member may transfer all or any of his shares which are in certificated form by means of an instrument of transfer in any usual form or in any other form which the board of directors may approve. Each member may transfer all or any of his shares which are in uncertificated form by means of a "relevant system" (i.e., the CREST System) in such manner provided for, and subject as provided in, the CREST Regulations.

The Board may, in its absolute discretion, refuse to register a transfer of certificated shares unless:

(i) it is for a share which is fully paid up;

(ii) it is for a share upon which the company has no lien;

(iii) it is only for one class of share;

(iv) it is in favor of a single transferee or no more than four joint transferees;

(v) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the board of directors to be exempt from stamp duty; and

(vi) it is delivered for registration to the registered office of the company (or such other place as the board of directors may determine), accompanied (except in the case of a transfer by a person to whom the company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the board of directors may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

The board of directors may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the CREST Regulations and the CREST System.

Allotment of Shares and Preemption Rights

Subject to the Companies Act and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the board of directors may determine (including shares which are to be redeemed, or are liable to be redeemed at the option of the company or the holder of such shares).

In accordance with section 551 of the Companies Act, the board of directors may be generally and unconditionally authorized to exercise all the powers of the company to allot shares up to an aggregate nominal amount equal to the amount stated in the relevant ordinary resolution authorizing such allotment. The authorities passed on 2019 and remains in force at the date of this prospectus.

The provisions of section 561 of the Companies Act (which confer on shareholders rights of preemption in respect of the allotment of equity securities which are paid up in cash) apply to the company except to the extent disapplied by special resolution of the company. Such preemption rights have been disapplied pursuant to the special resolution passed on 2019.

Alteration of Share Capital

The company may by ordinary resolution consolidate or divide all of its share capital into shares of larger nominal value than its existing shares, or cancel any shares which, at the date of the ordinary resolution, have not been taken or agreed to be taken by any person and diminish the amount of its share capital by the nominal amount of shares so cancelled or sub-divide its shares, or any of them, into shares of smaller nominal value.

The company may, in accordance with the Companies Act, reduce or cancel its share capital or any capital redemption reserve or share premium account in any manner and with and subject to any conditions, authorities and consents required by law.

Board of Directors

Unless otherwise determined by the company by ordinary resolution, the number of directors (other than any alternate directors) shall not be less than two, but there shall be no maximum number of directors.

Subject to the Articles and the Companies Act, the company may by ordinary resolution appoint a person who is willing to act as a director and the board of directors shall have power at any time to appoint any person who is willing to act as a director, in both cases either to fill a vacancy or as an addition to the existing board of directors.

The Articles of Association provide that upon completion of this offering, our board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution.

Subject to the provisions of the Articles, the board of directors may regulate their proceedings as they deem appropriate. A director may, and the secretary at the request of a director shall, call a meeting of the directors.

The quorum for a meeting of the board of directors shall be fixed from time to time by a decision of the board of directors, but it must never be less than two and unless otherwise fixed, it is two.

Questions and matters requiring resolution arising at a meeting shall be decided by a majority of votes of the participating directors, with each director having one vote. In the case of an equality of votes, the chairman will only have a casting vote or second vote when an acquisition has been completed.

Directors shall be entitled to receive such remuneration as the board shall determine for their services to the company as directors, and for any other service which they undertake for the company provided that the aggregate fees payable to the directors must not exceed £ per annum. The directors shall also be entitled to be paid all reasonable expenses properly incurred by them in connection with their attendance at meetings of shareholders or class meetings, board of director or committee meetings or otherwise in connection with the exercise of their powers and the discharge of their responsibilities in relation to the company.

The board of directors may, in accordance with the requirements in the Articles, authorize any matter proposed to them by any director which would, if not authorized, involve a director breaching his duty under the Companies Act, to avoid conflicts of interests.

A director seeking authorization in respect of such conflict shall declare to the board of directors the nature and extent of his interest in a conflict as soon as is reasonably practicable. The director shall provide the board with such details of the matter as are necessary for the board to decide how to address the conflict together with such additional information as may be requested by the board.

Any authorization by the board of directors will be effective only if:

(i) to the extent permitted by the Companies Act, the matter in question shall have been proposed by any director for consideration in the same way that any other matter may be proposed to the directors under the provisions of the Articles;

(ii) any requirement as to the quorum for consideration of the relevant matter is met without counting the conflicted director and any other conflicted director; and

(iii) the matter is agreed to without the conflicted director voting or would be agreed to if the conflicted director's and any other interested director's vote is not counted.

Subject to the provisions of the Companies Act, every director, secretary or other officer of the company (other than an auditor) is entitled to be indemnified against all costs, charges, losses, damages and liabilities incurred by him in the actual purported exercise or discharge of his duties or exercise of his powers or otherwise in relation to them.

General Meetings

The company must convene and hold general meetings in accordance with the Companies Act. Under the Companies Act, an annual general meeting must be called by notice of at least 21 days and a general meeting must be called by notice of at least 14 days.

No business shall be transacted at any general meeting unless a quorum is present when the meeting proceeds to business, but the absence of a quorum shall not preclude the choice or appointment of a chairman of the meeting which shall not be treated as part of the business of the meeting. Save as otherwise provided by the Articles, two shareholders present in person or by proxy and entitled to vote shall be a quorum for all purposes.

Borrowing Powers

Subject to the Articles and the Companies Act, the board of directors may exercise all of the powers of the company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the company or of any third party.

Capitalization of Profits

The directors may, if they are so authorized by an ordinary resolution of the shareholders, decide to capitalize any undivided profits of the company (whether or not they are available for distribution), or any sum standing to the credit of the company's share premium account or capital redemption reserve. The directors may also, subject to the aforementioned ordinary resolution, appropriate any sum which they so decide to capitalize to the persons who would have been entitled to it if it were distributed by way of dividend and in the same proportions.

Limitation on Owning Securities

Our articles of association do not restrict in any way the ownership or voting of our shares by non-residents.

Uncertificated Shares

Subject to the Companies Act, the board of directors may permit title to shares of any class to be issued or held otherwise than by a certificate and to be transferred by means of a "relevant system" (i.e., the CREST System) without a certificate.

The board of directors may take such steps as it sees fit in relation to the evidencing of and transfer of title to uncertificated shares, any records relating to the holding of uncertificated shares and the conversion of uncertificated shares to certificated shares, or vice-versa.

The company may by notice to the holder of an uncertificated share, require that share to be converted into certificated form.

The board of directors may take such other action that the board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of an uncertified share or otherwise to enforce a lien in respect of it.

Other Relevant Laws and Regulations

Mandatory Bid

(i) The Takeover Code will apply to the company for so long as its central management and control is considered to be in the United Kingdom. Under the Takeover Code, where:

(a) any person, together with persons acting in concert with him, acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares in which he is already interested, and in which persons acting in concert with him are interested) carry 30% or more of the voting rights of a company; or

(b) any person who, together with persons acting in concert with him, is interested in shares which in the aggregate carry not less than 30% of the voting rights of a company but does not hold shares carrying more than 50% of such voting rights and such person, or any person acting in concert with him, acquires an interest in any other shares which increases the percentage of shares carrying voting rights in which he is interested;

such person shall, except in limited circumstances, be obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights. Offers for different classes of equity share capital must be comparable; the Takeover Panel should be consulted in advance in such cases.

(ii) An offer under Rule 9 of the Takeover Code must be in cash and at the highest price paid for any interest in the shares by the person required to make an offer or any person acting in concert with him during the 12 months prior to the announcement of the offer.

(iii) Under the Takeover Code, a "concert party" arises where persons acting together pursuant to an agreement or understanding (whether formal or informal and whether or not in writing) actively cooperate, through the acquisition by them of an interest in shares in a company, to obtain or consolidate control of the company. "Control" means holding, or aggregate holdings, of an interest in shares carrying 30% or more of the voting rights of the company, irrespective of whether the holding or holdings give *de facto* control.

Squeeze-Out

(i) Under sections 979 to 982 of the Companies Act, if an offeror were to acquire, or unconditionally contract to acquire, not less than 90% of the ordinary shares of the company, it could then compulsorily acquire the remaining 10%. It would do so by sending a notice to outstanding shareholders telling them that it will compulsorily acquire their shares, provided that no such notice may be served after the end of: (a) the period of three months beginning with the day after the last day on which the offer can be accepted; or (b) if earlier, and the offer is not one to which section 943(1) of the Companies Act applies, the period of six months beginning with the date of the offer.

(ii) Six weeks following service of the notice, the offeror must send a copy of it to the company together with the consideration for the ordinary shares to which the notice relates, and an instrument of transfer executed on behalf of the outstanding shareholder(s) by a person appointed by the offeror.

(iii) The company will hold the consideration on trust for the outstanding shareholders.

Sell-out

(i) Sections 983 to 985 of the Companies Act also give minority shareholders in the company a right to be bought out in certain circumstances by an offeror who has made a takeover offer. If a takeover offer relating to all the ordinary shares of the company is made at any time before the end of the period within which the offer could be accepted and the offeror held or had agreed to acquire not less than 90% of the ordinary shares, any holder of shares to which the offer related who had not accepted the offer could by a written communication to the offeror require it to acquire those shares. The offeror is required to give any shareholder notice of his right to be bought out within one month of that right arising. The offeror may impose a time limit on the rights of minority shareholders to be bought out, but that period cannot end less than three months after the end of the acceptance period, or, if longer a period of three months from the date of the notice.

(ii) If a shareholder exercises his rights, the offeror is bound to acquire those shares on the terms of the offer or on such other terms as may be agreed.

Differences in Corporate Law

The applicable provisions of the Companies Act differ from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of certain differences between the provisions of the Companies Act applicable to us and the General Corporation Law of the State of Delaware relating to shareholders' rights and protections. This summary is not intended to be a complete discussion of the respective rights and it is qualified in its entirety by reference to Delaware law and English law.

	England and Wales	Delaware
Number of Directors	Under the Companies Act, a public limited company must have at least two directors and the number of directors may be fixed by or in the manner provided in a company's articles of association.	Under Delaware law, a corporation must have at least one director and the number of directors shall be fixed by or in the manner provided in the bylaws.

	England and Wales	Delaware
Removal of Directors	Under the Companies Act, shareholders may remove a director without cause by an ordinary resolution (which is passed by a simple majority of those voting in person or by proxy at a general meeting) irrespective of any provisions of any service contract the director has with the company, provided 28 clear days' notice of the resolution has been given to the company and its shareholders. On receipt of notice of an intended resolution to remove a director, the company must forthwith send a copy of the notice to the director concerned. Certain other procedural requirements under the Companies Act must also be followed, such as allowing the director to make representations against his or her removal either at the meeting or in writing.	Under Delaware law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (i) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board of directors is classified, stockholders may effect such removal only for cause, or (ii) in the case of a corporation having cumulative voting, if less than the entire board of directors is to be removed, no director may be removed without cause if the votes cast against his removal would be sufficient to elect him if then cumulatively voted at an election of the entire board of directors, or, if there are classes of directors, at an election of the class of directors of which he is a part.
Vacancies on the Board of Directors	Under English law, the procedure by which directors, other than a company's initial directors, are appointed is generally set out in a company's articles of association, provided that where two or more persons are appointed as directors of a public limited company by resolution of the shareholders, resolutions appointing each director must be voted on individually.	Under Delaware law, vacancies and newly created directorships may be filled by a majority of the directors then in office (even though less than a quorum) or by a sole remaining director unless (i) otherwise provided in the certificate of incorporation or bylaws of the corporation or (ii) the certificate of incorporation directs that a particular class of stock is to elect such director, in which case a majority of the other directors elected by such class, or a sole remaining director elected by such class, will fill such vacancy.
Annual General Meeting	Under the Companies Act, a public limited company must hold an annual general meeting in each six-month period following the company's annual accounting reference date.	Under Delaware law, the annual meeting of stockholders shall be held at such place, on such date and at such time as may be designated from time to time by the board of directors or as provided in the certificate of incorporation or by the bylaws.

	England and Wales	Delaware
General Meeting	Under the Companies Act, a general meeting of the shareholders of a public limited company may be called by the directors. Shareholders holding at least 5% of the paid-up capital of the company carrying voting rights at general meetings (excluding any paid up capital held as treasury shares) can require the directors to call a general meeting and, if the directors fail to do so within a certain period, may themselves convene a general meeting.	Under Delaware law, special meetings of the stockholders may be called by the board of directors or by such person or persons as may be authorized by the certificate of incorporation or by the bylaws.
Notice of General Meetings	Under the Companies Act, at least 21 days' notice must be given for an annual general meeting and any resolutions to be proposed at the meeting. Subject to a company's articles of association providing for a longer period, at least 14 days' notice is required for any other general meeting of a public limited company. In addition, certain matters, such as the removal of directors or auditors, require special notice, which is 28 days' notice. The shareholders of a company may in all cases consent to a shorter notice period, the proportion of shareholders' consent required being 100% of those entitled to attend and vote in the case of an annual general meeting and, in the case of any other general meeting, a majority in number of the members having a right to attend and vote at the meeting, being a majority who together hold not less than 95% in nominal value of the shares giving a right to attend and vote at the meeting.	Under Delaware law, unless otherwise provided in the certificate of incorporation or bylaws, written notice of any meeting of the stockholders must be given to each stockholder entitled to vote at the meeting not less than ten nor more than 60 days before the date of the meeting and shall specify the place, date, hour and purpose or purposes of the meeting.
Quorum	Subject to the provisions of a company's articles of association, the Companies Act provides that two shareholders present at a meeting (in person or by proxy) shall constitute a quorum.	The certificate of incorporation or bylaws may specify the number of shares, the holders of which shall be present or represented by proxy at any meeting in order to constitute a quorum, but in no event shall a quorum consist of less than one third of the shares entitled to vote at the meeting. In the absence of such specification in the certificate of incorporation or bylaws, a majority of the shares entitled to vote, present in person or represented by proxy, shall constitute a quorum at a meeting of stockholders.

	England and Wales	Delaware
Proxy	Under the Companies Act, at any meeting of shareholders, a shareholder may designate another person to attend, speak and vote at the meeting on their behalf by proxy.	Under Delaware law, at any meeting of stockholders, a stockholder may designate another person to act for such stockholder by proxy, but no such proxy shall be voted or acted upon after three years from its date, unless the proxy provides for a longer period. A director of a Delaware corporation may not issue a proxy representing the director's voting rights as a director.
Issue of New Shares	Under the Companies Act, the directors of a company must not exercise any power to allot shares or grant rights to subscribe for, or to convert any security into, shares unless they are authorized to do so by the company's articles of association or by an ordinary resolution of the shareholders. Any authorization given must state the maximum amount of shares that may be allotted under it and specify the date on which it will expire, which must be not more than five years from the date the authorization was given. The authority can be renewed by a further resolution of the shareholders.	Under Delaware law, if the company's certificate of incorporation so provides, the directors have the power to authorize the issuance of additional stock. The directors may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the company or any combination thereof.
Preemptive Rights	Under the Companies Act, "equity securities," being (i) shares in the company other than shares that, with respect to dividends and capital, carry a right to participate only up to a specified amount in a distribution, referred to as "ordinary shares," or (ii) rights to subscribe for, or to convert securities into, ordinary shares, proposed to be allotted for cash must be offered first to the existing equity shareholders in the company in proportion to the respective nominal value of their holdings, unless an exception applies or a special resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise in each case in accordance with the provisions of the Companies Act.	Under Delaware law, shareholders have no preemptive rights to subscribe to additional issues of stock or to any security convertible into such stock unless, and except to the extent that, such rights are expressly provided for in the certificate of incorporation.

	England and Wales	Delaware
Authority to Allot	Under the Companies Act, the directors of a company must not allot shares or grant rights to subscribe for or convert any security into shares unless an exception applies or an ordinary resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise, in each case in accordance with the provisions of the Companies Act.	Under Delaware law, if the corporation's charter or certificate of incorporation so provides, the board of directors has the power to authorize the issuance of stock. The board may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the corporation or any combination thereof. It may determine the amount of such consideration by approving a formula. In the absence of actual fraud in the transaction, the judgment of the directors as to the value of such consideration is conclusive.
Liability of Directors and Officers	Under the Companies Act, any provision, whether contained in a company's articles of association or any contract or otherwise, that purports to exempt a director of a company, to any extent, from any liability that would otherwise attach to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company, is void. Any provision by which a company directly or indirectly provides an indemnity, to any extent, for a director of the company or of an associated company against any liability attaching to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act, which provides exceptions for the company to company against any liability attaching to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act, which provides exceptions for the company to (i) purchase and maintain insurance against such liability; (ii) provide a "qualifying third party indemnity," or an indemnity against liability incurred by the director to a person other than the company or an associated company or criminal proceedings in which he is convicted; and (iii) provide a "qualifying pension scheme indemnity," or an indemnity against liability incurred in connection with the company's activities as trustee of an occupational pension plan.	Under Delaware law, a corporation's certificate of incorporation may include a provision eliminating or limiting the personal liability of a director to the corporation and its stockholders for damages arising from a breach of fiduciary duty as a director. However, no provision can limit the liability of a director for: • any breach of the director's duty of loyalty to the corporation or its stockholders; • acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law; • intentional or negligent payment of unlawful dividends or stock purchases or redemptions; or • any transaction from which the director derives an improper personal benefit.

	England and Wales	Delaware
Voting Rights	Under English law, unless a poll is demanded by the shareholders of a company or is required by the chairman of the meeting or the company's articles of association, shareholders shall vote on all resolutions on a show of hands. Under the Companies Act, a poll may be demanded by (i) not fewer than five shareholders having the right to vote on the resolution; (ii) any shareholder(s) representing not less than 10% of the total voting rights of all the shareholders having the right to vote on the resolution (excluding any voting rights attaching to treasury shares); or (iii) any shareholder(s) holding shares in the company conferring a right to vote on the resolution (excluding any voting rights attaching to treasury shares) being shares on which an aggregate sum has been paid up equal to not less than 10% of the total sum paid up on all the shares conferring that right. A company's articles of association may provide more extensive rights for shareholders to call a poll. Under English law, an ordinary resolution is passed on a show of hands if it is approved by a simple majority (more than 50%) of the votes cast by shareholders present (in person or by proxy) and entitled to vote. If a poll is demanded, an ordinary resolution is passed if it is approved by holders representing a simple majority of the total voting rights of shareholders present, in person or by proxy, who, being entitled to vote, vote on the resolution. Special resolutions require the affirmative vote of not less than 75% of the votes cast by shareholders present, in person or by proxy, at the meeting.	Delaware law provides that, unless otherwise provided in the certificate of incorporation, each stockholder is entitled to one vote for each share of capital stock held by such stockholder.

	England and Wales	Delaware
Shareholder Vote on Certain Transactions	The Companies Act provides for schemes of arrangement, which are arrangements or compromises between a company and any class of shareholders or creditors and used in certain types of reconstructions, amalgamations, capital reorganizations or takeovers. These arrangements require: • the approval at a shareholders' or creditors' meeting convened by order of the court, of a majority in number of shareholders or creditors representing 75% in value of the capital held by, or debt owed to, the shareholders or creditors or class thereof present and voting, either in person or by proxy; and • the approval of the court.	Generally, under Delaware law, unless the certificate of incorporation provides for the vote of a larger portion of the stock, completion of a merger, consolidation, sale, lease or exchange of all or substantially all of a corporation's assets or dissolution requires: • the approval of the board of directors; and • the approval by the vote of the holders of a majority of the outstanding stock or, if the certificate of incorporation provides for more or less than one vote per share, a majority of the votes of the outstanding stock of the corporation entitled to vote on the matter.

	England and Wales	Delaware
Standard of Conduct for Directors	Under English law, a director owes various statutory and fiduciary duties to the company, including: • to act in the way he considers, in good faith, would be most likely to promote the success of the company for the benefit of its members as a whole; • to avoid a situation in which he has, or can have, a direct or indirect interest that conflicts, or possibly conflicts, with the interests of the company; • to act in accordance with the company's constitution and only exercise his powers for the purposes for which they are conferred; • to exercise independent judgment; • to exercise reasonable care, skill and diligence; • not to accept benefits from a third party conferred by reason of his being a director or doing, or not doing, anything as a director; and • to declare any interest that he has, whether directly or indirectly, in a proposed or existing transaction or arrangement with the company.	Delaware law does not contain specific provisions setting forth the standard of conduct of a director. The scope of the fiduciary duties of directors is generally determined by the courts of the State of Delaware. In general, directors have a duty to act without self-interest, on a well-informed basis and in a manner they reasonably believe to be in the best interest of the stockholders. Directors of a Delaware corporation owe fiduciary duties of care and loyalty to the corporation and to its shareholders. The duty of care generally requires that a director act in good faith, with the care that an ordinarily prudent person would exercise under similar circumstances. Under this duty, a director must inform himself of all material information reasonably available regarding a significant transaction. The duty of loyalty requires that a director act in a manner he reasonably believes to be in the best interests of the corporation. He must not use his corporate position for personal gain or advantage. In general, but subject to certain exceptions, actions of a director are presumed to have been made on an informed basis, in good faith and in the honest belief that the action taken was in the best interests of the corporation. However, this presumption may be rebutted by evidence of a breach of one of the fiduciary duties. Delaware courts have also imposed a heightened standard of conduct upon directors of a Delaware corporation who take any action designed to defeat a threatened change in control of the corporation. In addition, under Delaware law, when the board of directors of a Delaware corporation approves the sale or break-up of a corporation, the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the shareholders.

	England and Wales	Delaware
Stockholder Suits	Under English law, generally, the company, rather than its shareholders, is the proper claimant in an action in respect of a wrong done to the company or where there is an irregularity in the company's internal management. Notwithstanding this general position, the Companies Act provides that (i) a court may allow a shareholder to bring a derivative claim (that is, an action in respect of and on behalf of the company) in respect of a cause of action arising from a director's negligence, default, breach of duty or breach of trust and (ii) a shareholder may bring a claim for a court order where the company's affairs have been or are being conducted in a manner that is unfairly prejudicial to some of its shareholders.	Under Delaware law, a stockholder may initiate a derivative action to enforce a right of a corporation if the corporation fails to enforce the right itself. The complaint must: • state that the plaintiff was a stockholder at the time of the transaction of which the plaintiff complains or that the plaintiffs shares thereafter devolved on the plaintiff by operation of law; and • allege with particularity the efforts made by the plaintiff to obtain the action the plaintiff desires from the directors and the reasons for the plaintiff's failure to obtain the action; or • state the reasons for not making the effort. Additionally, the plaintiff must remain a stockholder through the duration of the derivative suit. The action will not be dismissed or compromised without the approval of the Delaware Court of Chancery.

Stock Exchange Listing

We intend to apply to list our ADSs on the Nasdaq Global Market under the symbol "BCYC."

Transfer Agent and Registrar of Shares

Our share register will be maintained by upon the closing of this offering. The share register reflects only record owners of our ordinary shares. Holders of our ADSs will not be treated as our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the ordinary shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see "Description of American Depositary Shares" in this prospectus.

DESCRIPTION OF AMERICAN DEPOSITARY SHARES

has agreed to act as the depositary bank for the American Depositary Shares. The depositary offices are located at . American Depositary Shares are frequently referred to as "ADSs" and represent ownership interests in securities that are on deposit with the depositary bank. ADSs may be represented by certificates that are commonly known as "American Depositary Receipts" or "ADRs." The depositary bank typically appoints a custodian to safekeep the securities on deposit. In this case, the custodian is .

We have appointed as depositary bank pursuant to a deposit agreement. A copy of the deposit agreement is on file with the SEC under cover of a Registration Statement on Form F-6. You may obtain a copy of the deposit agreement from the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 and from the SEC's website (www.sec.gov). Please refer to Registration Number 333- when retrieving such copy.

We are providing you with a summary description of the material terms of the ADSs and of your material rights as an owner of ADSs. Please remember that summaries by their nature lack the precision of the information summarized and that the rights and obligations of an owner of ADSs will be determined by reference to the terms of the deposit agreement and not by this summary. We urge you to review the deposit agreement in its entirety. The portions of this summary description that are italicized describe matters that may be relevant to the ownership of ADSs but that may not be contained in the deposit agreement.

Each ADS represents the right to receive, and to exercise the beneficial ownership interests in, ordinary shares that are on deposit with the depositary bank and/or custodian. An ADS also represents the right to receive, and to exercise the beneficial interests in, any other property received by the depositary bank or the custodian on behalf of the owner of the ADS but that has not been distributed to the owners of ADSs because of legal restrictions or practical considerations. The custodian, the depositary bank and their respective nominees will hold all deposited property for the benefit of the holders and beneficial owners of ADSs. The deposited property does not constitute the proprietary assets of the depositary bank, the custodian or their nominees. Beneficial ownership in the deposited property will under the terms of the deposit agreement be vested in the beneficial owners of the ADSs. The depositary bank, the custodian and their respective nominees will be the record holders of the deposited property represented by the ADSs for the benefit of the holders and beneficial owners of the corresponding ADSs. A beneficial owner of ADSs may or may not be the holder of ADSs. Beneficial owners of ADSs will be able to receive, and to exercise beneficial ownership interests in, the deposited property only through the registered holders of the ADSs, the registered holders of the ADSs (on behalf of the applicable ADS owners) only through the depositary bank, and the depositary bank (on behalf of the owners of the corresponding ADSs) directly, or indirectly, through the custodian or their respective nominees, in each case upon the terms of the deposit agreement.

If you become an owner of ADSs, you will become a party to the deposit agreement and therefore will be bound to its terms and to the terms of any ADR that represents your ADSs. The deposit agreement and the ADR specify our rights and obligations as well as your rights and obligations as owner of ADSs and those of the depositary bank. As an ADS holder you appoint the depositary bank to act on your behalf in certain circumstances. The deposit agreement and the ADRs are governed by New York law. However, our obligations to the holders of the ordinary shares will continue to be governed by the laws and regulations of England and Wales, which may be different from the laws in the United States.

In addition, applicable laws and regulations may require you to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. You are solely responsible for complying with such reporting requirements and obtaining such approvals. Neither the depositary bank, the

custodian, us or any of their or our respective agents or affiliates shall be required to take any actions whatsoever on your behalf to satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

As an owner of ADSs, we will not treat you as one of our shareholders and you will not have direct shareholder rights. The depositary bank will hold on your behalf the shareholder rights attached to the ordinary shares underlying your ADSs. As an owner of ADSs you will be able to exercise the shareholders rights for the ordinary shares represented by your ADSs through the depositary bank only to the extent contemplated in the deposit agreement. To exercise any shareholder rights not contemplated in the deposit agreement you will, as an ADS owner, need to arrange for the cancellation of your ADSs and become a direct shareholder.

As an owner of ADSs, you may hold your ADSs either by means of an ADR registered in your name, through a brokerage or safekeeping account, or through an account established by the depositary bank in your name reflecting the registration of uncertificated ADSs directly on the books of the depositary bank (commonly referred to as the "direct registration system" or "DRS"). The direct registration system reflects the uncertificated (book-entry) registration of ownership of ADSs by the depositary bank. Under the direct registration system, ownership of ADSs is evidenced by periodic statements issued by the depositary bank to the holders of the ADSs. The direct registration system includes automated transfers between the depositary bank and The Depository Trust Company ("DTC"), the central book-entry clearing and settlement system for equity securities in the United States. If you decide to hold your ADSs through your brokerage or safekeeping account, you must rely on the procedures of your broker or bank to assert your rights as ADS owner. Banks and brokers typically hold securities such as the ADSs through clearing and settlement systems such as DTC. The procedures of such clearing and settlement systems may limit your ability to exercise your rights as an owner of ADSs. Please consult with your broker or bank if you have any questions concerning these limitations and procedures. All ADSs held through DTC will be registered in the name of a nominee of DTC. This summary description assumes you have opted to own the ADSs directly by means of an ADS registered in your name and, as such, we will refer to you as the "holder." When we refer to "you," we assume the reader owns ADSs and will own ADSs at the relevant time.

The registration of the ordinary shares in the name of the depositary bank or the custodian shall, to the maximum extent permitted by applicable law, vest in the depositary bank or the custodian the record ownership in the applicable ordinary shares with the beneficial ownership rights and interests in such ordinary shares being at all times vested with the beneficial owners of the ADSs representing the ordinary shares. The depositary bank or the custodian shall at all times be entitled to exercise the beneficial ownership rights in all deposited property, in each case only on behalf of the holders and beneficial owners of the ADSs representing the deposited property.

Dividends and Distributions

As a holder of ADSs, you generally have the right to receive the distributions we make on the securities deposited with the custodian. Your receipt of these distributions may be limited, however, by practical considerations and legal limitations. Holders of ADSs will receive such distributions under the terms of the deposit agreement in proportion to the number of ADSs held as of the specified record date, after deduction the applicable fees, taxes and expenses.

Distributions of Cash

Whenever we make a cash distribution for the securities on deposit with the custodian, we will deposit the funds with the custodian. Upon receipt of confirmation of the deposit of the requisite funds, the depositary bank will arrange for the funds to be converted into U.S. dollars and for the

distribution of the U.S. dollars to the holders, subject to the laws and regulations of England and Wales.

The conversion into U.S. dollars will take place only if practicable and if the U.S. dollars are transferable to the United States. The depositary bank will apply the same method for distributing the proceeds of the sale of any property (such as undistributed rights) held by the custodian in respect of securities on deposit.

The distribution of cash will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. The depositary bank will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable holders and beneficial owners of ADSs until the distribution can be effected or the funds that the depositary bank holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States.

Distributions of Shares

Whenever we make a free distribution of the ordinary shares for the securities on deposit with the custodian, we will deposit the applicable number of the ordinary shares with the custodian. Upon receipt of confirmation of such deposit, the depositary bank will *either* distribute to holders new ADSs representing the ordinary shares deposited *or* modify the ADS-to-ordinary share ratio, in which case each ADS you hold will represent rights and interests in the additional ordinary shares so deposited. Only whole new ADSs will be distributed. Fractional entitlements will be sold and the proceeds of such sale will be distributed as in the case of a cash distribution.

The distribution of new ADSs or the modification of the ADS-to-ordinary share ratio upon a distribution of the ordinary shares will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes or governmental charges, the depositary bank may sell all or a portion of the new ordinary shares so distributed.

No such distribution of new ADSs will be made if it would violate a law (i.e., the U.S. securities laws) or if it is not operationally practicable. If the depositary bank does not distribute new ADSs as described above, it may sell the ordinary shares received upon the terms described in the deposit agreement and will distribute the proceeds of the sale as in the case of a distribution of cash.

Distributions of Rights

Whenever we intend to distribute rights to purchase additional ordinary shares, we will give prior notice to the depositary bank and we will assist the depositary bank in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depositary bank will establish procedures to distribute rights to purchase additional ADSs to holders and to enable such holders to exercise such rights if it is lawful and reasonably practicable to make the rights available to holders of ADSs, and if we provide all of the documentation contemplated in the deposit agreement (such as opinions to address the lawfulness of the transaction). You may have to pay fees, expenses, taxes and other governmental charges to subscribe for the new ADSs upon the exercise of your rights. The depositary bank is not obligated to establish procedures to facilitate the distribution and exercise by holders of rights to purchase new ordinary shares other than in the form of ADSs.

The depositary bank will *not* distribute the rights to you if:

- We do not timely request that the rights be distributed to you or we request that the rights not be distributed to you; or

- We fail to deliver satisfactory documents to the depositary bank; or
- It is not reasonably practicable to distribute the rights.

The depositary bank will sell the rights that are not exercised or not distributed if such sale is lawful and reasonably practicable. The proceeds of such sale will be distributed to holders as in the case of a cash distribution. If the depositary bank is unable to sell the rights, it will allow the rights to lapse.

Elective Distributions

Whenever we intend to distribute a dividend payable at the election of shareholders either in cash or in additional shares, we will give prior notice thereof to the depositary bank and will indicate whether we wish the elective distribution to be made available to you. In such case, we will assist the depositary bank in determining whether such distribution is lawful and reasonably practicable.

The depositary bank will make the election available to you only if it is reasonably practicable and if we have provided all of the documentation contemplated in the deposit agreement. In such case, the depositary bank will establish procedures to enable you to elect to receive either cash or additional ADSs, in each case as described in the deposit agreement.

If the election is not made available to you, you will receive either cash or additional ADSs, depending on what a shareholder in England and Wales would receive upon failing to make an election, as more fully described in the deposit agreement.

Other Distributions

Whenever we intend to distribute property other than cash, ordinary shares or rights to purchase additional ordinary shares, we will notify the depositary bank in advance and will indicate whether we wish such distribution to be made to you. If so, we will assist the depositary bank in determining whether such distribution to holders is lawful and reasonably practicable.

If it is reasonably practicable to distribute such property to you and if we provide all of the documentation contemplated in the deposit agreement, the depositary bank will distribute the property to the holders in a manner it deems practicable.

The distribution will be made net of fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes and governmental charges, the depositary bank may sell all or a portion of the property received.

The depositary bank will *not* distribute the property to you and will sell the property if:

- We do not request that the property be distributed to you or if we ask that the property not be distributed to you; or
- We do not deliver satisfactory documents to the depositary bank; or
- The depositary bank determines that all or a portion of the distribution to you is not reasonably practicable.

The proceeds of such a sale will be distributed to holders as in the case of a cash distribution.

Redemption

Whenever we decide to redeem any of the securities on deposit with the custodian, we will notify the depositary bank in advance. If it is practicable and if we provide all of the documentation

contemplated in the deposit agreement, the depositary bank will provide notice of the redemption to the holders.

The custodian will be instructed to surrender the shares being redeemed against payment of the applicable redemption price. The depositary bank will convert the redemption funds received into U.S. dollars upon the terms of the deposit agreement and will establish procedures to enable holders to receive the net proceeds from the redemption upon surrender of their ADSs to the depositary bank. You may have to pay fees, expenses, taxes and other governmental charges upon the redemption of your ADSs. If less than all ADSs are being redeemed, the ADSs to be retired will be selected by lot or on a *pro rata* basis, as the depositary bank may determine.

Changes Affecting Ordinary Shares

The ordinary shares held on deposit for your ADSs may change from time to time. For example, there may be a change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of such ordinary shares or a recapitalization, reorganization, merger, consolidation or sale of assets of the Company.

If any such change were to occur, your ADSs would, to the extent permitted by law, represent the right to receive the property received or exchanged in respect of the ordinary shares held on deposit. The depositary bank may in such circumstances deliver new ADSs to you, amend the deposit agreement, the ADRs and the applicable Registration Statement(s) on Form F-6, call for the exchange of your existing ADSs for new ADSs and take any other actions that are appropriate to reflect as to the ADSs the change affecting the ordinary shares. If the depositary bank may not lawfully distribute such property to you, the depositary bank may sell such property and distribute the net proceeds to you as in the case of a cash distribution.

Issuance of ADSs upon Deposit of Ordinary Shares

Upon completion of this offering, the ordinary shares being offered pursuant to this prospectus will be deposited by us with the custodian. Upon receipt of confirmation of such deposit, the depositary bank will issue ADSs to the underwriters named in this prospectus. After the completion of this offering, the ordinary shares that are being offered for sale pursuant to this prospectus will be deposited by us with the custodian. Upon receipt of confirmation of such deposit, the depositary bank will issue ADSs to the underwriters named in this prospectus.

After the closing of this offering, the depositary may create ADSs on your behalf if you or your broker deposit ordinary shares with the custodian. The depositary will deliver these ADSs to the person you indicate only after you pay any applicable issuance fees and any charges and taxes payable for the transfer of the ordinary shares to the custodian. Your ability to deposit ordinary shares and receive ADSs may be limited by the legal considerations in the United States and England and Wales applicable at the time of deposit.

The issuance of ADSs may be delayed until the depositary bank or the custodian receives confirmation that all required approvals have been given and that the ordinary shares have been duly transferred to the custodian. The depositary bank will only issue ADSs in whole numbers.

When you make a deposit of the ordinary shares, you will be responsible for transferring good and valid title to the depositary bank. As such, you will be deemed to represent and warrant that:

- The ordinary shares are duly authorized, validly issued, fully paid, non-assessable and legally obtained.
- All preemptive (and similar) rights, if any, with respect to such ordinary shares have been validly waived or exercised.

- You are duly authorized to deposit the ordinary shares.
- The ordinary shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, and are not, and the ADSs issuable upon such deposit will not be, "restricted securities" (as defined in the deposit agreement).
- The ordinary shares presented for deposit have not been stripped of any rights or entitlements.

If any of the representations or warranties are incorrect in any way, we and the depositary bank may, at your cost and expense, take any and all actions necessary to correct the consequences of the misrepresentations.

Transfer, Combination and Split Up of ADRs

As an ADR holder, you will be entitled to transfer, combine or split up your ADRs and the ADSs evidenced thereby. For transfers of ADRs, you will have to surrender the ADRs to be transferred to the depositary bank and also must:

- ensure that the surrendered ADR is properly endorsed or otherwise in proper form for transfer;
- provide such proof of identity and genuineness of signatures as the depositary bank deems appropriate;
- provide any transfer stamps required by the State of New York or the United States; and
- pay all applicable fees, charges, expenses, taxes and other government charges payable by ADR holders pursuant to the terms of the deposit agreement, upon the transfer of ADRs.

To have your ADRs either combined or split up, you must surrender the ADRs in question to the depositary bank with your request to have them combined or split up, and you must pay all applicable fees, charges and expenses payable by ADR holders, pursuant to the terms of the deposit agreement, upon a combination or split up of ADRs.

Withdrawal of Ordinary Shares Upon Cancellation of ADSs

As a holder, you will be entitled to present your ADSs to the depositary for cancellation and then receive the corresponding number of underlying ordinary shares at the custodian's offices. Your ability to withdraw the ordinary shares held in respect of the ADSs may be limited by the legal consideration in the United States and England and Wales applicable at the time of withdrawal. In order to withdraw the ordinary shares represented by your ADSs, you will be required to pay to the depositary the fees for cancellation of ADSs and any charges and taxes payable upon the transfer of the ordinary shares. You assume the risk for delivery of all funds and securities upon withdrawal. Once canceled, the ADSs will not have any rights under the deposit agreement.

If you hold ADSs registered in your name, the depositary bank may ask you to provide proof of identity and genuineness of any signature and such other documents as the depositary bank may deem appropriate before it will cancel your ADSs. The withdrawal of the ordinary shares represented by your ADSs may be delayed until the depositary bank receives satisfactory evidence of compliance with all applicable laws and regulations. Please keep in mind that the depositary bank will only accept ADSs for cancellation that represent a whole number of securities on deposit.

You will have the right to withdraw the securities represented by your ADSs at any time except for:

- Temporary delays that may arise because (i) the transfer books for the ordinary shares or ADSs are closed, or (ii) the ordinary shares are immobilized on account of a shareholders' meeting or a payment of dividends.
- Obligations to pay fees, taxes and similar charges.
- Restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit.

The deposit agreement may not be modified to impair your right to withdraw the securities represented by your ADSs except to comply with mandatory provisions of law.

Voting Rights

As a holder, you generally have the right under the deposit agreement to instruct the depositary bank to exercise the voting rights for the ordinary shares represented by your ADSs. The voting rights of holders of ordinary shares are described in "Description of Share Capital and Articles of Association."

At our request, the depositary bank will distribute to you any notice of shareholders' meeting received from us together with information explaining how to instruct the depositary bank to exercise the voting rights of the securities represented by ADSs.

If the depositary bank timely receives voting instructions from a holder of ADSs, it will endeavor to vote the securities (in person or by proxy) represented by the holder's ADSs as follows:

- *In the event of voting by show of hands*, the depositary bank will vote (or cause the custodian to vote) all ordinary shares held on deposit at that time in accordance with the voting instructions received from a majority of holders of ADSs who provide timely voting instructions.
- *In the event of voting by poll*, the depositary bank will vote (or cause the Custodian to vote) the ordinary shares held on deposit in accordance with the voting instructions received from the holders of ADSs.

In the event of voting by poll, holders of ADSs in respect of which no timely voting instructions have been received shall be deemed to have instructed the depositary to give a discretionary proxy to a person designated by us to vote the ordinary shares represented by such holders' ADSs; provided, that no such instruction shall be deemed given and no such discretionary proxy shall be given with respect to any matter as to which we inform the depositary that we do not wish such proxy to be given; provided, further, that no such discretionary proxy shall be given (x) with respect to any matter as to which we inform the depositary that (i) there exists substantial opposition, or (ii) the rights of holders of ADSs or the shareholders of our company will be materially adversely affected, and (y) in the event that the vote is on a show of hands.

Please note that the ability of the depositary bank to carry out voting instructions may be limited by practical and legal limitations and the terms of the securities on deposit. We cannot assure you that you will receive voting materials in time to enable you to return voting instructions to the depositary bank in a timely manner.

Fees and Charges

As an ADS holder, you will be required to pay the following fees under the terms of the deposit agreement:

Service	Fees
• Issuance of ADSs upon deposit of shares (excluding issuances as a result of distributions of shares)	Up to U.S. ¢ per ADS issued
• Cancellation of ADSs	Up to U.S. ¢ per ADS canceled
• Distribution of cash dividends or other cash distributions (i.e., sale of rights and other entitlements)	Up to U.S. ¢ per ADS held
• Distribution of ADSs pursuant to (i) stock dividends or other free stock distributions, or (ii) exercise of rights to purchase additional ADSs	Up to U.S. ¢ per ADS held
• Distribution of securities other than ADSs or rights to purchase additional ADSs (i.e., spin-off shares)	Up to U.S. ¢ per ADS held
• ADS Services	Up to U.S. ¢ per ADS held on the applicable record date(s) established by the depositary bank

As an ADS holder you will also be responsible to pay certain charges such as:

- taxes (including applicable interest and penalties) and other governmental charges;
- the registration fees as may from time to time be in effect for the registration of the ordinary shares on the share register and applicable to transfers of the ordinary shares to or from the name of the custodian, the depositary bank or any nominees upon the making of deposits and withdrawals, respectively;
- certain cable, telex and facsimile transmission and delivery expenses;
- the expenses and charges incurred by the depositary bank in the conversion of foreign currency;
- the fees and expenses incurred by the depositary bank in connection with compliance with exchange control regulations and other regulatory requirements applicable to the ordinary shares, ADSs and ADRs; and
- the fees and expenses incurred by the depositary bank, the custodian, or any nominee in connection with the servicing or delivery of deposited property.

ADS fees and charges payable upon (i) deposit of the ordinary shares against issuance of ADSs and (ii) surrender of ADSs for cancellation and withdrawal of the ordinary shares are charged to the person to whom the ADSs are delivered (in the case of ADS issuances) and to the person who delivers the ADSs for cancellation (in the case of ADS cancellations). In the case of ADSs issued by the depositary bank into DTC or presented to the depositary bank via DTC, the ADS issuance and cancellation fees and charges may be deducted from distributions made through DTC, and may be charged to the DTC participant(s) receiving the ADSs or the DTC participant(s) surrendering the ADSs for cancellation, as the case may be, on behalf of the beneficial owner(s) and will be charged by the DTC participant(s) to the account(s) of the applicable beneficial owner(s) in accordance with the procedures and practices of the DTC participant(s) as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are charged to

the holders as of the applicable ADS record date. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, holders as of the ADS record date will be invoiced for the amount of the ADS fees and charges and such ADS fees and charges may be deducted from distributions made to holders of ADSs. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC participants in accordance with the procedures and practices prescribed by DTC and the DTC participants in turn charge the amount of such ADS fees and charges to the beneficial owners for whom they hold ADSs.

In the event of refusal to pay the depositary bank fees, the depositary bank may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary bank fees from any distribution to be made to the ADS holder. Certain of the depositary fees and charges (such as the ADS services fee) may become payable shortly after the closing of the ADS offering. Note that the fees and charges you may be required to pay may vary over time and may be changed by us and by the depositary bank. You will receive prior notice of such changes. The depositary bank may reimburse us for certain expenses incurred by us in respect of the ADR program, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as we and the depositary bank agree from time to time.

Amendments and Termination

We may agree with the depositary bank to modify the deposit agreement at any time without your consent. We undertake to give holders 30 days' prior notice of any modifications that would materially prejudice any of their substantial rights under the deposit agreement. We will not consider to be materially prejudicial to your substantial rights any modifications or supplements that are reasonably necessary for the ADSs to be registered under the Securities Act or to be eligible for book-entry settlement, in each case without imposing or increasing the fees and charges you are required to pay. In addition, we may not be able to provide you with prior notice of any modifications or supplements that are required to accommodate compliance with applicable provisions of law.

You will be bound by the modifications to the deposit agreement if you continue to hold your ADSs after the modifications to the deposit agreement become effective. The deposit agreement cannot be amended to prevent you from withdrawing the ordinary shares represented by your ADSs (except as permitted by law).

We have the right to direct the depositary bank to terminate the deposit agreement. Similarly, the depositary bank may in certain circumstances on its own initiative terminate the deposit agreement. In either case, the depositary bank must give notice to the holders at least 30 days before termination. Until termination, your rights under the deposit agreement will be unaffected.

Termination

After termination, the depositary bank will continue to collect distributions received (but will not distribute any such property until you request the cancellation of your ADSs) and sell the securities held on deposit. After the sale, the depositary bank will hold the proceeds from such sale and any other funds then held for the holders of ADSs in a non-interest bearing account. At that point, the depositary bank will have no further obligations to holders other than to account for the funds then held for the holders of ADSs still outstanding (after deduction of applicable fees, taxes and expenses).

In connection with the termination of the deposit agreement, the depositary may, independently and without the need for any action by us, make available to holders a means to withdraw the ordinary shares and other deposited securities represented by their ADSs and to direct the deposit of such ordinary shares and other deposited securities into an unsponsored ADS program established by the depositary, upon such terms and conditions as the depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored ADS program under the Securities Act, and to receipt by the depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the depositary.

Books of Depositary

The depositary bank will maintain ADS holder records at its depositary office. You may inspect such records at such office during regular business hours but solely for the purpose of communicating with other holders in the interest of business matters relating to the ADSs and the deposit agreement.

The depositary bank will maintain in New York facilities to record and process the issuance, cancellation, combination, split-up and transfer of ADSs. These facilities may be closed from time to time, to the extent not prohibited by law.

Transmission of Notices, Reports and Proxy Soliciting Material

The depositary will make available for your inspection at its office all communications that it receives from us as a holder of deposited securities that we make generally available to holders of deposited securities. Subject to the terms of the deposit agreement, the depositary will send you copies of those communications or otherwise make those communications available to you if we ask it to.

Limitations on Obligations and Liabilities

The deposit agreement limits our obligations and the depositary bank's obligations to you. Please note the following:

- We and the depositary bank are obligated only to take the actions specifically stated in the deposit agreement without negligence or bad faith.
- The depositary bank disclaims any liability for any failure to carry out voting instructions, for any manner in which a vote is cast or for the effect of any vote, provided it acts in good faith and in accordance with the terms of the deposit agreement.
- The depositary bank disclaims any liability for any failure to determine the lawfulness or practicality of any action, for the content of any document forwarded to you on our behalf or for the accuracy of any translation of such a document, for the investment risks associated with investing in the ordinary shares, for the validity or worth of the ordinary shares, for any tax consequences that result from the ownership of ADSs, for the credit-worthiness of any third party, for allowing any rights to lapse under the terms of the deposit agreement, for the timeliness of any of our notices or for our failure to give notice.
- We and the depositary bank will not be obligated to perform any act that is inconsistent with the terms of the deposit agreement.
- We and the depositary bank disclaim any liability if we or the depositary bank are prevented or forbidden from or subject to any civil or criminal penalty or restraint on account of, or delayed in, doing or performing any act or thing required by the terms of the deposit

agreement, by reason of any provision, present or future of any law or regulation, or by reason of present or future provision of any provision of our memorandum and articles of association, or any provision of or governing the securities on deposit, or by reason of any act of God or war or other circumstances beyond our control.

- We and the depositary bank disclaim any liability by reason of any exercise of, or failure to exercise, any discretion provided for in the deposit agreement or in our memorandum and articles of association or in any provisions of or governing the securities on deposit.
- We and the depositary bank further disclaim any liability for any action or inaction in reliance on the advice or information received from legal counsel, accountants, any person presenting ordinary shares for deposit, any holder of ADSs or authorized representatives thereof, or any other person believed by either of us in good faith to be competent to give such advice or information.
- We and the depositary bank also disclaim liability for the inability by a holder to benefit from any distribution, offering, right or other benefit that is made available to holders of the ordinary shares but is not, under the terms of the deposit agreement, made available to you.
- We and the depositary bank may rely without any liability upon any written notice, request or other document believed to be genuine and to have been signed or presented by the proper parties.
- We and the depositary bank also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.
- No disclaimer of any Securities Act liability is intended by any provision of the deposit agreement.

Nothing in the deposit agreement gives rise to a partnership or joint venture, or establishes a fiduciary relationship, among us, the depositary bank and you as ADS holder.

Nothing in the deposit agreement precludes (or its affiliates) from engaging in transactions in which parties adverse to us or the ADS owners have interests, and nothing in the deposit agreement obligates to disclose those transactions, or any information obtained in the course of those transactions, to us or to the ADS owners, or to account for any payment received as part of those transactions.

Pre-Release Transactions

Subject to the terms and conditions of the deposit agreement, the depositary bank may issue to broker/dealers ADSs before receiving a deposit of the ordinary shares. These transactions are commonly referred to as "pre-release transactions," and are entered into between the depositary bank and the applicable broker/dealer. The deposit agreement limits the aggregate size of pre-release transactions (generally not to exceed 30% of the ordinary shares on deposit in the aggregate) and imposes a number of conditions on such transactions (i.e., the need to receive collateral, the type of collateral required, the representations required from brokers, etc.). The depositary bank may retain the compensation received from the pre-release transactions.

Taxes

You will be responsible for the taxes and other governmental charges payable on the ADSs and the securities represented by the ADSs. We, the depositary bank and the custodian may deduct from any distribution the taxes and governmental charges payable by holders and may sell

any and all property on deposit to pay the taxes and governmental charges payable by holders. You will be liable for any deficiency if the sale proceeds do not cover the taxes that are due.

The depositary bank may refuse to issue ADSs, to deliver, transfer, split and combine ADRs or to release securities on deposit until all taxes and charges are paid by the applicable holder. The depositary bank and the custodian may take reasonable administrative actions to obtain tax refunds and reduced tax withholding for any distributions on your behalf. However, you may be required to provide to the depositary bank and to the custodian proof of taxpayer status and residence and such other information as the depositary bank and the custodian may require to fulfill legal obligations. You are required to indemnify us, the depositary bank and the custodian for any claims with respect to taxes based on any tax benefit obtained for you.

Foreign Currency Conversion

The depositary bank will arrange for the conversion of all foreign currency received into U.S. dollars if such conversion is practical, and it will distribute the U.S. dollars in accordance with the terms of the deposit agreement. You may have to pay fees and expenses incurred in converting foreign currency, such as fees and expenses incurred in complying with currency exchange controls and other governmental requirements.

If the conversion of foreign currency is not practical or lawful, or if any required approvals are denied or not obtainable at a reasonable cost or within a reasonable period, the depositary bank may take the following actions in its discretion:

- Convert the foreign currency to the extent practical and lawful and distribute the U.S. dollars to the holders for whom the conversion and distribution is lawful and practical.
- Distribute the foreign currency to holders for whom the distribution is lawful and practical.
- Hold the foreign currency (without liability for interest) for the applicable holders.

Governing Law/Waiver of Jury Trial

The deposit agreement and the ADRs will be interpreted in accordance with the laws of the State of New York. The rights of holders of the ordinary shares (including the ordinary shares represented by ADSs) is governed by the laws and regulations of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, YOU WAIVE YOUR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT OR THE ADRs AGAINST US AND/OR THE DEPOSITARY BANK. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable in the facts and circumstances of that case in accordance with applicable case law. However, you will not be deemed by agreeing to the terms of the deposit agreement to have waived our or the depositary's compliance with U.S. federal securities laws and the rules and regulations promulgated thereunder.

SHARES AND AMERICAN DEPOSITARY SHARES ELIGIBLE FOR FUTURE SALE

Upon completion of this offering, we will have ADSs outstanding representing approximately % of our ordinary shares (or ADSs outstanding representing approximately % of our ordinary shares, if the underwriters exercise in full their option to purchase additional ADSs), based on the number of ordinary shares outstanding as of December 31, 2018. All of the ADSs sold in this offering and the ordinary shares they represent will be freely transferable by persons other than our "affiliates" without restriction or further registration under the Securities Act. Rule 144 under the Securities Act defines an "affiliate" of a company as a person that, directly or indirectly, through one or more intermediaries, controls or is controlled by, or is under common control with, our company. All outstanding ordinary shares prior to this offering are "restricted securities" as that term is defined in Rule 144 because they were issued in a transaction or series of transactions not involving a public offering. Restricted securities, in the form of ADSs or otherwise, may be sold only if they are the subject of an effective registration statement under the Securities Act or if they are sold pursuant to an exemption from the registration requirement of the Securities Act such as those provided for in Rule 144 or 701 promulgated under the Securities Act, which rules are summarized below. Restricted ordinary shares may also be sold outside of the United States to non-U.S. persons in accordance with Rule 904 of Regulation S under the Securities Act. This prospectus may not be used in connection with any resale of the ADSs acquired in this offering by our affiliates.

Sales of substantial amounts of the ADSs in the public market could materially and adversely affect prevailing market prices of the ADSs. Prior to this offering, there has been no public market for our ordinary shares or ADSs, and while we have applied to list the ADSs on the Nasdaq, we cannot assure you that a regular trading market will develop in the ADSs. We do not expect that a trading market will develop for our ordinary shares not represented by ADSs.

Lock-up Agreements

In connection with this offering, all of our directors and executive officers and certain holders of our shares, who collectively held substantially all ordinary shares (assuming conversion of all of our outstanding convertible preferred shares, issuance of the bonus shares and exercise of the warrants) as of December 31, 2018, and substantially all of our optionholders who are not shareholders, have signed lock-up agreements which, subject to certain exceptions, prevent them from selling any of our ordinary shares or ADSs, or any securities convertible into or exercisable or exchangeable for ordinary shares or ADSs for a period of not less than 180 days from the date of this prospectus without the prior written consent of each of the representatives. The representatives may in their sole discretion and at any time without notice release some or all of the shares or ADSs subject to lock-up agreements prior to the expiration of the 180-day period. When determining whether or not to release shares or ADSs from the lock-up agreements, the representatives may consider, among other factors, the shareholder's reasons for requesting the release, the number of shares or ADSs for which the release is being requested and market conditions at the time. In addition, our optionholders who have not executed lock-up agreements are nevertheless subject to similar restrictions set forth in their respective option agreements.

Rule 144

In general, under Rule 144 as currently in effect, a person who has beneficially owned our restricted securities for at least six months is entitled to sell the restricted securities without registration under the Securities Act, subject to certain restrictions. Persons who are our affiliates (which may include persons beneficially owning 10% or more of our outstanding shares) may sell

within any three-month period a number of restricted securities that does not exceed the greater of the following:

- 1% of the number of our ordinary shares then outstanding, in the form of ADSs or otherwise, which will equal approximately ordinary shares immediately after this offering; and
- the average weekly trading volume of the ordinary shares, in the form of ADSs or otherwise, on Nasdaq during the four calendar weeks preceding the date on which notice of the sale is filed with the SEC.

Such sales are also subject to manner-of-sale provisions, notice requirements and the availability of current public information about us.

In general, under Rule 144 as currently in effect, once we have been subject to the public company reporting requirements of Section 13 or Section 15(d) of the Exchange Act for at least 90 days, persons who are not our affiliates and have beneficially owned our restricted securities for more than six months but not more than one year may sell the restricted securities without registration under the Securities Act subject to the availability of current public information about us. Persons who are not our affiliates and have beneficially owned our restricted securities for more than one year may freely sell the restricted securities without registration under the Securities Act.

Rule 701

Beginning 90 days after the date of this prospectus, persons other than affiliates who purchased ordinary shares under a written compensatory plan or contract may be entitled to sell such shares in the United States in reliance on Rule 701 under the Securities Act, or Rule 701. Rule 701 permits affiliates to sell their Rule 701 shares under Rule 144 without complying with the holding period requirements of Rule 144. Rule 701 further provides that non-affiliates may sell these shares in reliance on Rule 144 subject only to its manner-of-sale requirements. However, the Rule 701 shares would remain subject to any applicable lock-up arrangements and would only become eligible for sale when the lock-up period expires.

Registration Rights

Upon completion of this offering, certain holders of our ordinary shares or their transferees will be entitled to request that we register their ordinary shares under the Securities Act, following the expiration of the lock-up agreements described above. See "Description of Share Capital and Articles of Association — Registration Rights."

Share Option Plans

We intend to file one or more registration statements on Form S-8 under the Securities Act to register our shares issued or reserved for issuance under our share option plans or independent options. The first such registration statement is expected to be filed soon after the date of this prospectus and will automatically become effective upon filing with the SEC. Accordingly, shares registered under such registration statement will be available for sale in the open market, unless such shares are subject to vesting restrictions with us or the lock-up restrictions described above. As of December 31, 2018, we estimate that such registration statement on Form S-8 will cover approximately shares.

MATERIAL INCOME TAX CONSIDERATIONS

The following summary contains a description of material U.K. and U.S. federal income tax consequences of the acquisition, ownership and disposition of our ordinary shares or ADSs. This summary should not be considered a comprehensive description of all the tax considerations that may be relevant to the decision to acquire ordinary shares or ADSs in this offering.

Material United States Federal Income Tax Considerations for U.S. Holders

The following is a description of the material U.S. federal income tax consequences to the U.S. Holders described below of owning and disposing of our ordinary shares or ADSs. It is not a comprehensive description of all tax considerations that may be relevant to a particular person's decision to acquire securities. This discussion applies only to a U.S. Holder that is an initial purchaser of the ordinary shares or ADSs pursuant to the offering and that holds our ordinary shares or ADSs as a capital asset for tax purposes (generally, property held for investment). In addition, it does not describe all of the tax consequences that may be relevant in light of a U.S. Holder's particular circumstances, including state and local tax consequences, estate tax consequences, alternative minimum tax consequences, the potential application of the Medicare contribution tax, and tax consequences applicable to U.S. Holders subject to special rules, such as:

- banks, insurance companies, and certain other financial institutions;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- dealers or traders in securities who use a mark-to-market method of tax accounting;
- persons holding ordinary shares or ADSs as part of a hedging transaction, "straddle," wash sale, conversion transaction or integrated transaction or persons entering into a constructive sale with respect to ordinary shares or ADSs;
- persons whose "functional currency" for U.S. federal income tax purposes is not the U.S. dollar;
- brokers, dealers or traders in securities, commodities or currencies;
- tax-exempt entities or government organizations;
- S corporations, partnerships, or other entities or arrangements classified as partnerships for U.S. federal income tax purposes;
- regulated investment companies or real estate investment trusts;
- persons who acquired our ordinary shares or ADSs pursuant to the exercise of any employee stock option or otherwise as compensation;
- persons holding our ordinary shares or ADSs in connection with a trade or business, permanent establishment, or fixed base outside the United States; and
- persons who own (directly or through attribution) 10% or more (by vote or value) of our outstanding ordinary shares.

If an entity that is classified as a partnership for U.S. federal income tax purposes holds ordinary shares or ADSs, the U.S. federal income tax treatment of a partner will generally depend on the status of the partner and the activities of the partnership. Partnerships holding ordinary shares or ADSs and partners in such partnerships are encouraged to consult their tax advisers as to the particular U.S. federal income tax consequences of holding and disposing of ordinary shares or ADSs.

The discussion is based on the Code, administrative pronouncements, judicial decisions, final, temporary and proposed Treasury Regulations, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as of the date hereof, changes to any of which may affect the tax consequences described herein — possibly with retroactive effect.

A "U.S. Holder" is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

(i) An individual who is a citizen or individual resident of the United States;

(ii) a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;

(iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

(iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election in effect to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

Based on our analysis of our income, assets, activities and market capitalization, we believe that we were a PFIC in the 2018 taxable year. We have not yet determined our PFIC status for the current taxable year, but we may be a PFIC. A separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a "deemed sale" election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the "deemed sale" election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder's ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any "excess distribution" the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any "excess distribution" such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute "marketable" securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder's holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder's holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and
- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or "excess distribution" cannot be offset by any net operating losses for such years, and gains (but not losses)

realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

If a U.S. Holder makes an effective QEF Election, the U.S. Holder will be required to include in gross income each year, whether or not we make distributions, as capital gains, such U.S. Holder's pro rata share of our net capital gains and, as ordinary income, such U.S. Holder's pro rata share of our earnings in excess of our net capital gains. If we determine that we are a PFIC for this year or any future taxable year, we currently expect that we would provide the information necessary for U.S. Holders to make a QEF Election.

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are "marketable." Ordinary shares or ADSs will be marketable if they are "regularly traded" on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, and you are a holder of ADSs, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder's adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder's adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves "marketable." As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an annual report containing such information as the U.S. Treasury may require. A U.S.

Holder's failure to file the annual report will cause the statute of limitations for such U.S. Holder's U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the annual report, and, unless such failure is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder's entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE YOU TO CONSULT YOUR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs.

Taxation of Distributions

Subject to the discussion above under "PFIC rules," distributions paid on ordinary shares or ADSs, other than certain pro rata distributions of ordinary shares or ADSs, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we may not calculate our earnings and profits under U.S. federal income tax principles, we expect that distributions generally will be reported to U.S. Holders as dividends. Subject to applicable limitations and the discussions above regarding concerns expressed by the U.S. Treasury, dividends paid to certain non-corporate U.S. Holders may be taxable at preferential rates applicable to "qualified dividend income" if we are a "qualified foreign corporation" and certain other requirements are met. However, the qualified dividend income treatment may not apply if we are treated as a PFIC with respect to the U.S. Holder. The amount of the dividend will be treated as foreign-source dividend income to U.S. Holders and will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Dividends will generally be included in a U.S. Holder's income on the date of the U.S. Holder's receipt of the dividend. The amount of any dividend income paid in foreign currency will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual or constructive receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt. Such gain or loss would generally be treated as U.S.-source ordinary income or loss. The amount of any distribution of property other than cash (and other than certain pro rata distributions of ordinary shares or ADSs or rights to acquire ordinary shares or ADSs) will be the fair market value of such property on the date of distribution.

For foreign tax credit limitation purposes, our dividends will generally be treated as passive category income. Because no U.K. income taxes will be withheld from dividends on ordinary shares or ADSs, there will be no creditable foreign taxes associated with any dividends that a U.S. Holder will receive. The rules governing foreign tax credits are complex and U.S. Holders should therefore consult their tax advisers regarding the effect of the receipt of dividends for foreign tax credit limitation purposes.

Sale or Other Taxable Disposition of Ordinary Shares and ADSs

Subject to the discussion above under "PFIC rules," gain or loss realized on the sale or other taxable disposition of ordinary shares or ADSs will be capital gain or loss, and will be long-term capital gain or loss if the U.S. Holder held the ordinary shares or ADSs for more than one year. The amount of the gain or loss will equal the difference between the U.S. Holder's tax basis in the ordinary shares or ADSs disposed of and the amount realized on the disposition, in each case as

determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

If the consideration received by a U.S. Holder is not paid in U.S. dollars, the amount realized will be the U.S. dollar value of the payment received determined by reference to the spot rate of exchange on the date of the sale or other disposition. However, if the ordinary shares or ADSs are treated as traded on an "established securities market" and you are either a cash basis taxpayer or an accrual basis taxpayer that has made a special election (which must be applied consistently from year to year and cannot be changed without the consent of the IRS), you will determine the U.S. dollar value of the amount realized in a non-U.S. dollar currency by translating the amount received at the spot rate of exchange on the settlement date of the sale. If you are an accrual basis taxpayer that is not eligible to or does not elect to determine the amount realized using the spot rate on the settlement date, you will recognize foreign currency gain or loss to the extent of any difference between the U.S. dollar amount realized on the date of sale or disposition and the U.S. dollar value of the currency received at the spot rate on the settlement date.

Information Reporting and Backup Withholding

Payments of dividends and sales proceeds that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) the U.S. Holder is a corporation or other exempt recipient or (ii) in the case of backup withholding, the U.S. Holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding on a duly executed IRS Form W-9 or otherwise establishes an exemption.

Backup withholding is not an additional tax. The amount of any backup withholding from a payment to a U.S. Holder will be allowed as a credit against the U.S. Holder's U.S. federal income tax liability and may entitle the U.S. Holder to a refund, provided that the required information is timely furnished to the IRS.

Information with Respect to Foreign Financial Assets

Certain U.S. Holders who are individuals (and, under regulations, certain entities) may be required to report information relating to the ordinary shares or ADSs, subject to certain exceptions (including an exception for ordinary shares or ADSs held in accounts maintained by certain U.S. financial institutions), by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. Such U.S. Holders who fail to timely furnish the required information may be subject to a penalty. Additionally, if a U.S. Holder does not file the required information, the statute of limitations with respect to tax returns of the U.S. Holder to which the information relates may not close until three years after such information is filed. U.S. Holders should consult their tax advisers regarding their reporting obligations with respect to their ownership and disposition of the ordinary shares or ADSs.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HM Revenue & Customs, or HMRC, published practice applying as at the date of this prospectus (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from U.K. taxation. It is written on the basis that the company does not (and will not) derive 75% or more of its qualifying asset value from U.K. land, and that the company is and remains solely resident in the U.K. for tax purposes and will

therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under "Material U.S. Federal Income Tax Considerations for U.S. Holders".

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and, in the case of individuals, domiciled or deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment, branch, agency (or equivalent) or fixed base in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and who hold the ADSs as investments.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- market makers, intermediaries, brokers or dealers in securities;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis.

Based on published HMRC guidance we would expect that HMRC will regard a holder of ADSs as holding the beneficial interest in the underlying shares and therefore these paragraphs assume that a holder of ADSs is the beneficial owner of the underlying ordinary shares and any dividends paid in respect of the underlying ordinary shares (where the dividends are regarded for U.K. purposes as that person's own income) for U.K. direct tax purposes.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade,

profession or vocation in the U.K. through a permanent establishment, branch or agency to which the ADSs are attributable. There are certain exceptions for trading in the UK through independent agents, such as some brokers and investment managers.

All dividends received by an individual U.K. Holder from us or from other sources will form part of that U.K. Holder's total income for income tax purposes and will constitute the top slice of that income. A nil rate of income tax will apply to the first £2,000 of taxable dividend income received by the individual U.K. Holder in a tax year. Income within the nil rate band will be taken into account in determining whether income in excess of the £2,000 tax-free allowance falls within the basic rate, higher rate or additional rate tax bands. Dividend income in excess of the tax-free allowance will (subject to the availability of any income tax personal allowance) be taxed at 7.5% to the extent that the excess amount falls within the basic rate tax band, 32.5% to the extent that the excess amount falls within the higher rate tax band and 38.1% to the extent that the excess amount falls within the additional rate tax band.

Corporation Tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate U.K. Holders should not be subject to U.K. corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, although certain conditions must be met. If the conditions for the exemption are not satisfied, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19%).

Chargeable Gains

A disposal or deemed disposal of ADSs by a U.K. Holder may, depending on the U.K. Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of U.K. capital gains tax and corporation tax on chargeable gains.

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the applicable rate will be 20% (2018/2019). For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to U.K. capital gains tax on such disposal, the applicable rate would be 10% (2018/2019), save to the extent that any capital gains exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (2018/2019).

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax (currently 19%) would apply. Indexation allowance is not available in respect of disposals of ADSs acquired on or after January 1, 2018 (and only covers the movement in the retail prices index up until December 31, 2017, in respect of assets acquired prior to that date).

A holder of ADSs which is not resident for tax purposes in the United Kingdom should not normally be liable to U.K. capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs, unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation in the United Kingdom through a permanent establishment, branch or agency to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the United Kingdom for a period of less than five years and who

disposes of ADSs during that period may be liable on his or her return to the United Kingdom to U.K. tax on any capital gain realized (subject to any available exemption or relief).

Stamp Duty and Stamp Duty Reserve Tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Ordinary Shares

No U.K. stamp duty or stamp duty reserve tax, or SDRT, is payable on the issue of the underlying ordinary shares in the company.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

An unconditional agreement to transfer ordinary shares to, or to a nominee or agent for, a person whose business is or includes the issue of depositary receipts or the provision of clearance services will generally be subject to SDRT (and, where the transfer is effected by a written instrument, stamp duty) at a higher rate of 1.5% of the amount or value of the consideration given for the transfer unless the clearance service has made and maintained an election under section 97A of the U.K. Finance Act 1986, or a section 97A election. It is understood that HMRC regards the facilities of DTC as a clearance service for these purposes and we are not aware of any section 97A election having been made by the DTC.

Based on current published HMRC practice and recent case law in respect of the European Council Directives 69/335/EEC and 2009/7/EC, or the Capital Duties Directives, no SDRT is generally payable where the transfer of ordinary shares to a clearance service or depositary receipt system outside the European Union is an integral part of an issue of share capital (although the relevant judgment refers to transfers which are integral to the raising of capital). In addition, a recent Court of Justice of the European Union judgment (Air Berlin plc v. HMRC (2017)) held on the relevant facts that the Capital Duties Directives preclude the taxation of a transfer of legal title to shares for the sole purpose of listing those shares on a stock exchange which does not impact the beneficial ownership of the shares, but, as yet, the U.K. domestic law and HMRC's published practice remain unchanged and, accordingly, we anticipate that amounts account of SDRT will continue to be collected by the depositary receipt issuer or clearance service. Holders of ordinary shares should consult their own independent professional advisers before incurring or reimbursing the costs of such a 1.5% SDRT charge.

Any stamp duty or SDRT payable on a transfer of ordinary shares to a depositary receipt system or clearance service will in practice generally be paid by the participants in the clearance service or depositary receipt system.

Issue or Transfers of ADSs

No U.K. stamp duty or SDRT is payable on the issue or transfer of (including an agreement to transfer) ADSs in the Company.

UNDERWRITING

We and the underwriters named below have entered into an underwriting agreement with respect to the ADSs being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of ADSs indicated in the following table. Goldman Sachs & Co. LLC, Jefferies LLC and Piper Jaffray & Co. are the representatives of the underwriters.

Underwriters	Number of ADSs
Goldman Sachs & Co. LLC	
Jefferies LLC	
Piper Jaffray & Co.	
Canaccord Genuity LLC	
Total	

The underwriters are committed to take and pay for all of the ADSs being offered, if any are taken, other than the ADSs covered by the option described below unless and until this option is exercised. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters have an option to buy up to an additional ADSs from us to cover sales by the underwriters of a greater number of ADSs than the total number set forth in the table above. They may exercise that option for 30 days. If any ADSs are purchased pursuant to this option, the underwriters will severally purchase ADSs in approximately the same proportion as set forth in the table above.

The following table shows the per ADS and total underwriting discounts and commissions to be paid to the underwriters by us. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to additional ADSs from us.

	No Exercise	Full Exercise
Per ADS	$	$
Total	$	$

ADSs sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus. Any ADSs sold by the underwriters to securities dealers may be sold at a discount of up to $ per ADS from the initial public offering price. After the initial offering of the ADSs, the representatives may change the offering price and the other selling terms. The offering of the ADSs by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part. Sales of ADSs made outside of the United States may be made by affiliates of the underwriters.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of ADSs to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make internet distributions on the same basis as other allocations.

We and our executive officers, directors, and holders of substantially all of our equity securities and securities convertible into or exchangeable for our equity securities have agreed or will agree with the underwriters, subject to certain exceptions, not to dispose of or hedge any of our or their equity securities or securities convertible into or exchangeable for equity securities during the

period from the date of this prospectus continuing through the date 180 days after the date of this prospectus, except with the prior written consent of the representatives.

Prior to the offering, there has been no public market for the ADSs. The initial public offering price was negotiated among us and the representatives. Among the factors considered in determining the initial public offering price of the ADSs, in addition to prevailing market conditions, were our historical performance, estimates of our business potential and earnings prospects, an assessment of our management and the consideration of the above factors in relation to market valuation of companies in related businesses.

We intend to apply to list the ADSs on the Nasdaq Global Market under the symbol "BCYC."

In connection with the offering, the underwriters may purchase and sell ADSs in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of ADSs than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by subsequent purchases. A "covered short position" is a short position that is not greater than the amount of additional ADSs for which the underwriters' option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional ADSs or purchasing ADSs in the open market. In determining the source of ADSs to cover the covered short position, the underwriters will consider, among other things, the price of ADSs available for purchase in the open market as compared to the price at which they may purchase additional ADSs pursuant to the option described above. "Naked" short sales are any short sales that create a short position greater than the amount of additional ADSs for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing ADSs in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the ADSs in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of ADSs made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased ADSs sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of our ADSs, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the ADSs. As a result, the price of the ADSs may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on the Nasdaq Global Market, in the over-the-counter market or otherwise.

We estimate that the expenses payable by us in this offering, excluding underwriting discounts and commissions, will be approximately $ million. We have agreed to reimburse the underwriters for certain of their expenses in an amount up to $.

We have agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking,

advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to the issuer and to persons and entities with relationships with the issuer, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively traded securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to assets, securities or instruments of the issuer (directly, as collateral securing other obligations or otherwise) or persons and entities with relationships with the issuer. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of our securities may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of our securities may be made at any time under the following exemptions under the Prospectus Directive:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), subject to obtaining the prior consent of the Representatives for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of our securities shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to public" in relation to our securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and our securities to be offered so as to enable an investor to decide to purchase our securities, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, and the expression "Prospectus Directive" means Directive 2003/71/EC (as amended), including by

Directive 2010/73/EU and includes any relevant implementing measure in the Relevant Member State.

This European Economic Area selling restriction is in addition to any other selling restrictions set out below.

United Kingdom

In the United Kingdom, this prospectus is only addressed to and directed at qualified investors who are (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order); or (ii) high net worth entities and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (e) of the Order (all such persons together being referred to as "relevant persons"). Any investment or investment activity to which this prospectus relates is available only to relevant persons and will only be engaged in with relevant persons. Any person who is not a relevant person should not act or rely on this prospectus or any of its contents.

Canada

The securities may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions, and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption form, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The securities may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32 of the Laws of Hong Kong) ("Companies (Winding Up and Miscellaneous Provisions) Ordinance") or which do not constitute an invitation to the public within the meaning of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) ("Securities and Futures Ordinance"), or (ii) to "professional investors" as defined in the Securities and Futures Ordinance and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance, and no advertisement, invitation or document relating to the securities may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only

to "professional investors" in Hong Kong as defined in the Securities and Futures Ordinance and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA")) under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for 6 months after that corporation has acquired the securities under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore ("Regulation 32").

Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is a trust (where the trustee is not an accredited investor (as defined in Section 4A of the SFA)) whose sole purpose is to hold investments and each beneficiary of the trust is an accredited investor, the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferable for 6 months after that trust has acquired the securities under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer that is made on terms that such rights or interest are acquired at a consideration of not less than S$200,000 (or its equivalent in a foreign currency) for each transaction (whether such amount is to be paid for in cash or by exchange of securities or other assets), (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32.

Solely for the purposes of its obligations pursuant to Section 309B of the SFA, we have determined, and hereby notify all relevant persons (as defined in the CMP Regulations 2018), that the shares are "prescribed capital markets products" (as defined in the CMP Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04-N12: Notice on the Sale of Investment Products and MAS Notice FAA-N16: Notice on Recommendations on Investment Products).

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The securities may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission ("ASIC"), in relation to the offering. This offering document does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001 (the "Corporations Act"), and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the securities may only be made to persons (the "Exempt Investors") who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the securities without disclosure to investors under Chapter 6D of the Corporations Act.

The securities applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring securities must observe such Australian on-sale restrictions.

This offering document contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this offering document is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Dubai International Financial Centre

This offering document relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority ("DFSA"). This offering document is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth in this prospectus and has no responsibility for the offering document. The securities to which this offering document relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the securities offered should conduct their own due diligence on the securities. If you do not understand the contents of this offering document you should consult an authorized financial advisor.

Switzerland

We have not and will not register with the Swiss Financial Market Supervisory Authority ("FINMA") as a foreign collective investment scheme pursuant to Article 119 of the Federal Act on Collective Investment Scheme of 23 June 2006, as amended ("CISA"), and accordingly the securities being offered pursuant to this prospectus have not and will not be approved, and may not be licenseable, with FINMA. Therefore, the securities have not been authorized for distribution by FINMA as a foreign collective investment scheme pursuant to Article 119 CISA and the securities offered hereby may not be offered to the public (as this term is defined in Article 3 CISA) in or from Switzerland. The securities may solely be offered to "qualified investors," as this term is defined in Article 10 CISA, and in the circumstances set out in Article 3 of the Ordinance on Collective Investment Scheme of 22 November 2006, as amended ("CISO"), such that there is no public offer. Investors, however, do not benefit from protection under CISA or CISO or supervision by FINMA. This prospectus and any other materials relating to the securities are strictly personal and confidential to each offeree and do not constitute an offer to any other person. This prospectus may only be used by those qualified investors to whom it has been handed out in connection with the offer described in this prospectus and may neither directly or indirectly be distributed or made available to any person or entity other than its recipients. It may not be used in connection with any other offer and shall in particular not be copied and/or distributed to the public in Switzerland or from Switzerland. This prospectus does not constitute an issue prospectus as that term is understood pursuant to Article 652a and/or 1156 of the Swiss Federal Code of Obligations. We have not applied for a listing of the securities on the SIX Swiss Exchange or any other regulated securities market in Switzerland, and consequently, the information presented in this prospectus does not necessarily comply with the information standards set out in the listing rules of the SIX Swiss Exchange and corresponding prospectus schemes annexed to the listing rules of the SIX Swiss Exchange.

LEGAL MATTERS

The validity of our ADSs and certain other matters of English law and U.S. federal law will be passed upon for us by Goodwin Procter LLP. Legal counsel to the underwriters in connection with this offering are Cooley LLP.

EXPERTS

The financial statements as of December 31, 2017 and 2018 and for the years then ended included in this prospectus have been so included in reliance on the report (which contains an explanatory paragraph relating to the Company's restatement of previously issued financial statements as described in Note 1 to the consolidated financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

The registered business address of PricewaterhouseCoopers LLP is 1 Embankment Place, London, WC2N 6RH, United Kingdom.

SERVICE OF PROCESS AND ENFORCEMENT OF LIABILITIES

We are incorporated and currently existing under the laws of England and Wales. In addition, certain of our directors and officers reside outside of the United States and most of the assets of our non-U.S. subsidiaries are located outside of the United States. As a result, it may be difficult for investors to effect service of process on us or those persons in the United States or to enforce in the United States judgments obtained in United States courts against us or those persons based on the civil liability or other provisions of the United States securities laws or other laws.

In addition, uncertainty exists as to whether the courts of England and Wales would:

- recognize or enforce judgments of United States courts obtained against us or our directors or officers predicated upon the civil liabilities provisions of the securities laws of the United States or any state in the United States; or

- entertain original actions brought in England and Wales against us or our directors or officers predicated upon the securities laws of the United States or any state in the United States.

We have been advised by Goodwin Procter LLP that there is currently no treaty between (i) the United States and (ii) England and Wales providing for reciprocal recognition and enforcement of judgments of United States courts in civil and commercial matters (although the United States and the United Kingdom are both parties to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards) and that a final judgment for the payment of money rendered by any general or state court in the United States based on civil liability, whether predicated solely upon the United States securities laws, would not be automatically enforceable in England and Wales. We have also been advised by Goodwin Procter LLP that any final and conclusive monetary judgment for a definite sum obtained against us in United States courts would be treated by the courts of England and Wales as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that:

- the relevant U.S. court had jurisdiction over the original proceedings according to English conflicts of laws principles at the time when proceedings were initiated;

- England and Wales courts had jurisdiction over the matter on enforcement and we either submitted to such jurisdiction or were resident or carrying on business within such jurisdiction and were duly served with process;

- the U.S. judgment was final and conclusive on the merits in the sense of being final and unalterable in the court that pronounced it and being for a definite sum of money;

- the judgment given by the courts was not in respect of penalties, taxes, fines or similar fiscal or revenue obligations (or otherwise based on a U.S. law that an English court considers to relate to a penal, revenue or other public law);

- the judgment was not procured by fraud;

- recognition or enforcement of the judgment in England and Wales would not be contrary to public policy or the Human Rights Act 1998;

- the proceedings pursuant to which judgment was obtained were not contrary to natural justice;

- the U.S. judgment was not arrived at by doubling, trebling or otherwise multiplying a sum assessed as compensation for the loss or damages sustained and not being otherwise in breach of Section 5 of the U.K. Protection of Trading Interests Act 1980, or is a judgment based on measures designated by the Secretary of State under Section 1 of that Act;

- there is not a prior decision of an English court or the court of another jurisdiction on the issues in question between the same parties; and
- the English enforcement proceedings were commenced within the limitation period.

Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the United States securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision.

Subject to the foregoing, investors may be able to enforce in England and Wales judgments in civil and commercial matters that have been obtained from U.S. federal or state courts. Nevertheless, we cannot assure you that those judgments will be recognized or enforceable in England and Wales.

If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement. In addition, it may not be possible to obtain an English judgment or to enforce that judgment if the judgment debtor is or becomes subject to any insolvency or similar proceedings, or if the judgment debtor has any set-off or counterclaim against the judgment creditor. Also note that, in any enforcement proceedings, the judgment debtor may raise any counterclaim that could have been brought if the action had been originally brought in England unless the subject of the counterclaim was in issue and denied in the U.S. proceedings.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 (File Number 333-) under the Securities Act with respect to the ADSs we are offering by this prospectus. A related registration statement on Form F-6 will be filed with the SEC to register the ADSs. This prospectus does not contain all of the information included in the registration statement. For further information pertaining to us and the ADSs, you should refer to the registration statement and to its exhibits. Whenever we make reference in this prospectus to any of our contracts, agreements or other documents, the references are not necessarily complete, and you should refer to the exhibits attached to the registration statement for copies of the actual contract, agreement or other document.

Upon the closing of the offering, we will be subject to the informational requirements of the Securities Exchange Act of 1934 and will file annual, quarterly and current reports, proxy statements and other information with the SEC. You can read our SEC filings, including the registration statement, over the Internet at the SEC's website at *www.sec.gov*.

We intend to furnish the depositary with our annual reports, which will include a review of operations and annual audited consolidated combined financial statements prepared in conformity with U.S. GAAP, and all notices of shareholders' meetings and other reports and communications that are made generally available to our shareholders. The depositary will make such notices, reports and communications available to holders of ADSs and will mail to all record holders of ADSs the information contained in any notice of a shareholders' meeting received by the depositary from us.

BICYCLE THERAPEUTICS LIMITED

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Index to Consolidated Financial Statements as of and for the Years Ended December 31, 2017 and 2018

Report of Independent Registered Public Accounting Firm

To the Board of Directors of Bicycle Therapeutics Limited

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Bicycle Therapeutics Limited and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, consolidated statements of convertible preferred shares and shareholders' (deficit) equity and consolidated statements of cash flows for the years then ended, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Restatement of Previously Issued Financial Statements

As discussed in Note 1 to the consolidated financial statements, the Company has restated its 2017 financial statements to correct an error.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB and in accordance with auditing standards generally accepted in the United States of America. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP
Cambridge, United Kingdom
March 22, 2019

We have served as the Company's or its predecessor's auditor since 2010, which includes periods before the Company became subject to SEC reporting requirements.

Bicycle Therapeutics Limited

Consolidated Balance Sheets

(amounts in thousands, except share and per share data)

	December 31,		Pro Forma December 31,
	2017	2018	2018
	(as restated)		(unaudited)
Assets			
Current assets:			
Cash	$ 67,663	$ 63,380	$ 63,387
Accounts receivable	—	5,021	5,021
Prepaid expenses and other current assets	848	2,076	2,076
Research and development incentives receivable	3,001	6,292	6,292
Total current assets	71,512	76,769	76,776
Property and equipment, net	1,362	1,818	1,818
Other assets	1,127	3,039	3,039
Total assets	$ 74,001	$ 81,626	$ 81,633
Liabilities, convertible preferred shares and shareholders' (deficit) equity			
Current liabilities:			
Accounts payable	$ 2,065	$ 1,887	$ 1,887
Accrued expenses and other current liabilities	3,405	7,032	7,032
Deferred revenue, current portion	3,981	10	10
Total current liabilities	9,451	8,929	8,929
Warrant liability	4,411	4,804	—
Deferred revenue, net of current portion	10,486	14,625	14,625
Other long-term liabilities	396	897	897
Total liabilities	24,744	29,255	24,451
Commitments and contingencies (Note 12)			
Series A convertible preferred shares, £0.01 nominal value; 3,000,001 shares authorized at December 31, 2017 and 2018; 2,800,001 shares issued and outstanding at December 31, 2017 and 2018; liquidation value of $35,753 at December 31, 2018; no shares authorized, issued or outstanding, pro forma as of December 31, 2018 (unaudited)	41,820	41,820	—
Series B1 convertible preferred shares, £0.01 nominal value; 4,690,485 shares authorized at December 31, 2017 and 2018; 3,947,198 shares issued and outstanding at December 31, 2017 and 2018; liquidation value of $57,460 at December 31, 2018; no shares authorized, issued or outstanding, pro forma as of December 31, 2018 (unaudited)	54,621	54,621	—
Series B2 convertible preferred shares, £0.01 nominal value; no shares authorized at December 31, 2017 and 1,403,633 shares authorized at December 31, 2018; no shares issued and outstanding at December 31, 2017 and 1,323,248 issued and outstanding at December 31, 2018; liquidation value of $26,274 at December 31, 2018; no shares authorized, issued or outstanding, pro forma as of December 31, 2018 (unaudited)	—	25,756	—
Shareholders' (deficit) equity:			
Ordinary shares, £0.01 nominal value; 8,905,805 shares authorized at December 31, 2017 and 10,813,450 shares authorized at December 31, 2018; 371,922 and 628,902 shares issued at December 31, 2017 and December 31, 2018, respectively; 258,228 and 570,156 shares outstanding at December 31, 2017 and December 31, 2018, respectively; 9,270,994 shares issued and 9,212,248 shares outstanding, pro forma at December 31, 2018 (unaudited)	4	8	118
Additional paid-in capital	839	1,859	128,757
Accumulated other comprehensive income (loss)	69	(1,751)	(1,751)
Accumulated deficit	(48,096)	(69,942)	(69,942)
Total shareholders' (deficit) equity	(47,184)	(69,826)	57,182
Total liabilities, convertible preferred shares and shareholders' (deficit) equity	$ 74,001	$ 81,626	$ 81,663

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics Limited

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except share and per share amounts)

	Year Ended December 31,	
	2017	2018
	(as restated)	
Collaboration revenues	$ 2,060	$ 7,136
Operating expenses:		
Research and development	11,866	20,761
General and administrative	6,407	8,121
Total operating expenses	18,273	28,882
Loss from operations	(16,213)	(21,746)
Other income (expense):		
Interest and other income	50	169
Other expense	(119)	(665)
Total other expense, net	(69)	(496)
Net loss before income tax provision	(16,282)	(22,242)
Benefit from income taxes	(23)	(396)
Net loss	$ (16,259)	$ (21,846)
Net loss attributable to ordinary shareholders	$ (16,259)	$ (21,846)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (69.74)	$ (71.13)
Weighted average ordinary shares outstanding, basic and diluted	233,134	307,123
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)		$ (2.76)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)		7,665,736
Comprehensives Loss:		
Net loss	$ (16,259)	$ (21,846)
Other comprehensive income (loss):		
Foreign currency translation adjustment	2,355	(1,820)
Total comprehensive loss	$ (13,904)	$ (23,666)

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics Limited
Consolidated Statements of Convertible Preferred Shares and Shareholders' (Deficit) Equity
(In thousands, except share amounts)

	Series A Convertible Preferred Shares		Series B1 Convertible Preferred Shares		Series B2 Convertible Preferred Shares		Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Shareholders (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2016	2,800,001	$ 41,820	—	$ —	—	$ —	221,292	$ 3	$ 324	$ (2,286)	$ (31,837)	$ (33,79
Issuance of convertible preferred shares, net of issuance costs of $587 and fair value of warrants to subscribe for convertible preferred shares of $3,254 (as restated)	—	—	3,947,198	54,621	—	—	—	—	—	—	—	-
Issuance of restricted share awards (as restated)	—	—	—	—	—	—	33,927	1	114	—	—	11
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	3,009	—	—	—	—	-
Share-based compensation expense (as restated)	—	—	—	—	—	—	—	—	401	—	—	40
Foreign currency translation adjustment (as restated)	—	—	—	—	—	—	—	—	—	2,355	—	2,35
Net loss (as restated)	—	—	—	—	—	—	—	—	—	—	(16,259)	(16,25
Balance at December 31, 2017 (as restated)	2,800,001	41,820	3,947,198	54,621	—	—	258,228	4	839	69	(48,096)	(47,18
Issuance of convertible preferred shares, net of issuance costs of $327	—	—	—	—	1,323,248	25,756	—	—	—	—	—	-
Issuance of restricted share awards	—	—	—	—	—	—	66,933	1	223	—	—	22
Issuance of ordinary shares in exchange for surrender of vested share options							238,443	3	(3)	—	—	-
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	6,552	—	—	—	—	-
Share-based compensation expense	—	—	—	—	—	—	—	—	800	—	—	80
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(1,820)	—	(1,82
Net loss	—	—	—	—	—	—	—	—	—	—	(21,846)	(21,84
Balance at December 31, 2018	2,800,001	$ 41,820	3,947,198	$ 54,621	1,323,248	$ 25,756	570,156	$ 8	$ 1,859	$ (1,751)	$ (69,942)	$ (69,82
Conversion of convertible preferred shares to ordinary shares (unaudited)	(2,800,001)	(41,820)	(3,947,198)	(54,621)	(1,323,248)	(25,756)	8,070,447	103	122,094	—	—	122,19
Conversion of warrant liability to equity (unaudited)	—	—	—	—	—	—	571,645	7	4,804	—	—	4,81
Pro forma balance at December 31, 2018 (unaudited)	—	$ —	—	$ —	—	$ —	9,212,248	$ 118	$ 128,757	$ (1,751)	$ (69,942)	$ 57,18

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics Limited

Consolidated Statements of Cash Flows

(In thousands)

	Year Ended December 31, 2017 (as restated)	Year Ended December 31, 2018
Cash flows from operating activities:		
Net loss	$ (16,259)	$ (21,846)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation expense	515	1,023
Depreciation and amortization	332	712
Non-cash research and development expense	856	—
Change in fair value of warrant liability	119	665
Changes in operating assets and liabilities:		
Accounts receivable	—	(400)
Research and development incentives receivable	(1,407)	(3,586)
Prepaid expenses and other current assets	(330)	(1,329)
Other assets	(1,039)	(301)
Accounts payable	67	(169)
Accrued expenses and other current liabilities	1,267	2,557
Deferred revenue	14,081	(3,947)
Other long-term liabilities	383	543
Net cash used in operating activities	(1,415)	(26,078)
Cash used in investing activities:		
Purchases of property and equipment	(1,113)	(1,186)
Net cash used in investing activities	(1,113)	(1,186)
Cash flows from financing activities:		
Proceeds from issuance of series B1 convertible preferred shares, net of issuance costs	57,875	—
Proceeds from issuance of series B2 convertible preferred shares, net of issuance costs	—	26,005
Proceeds from the sale of ordinary shares	1	1
Payments of initial public offering costs	—	(576)
Net cash provided by financing activities	57,876	25,430
Effect of exchange rate changes on cash	2,913	(2,449)
Net increase (decrease) in cash	58,261	(4,283)
Cash at beginning of year	9,402	67,663
Cash at end of year	$ 67,663	$ 63,380
Supplemental disclosure of cash flow information		
Cash paid for income taxes	—	73
Advance billings on deferred revenue included in accounts receivable	—	5,045
Series B2 convertible preferred financing costs accrued but not paid	—	249
Deferred initial public offering costs accrued but not paid	—	1,076

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements

1. Nature of the business and basis of presentation

Bicycle Therapeutics Limited (collectively with its subsidiaries, the "Company") is a clinical-stage biopharmaceutical company developing a novel class of medicines, which the Company refers to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic properties of a small molecule. The Company's initial internal programs are focused on oncology indications with high unmet medical need. The Company's lead product candidate, BT1718, is a *Bicycle* Toxin Conjugate ("BTC") that is being developed to target tumors that express Membrane Type 1 matrix metalloprotease. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK. The Company is also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2 and Nectin-4, respectively, for oncology indications. The Company is currently conducting Investigational New Drug application-enabling activities for BT5528 and BT8009. The Company's discovery pipeline in oncology includes *Bicycle*-targeted innate immune activators, as well as T-cell modulators. Beyond oncology, the Company is collaborating with biopharmaceutical companies and organizations in therapeutic areas that include anti-infective, cardiovascular, hematology, ophthalmology and respiratory indications.

The Company was incorporated in 2017 as a limited liability company in England and Wales to act as the holding company for three wholly-owned subsidiaries, two of which are based in the United Kingdom ("U.K.") and one of which has its principal office in Lexington, Massachusetts, near Boston. The English subsidiaries are BicycleTx Limited and BicycleRD Limited, and the U.S. subsidiary is Bicycle Therapeutics Inc.

2017 Reorganization

Prior to December 2017, the development of *Bicycles* was conducted by Bicycle Therapeutics Limited (for the purpose of the 2017 Reorganization referred to as "BTL OldCo."), a limited liability company incorporated in England and Wales on July 13, 2009, and its wholly-owned U.S. subsidiary, Bicycle Therapeutics Inc., which was incorporated in Delaware in April 2016.

During 2017, the Company entered into a series of transactions to effect a reorganization, and created a new holding company to facilitate its ability to pursue an initial public offering ("IPO"). These transactions are collectively referred to as the 2017 Reorganization.

On October 27, 2017, BTL OldCo. changed its name to BicycleRD Limited. In addition, a new holding company, Bicycle Therapeutics Limited (for the purpose of 2017 Reorganization referred to as "BTL NewCo."), was incorporated as a limited liability company in England and Wales, and BicycleTx Limited was incorporated as a limited liability company in England and Wales as a wholly-owned subsidiary of BTL NewCo.

On December 4, 2017, a share-for-share exchange was enacted pursuant to which the shareholders of BTL OldCo. exchanged their shares for equivalent shares of BTL NewCo. (both in terms of share class and number). As a result, the BTL NewCo. became the sole shareholder of BTL OldCo. In addition, the holders of warrants and/or share options to subscribe for shares in BTL OldCo. terminated or surrendered their warrants and/or share options in BTL OldCo. and were issued with warrants and share options on the same terms to subscribe for equivalent shares in BTL NewCo. (both in terms of share class and number). Those holders of restricted shares in BTL

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

OldCo. pursuant to share vesting agreements terminated their existing share vesting agreements with BTL OldCo. and entered into share vesting agreements on the same terms and in respect of equivalent shares with BTL NewCo. (both in terms of share class and number).

On December 5, 2017, BTL OldCo. transferred the entire issued share capital in Bicycle Therapeutics Inc. to BTL NewCo. and certain of its assets, including all employees, were transferred to BicycleTx Limited.

The 2017 Reorganization was accounted for as a transaction of entities under common control. Upon completion of the 2017 Reorganization, the historical consolidated financial statements of BTL OldCo. became the historical consolidated financial statements of the Company, which had nominal assets and liabilities and had not conducted any operations other than the actions incidental to the share exchange and its incorporation. The Company concluded that the reorganization resulted in no change in the material rights and preferences of each respective class of equity interests and no change in the fair value of each respective class of equity interests before and after the reorganization.

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel and collaboration partners, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations, and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval prior to commercialization. Even if the Company's research and development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Liquidity

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Through December 31, 2018, the Company has funded its operations with proceeds from sales of convertible preferred shares (Note 6) and proceeds received from its collaboration arrangements (Note 10). Since inception, the Company has incurred recurring losses, including net losses of $16.3 million for the year ended December 31, 2017 (restated) and $21.8 million for the year ended December 31, 2018. As of December 31, 2018, the Company had an accumulated deficit of $69.9 million. The Company expects to continue to generate operating losses in the foreseeable future.

In accordance with Accounting Standards Update ("ASU") No. 2014-15, *Presentation of Financial Statements — Going Concern,* the Company has evaluated whether there are certain conditions and events, considered in the aggregate, that raise substantial doubt and the Company's ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. As of March 22, 2019, the issuance date of the annual consolidated financial statements for the year ended December 31, 2018, the Company expects that its cash, will be sufficient to fund its operating expenses and capital expenditure requirements

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

through at least twelve months from the issuance date of the annual consolidated financial statements and the interim consolidated financial statements.

The Company is seeking to complete an initial public offering ("IPO") of its ordinary shares in the form of American Depositary Shares. Upon the completion of a public offering with at least £50.0 million of gross proceeds and at a price of at least £31.10 per share, subject to appropriate adjustment in the event of any share split or other similar recapitalization (a "Qualified IPO"), the Company's outstanding convertible preferred shares will automatically convert into ordinary shares (Note 6).

In the event the Company does not complete an IPO, the Company expects to seek additional funding through private equity financings, collaborations, government grants, strategic alliances and or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborations. The terms of any future financing may adversely affect the rights or interests of the Company's shareholders. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects.

Although management continues to pursue these plans, there can be no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Restatement of previously reported financial statements

In connection with the December 31, 2018 year-end financial statement close process, the Company identified misstatements in the historical consolidated financial statements, related to the fair value determination of (i) the warrant liability (Note 7) and (ii) ordinary shares utilized to calculate share based compensation expense. The fair value of the warrant liability and ordinary shares, which was derived from an independent third-party valuation report, included an error in an input to the valuation model related to the payment that would be made to the Series A and Series B1 preferred warrants holders in a sale liquidity event, following the exercise of the warrants.

The Company has corrected the misstatement by reflecting the impact of the revised valuation on the fair value of ordinary shares and the warrant liability for the periods that the warrants were outstanding which impacts all of the following:

- the fair value allocation between the Series B1 convertible preferred shares carrying amount and warrant liability on the date of issuance;
- the measurement of Series A convertible preferred share warrants recorded as research and development expense on issuance;
- the impact to the change in fair value of the warrant liability recorded as other expense;
- the impact of exchange rates on the translation of the warrant liability to USD included in accumulated other comprehensive income (loss);

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

- the impact of the revised valuation to share based compensation expense recorded as research and development and general and administrative expenses and additional paid-in capital; and
- the associated benefit from income taxes and respective deferred tax assets as recorded as other assets.

As a result, the Company has restated its consolidated balance sheet as of December 31, 2017, the related consolidated statement of operations and comprehensive loss, consolidated statement of convertible preferred shares and shareholders' (deficit) equity, and consolidated statement of cash flows for the year ended December 31, 2017. The Company has also disclosed the impact of the adjustments to the previously issued consolidated financial statements as of September 30, 2018 (unaudited) and for the nine month periods ended September 30, 2017 and 2018 (unaudited). The impact of these adjustments is detailed in the tables below.

Consolidated Balance Sheet

	Previously reported		As restated
	December 31, 2017	Adjustment	December 31, 2017
		(in thousands)	
Other assets	$ 1,058	$ 69	$ 1,127
Total assets	73,932	69	74,001
Warrant liability	10,497	(6,086)	4,411
Total liabilities	30,830	(6,086)	24,744
Series B1 convertible preferred shares	49,328	5,293	54,621
Additional paid-in capital	776	63	839
Accumulated other comprehensive income (loss)	(165)	234	69
Accumulated deficit	(48,661)	565	(48,096)
Total shareholders' (deficit) equity	(48,046)	862	(47,184)

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

Consolidated Statement of Operations and Comprehensive Loss

	Previously reported		As restated
	Year Ended December 31, 2017	Adjustment	Year Ended December 31, 2017
	(in thousands, except per share data)		
Research and development	$ 12,242	$ (376)	$ 11,866
General and administrative	6,346	61	6,407
Total operating expenses	18,588	(315)	18,273
Loss from operations	(16,528)	315	(16,213)
Other expense	(300)	181	(119)
Total other expense, net	(250)	181	(69)
Net loss before income tax provision	(16,778)	496	(16,282)
Provision for (benefit from) income taxes	46	(69)	(23)
Net loss	(16,824)	565	(16,259)
Net loss attributable to ordinary shareholders	(16,824)	565	(16,259)
Net loss per share attributable to ordinary shareholders, basic and diluted	(72.16)	2.42	(69.74)
Foreign currency translation adjustment	2,121	234	2,355
Total comprehensive loss	(14,703)	799	(13,904)

Consolidated Statement of Cash flows

	Previously reported		As restated
	Year Ended December 31, 2017	Adjustment	Year Ended December 31, 2017
		(in thousands)	
Cash flows from operating activities:			
Net loss	$ (16,824)	$ 565	$ (16,259)
Share-based compensation expense	452	63	515
Non-cash research and development expense	1,234	(378)	856
Change in fair value of warrant liability	300	(181)	119
Other assets	(970)	(69)	(1,039)

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

Consolidated Balance Sheet

	Previously reported		As restated
	September 30, 2018	Adjustment	September 30, 2018
		(in thousands)	
Other assets	$ 1,163	$ 260	$ 1,423
Total assets	62,337	260	62,597
Warrant liability	10,301	(4,580)	5,721
Total liabilities	33,706	(4,580)	29,126
Series B1 convertible preferred shares	49,328	5,293	54,621
Additional paid-in capital	1,357	298	1,655
Accumulated other comprehensive income (loss)	(1,336)	7	(1,329)
Accumulated deficit	(62,543)	(758)	(63,301)
Total shareholders' (deficit) equity	(62,517)	(453)	(62,970)

Consolidated Statements of Operations and Comprehensive Loss

	Previously reported		As restated	Previously reported		As restated
	Nine months ended September 30, 2017	Adjustment	Nine months ended September 30, 2017	Nine months ended September 30, 2018	Adjustment	Nine months ended September 30, 2018
	(unaudited) (in thousands, except per share data)					
Research and development	$ 7,761	$ (381)	$ 7,380	$ 14,162	$ 106	$ 14,268
General and administrative	3,837	29	3,866	5,886	129	6,015
Total operating expenses	11,598	(352)	11,246	20,048	235	20,283
Loss from operations	(10,193)	352	(9,841)	(13,969)	(235)	(14,204)
Other expense	(300)	181	(119)	(193)	(1,279)	(1,472)
Total other expense, net	(273)	181	(92)	(118)	(1,279)	(1,397)
Net loss before income tax provision	(10,466)	533	(9,933)	(14,087)	(1,514)	(15,601)
Benefit from income taxes	(32)	9	(23)	(205)	(191)	(396)
Net loss	(10,434)	524	(9,910)	(13,882)	(1,323)	(15,205)
Net loss attributable to ordinary shareholders	(10,434)	524	(9,910)	(13,882)	(1,323)	(15,205)
Net loss per share attributable to ordinary shareholders, basic and diluted	(45.48)	2.28	(43.19)	(47.54)	(4.53)	(52.08)
Foreign currency translation adjustment	1,708	166	1,874	(1,171)	(227)	(1,398)
Total comprehensive loss	(8,726)	690	(8,036)	(15,053)	(1,549)	(16,602)

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

1. Nature of the business and basis of presentation (Continued)

Consolidated Statements of Cash flows

	Previously reported		As restated	Previously reported		As restated
	Nine months ended September 30, 2017	Adjustment	Nine months ended September 30, 2017	Nine months ended September 30, 2018	Adjustment	Nine months ended September 30, 2018
	(unaudited, in thousands)					
Cash flows from operating activities:						
Net loss	$ (10,434)	$ 524	$ (9,910)	$ (13,882)	$ (1,323)	$ (15,205)
Share-based compensation expense	245	26	271	581	235	816
Non-cash research and development expense	1,234	(378)	856	—	—	—
Change in fair value of warrant liability	300	(181)	119	193	1,279	1,472
Other assets	(283)	(9)	(292)	(124)	(191)	(315)

Basis of presentation

The accompanying consolidated financial statements include the accounts of Bicycle Therapeutics Limited and its wholly owned subsidiaries, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics Inc. All intercompany balances and transactions have been eliminated on consolidation.

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP").

2. Summary of Significant Accounting Policies

Use of estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, revenue recognition, the fair value of ordinary shares and share based compensation, the valuation of the warrant liability, and income taxes. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. Estimates are periodically reviewed in light of reasonable changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates or assumptions.

The Company utilizes significant estimates and assumptions in determining the fair value of its ordinary shares. The Company has utilized various valuation methodologies in accordance with the framework of the 2004 American Institute of Certified Public Accountants Technical Practice Aid,

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Valuation of Privately-Held Company Equity Securities Issued as Compensation, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require the exercise of judgment by the Company. These estimates and assumptions include a number of objective and subjective factors, including external market conditions, the prices at which the Company sold convertible preferred shares, the superior rights and preferences of securities senior to the Company's ordinary shares at the time of, and the likelihood of, achieving a liquidity event, such as an initial public offering or sale. Significant changes to the key assumptions used in the valuations could result in different fair values of the Company's ordinary shares at each valuation date.

Unaudited pro forma information

On March 7, 2019, the holders of the Series B1 warrants to subscribe for Series B1 Preferred Shares agreed that 50% of the warrants will be exercised in conjunction with the IPO and 50% of the warrants will be extinguished (Note 7). The accompanying unaudited pro forma consolidated balance sheet and consolidated statements of convertible preferred shares and shareholders' (deficit) equity as of December 31, 2018 has been prepared to give effect, upon the closing of a Qualified IPO, to (i) the automatic conversion of all outstanding convertible preferred shares as of December 31, 2018 into ordinary shares, and (ii) the exercise of 200,000 warrants to subscribe for Series A convertible preferred shares immediately prior to an IPO, and (iii) the exercise of the 371,645 warrants to subscribe for Series B1 convertible preferred shares, as well as (iv) the resulting reclassification of the warrant liability to additional paid-in capital, as if the proposed IPO had occurred on December 31, 2018.

In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2018 have been prepared to give effect, upon the closing of a Qualified IPO, to (i) the automatic conversion of all outstanding shares of convertible preferred shares into ordinary shares, and (ii) the exercise of 200,000 warrants to subscribe for Series A convertible preferred shares immediately prior to an IPO, and (iii) the exercise of the warrants to subscribe for 371,645 Series B1 convertible preferred shares which would otherwise expire upon the completion of an IPO, as if the proposed IPO had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares or preferred share warrants.

Foreign currency and currency translation

The functional currency of Bicycle Therapeutics Limited and its wholly owned non-U.S. subsidiaries, BicycleTx Limited and BicycleRD Limited, is the British Pound Sterling and the consolidated financial statements are presented in United States dollars ("USD"). The functional currency of Bicycle Therapeutics Inc. is the USD. The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. The functional currency of the Company's subsidiaries is the same as the local currency.

Monetary assets and liabilities denominated in currencies other than the functional currency are remeasured into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. Adjustments that arise from exchange rate changes on transactions denominated in a currency other than the local currency are included in general and administrative expense in the consolidated statements of operations and comprehensive loss as incurred. The Company recorded a foreign exchange loss of $0.6 million and a foreign exchange gain of $0.3 million for the years ended December 31, 2017 and 2018, respectively.

The Company translates the assets and liabilities of Bicycle Therapeutics Limited, BicycleTx Limited and BicycleRD Limited into USD at the exchange rate in effect on the balance sheet date. Revenues and expenses are translated at the average exchange rate in effect during the period. Unrealized translation gains and losses are recorded as a cumulative translation adjustment, which is included in the consolidated statements of convertible preferred shares and shareholders' (deficit) equity as a component of accumulated other comprehensive income (loss).

Concentrations of credit risk and of significant suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and accounts receivable. The Company deposits its cash in financial institutions in amounts that may exceed federally insured limits and has not experienced any losses on such accounts. The Company does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

Accounts receivable primarily consist of amounts due under the collaboration agreements between BicycleTx Limited and AstraZeneca AB ("AstraZeneca") and Bioverativ, Inc. ("Bioverativ") and between BicycleRD Limited and Oxurion NV. ("Oxurion"), formerly ThromboGenics NV. (Note 10), for which the Company does not obtain collateral. As of December 31, 2017 and 2018, all of the Company's revenue to date has been generated from the collaboration agreements with AstraZeneca, Bioverativ, and Oxurion.

The Company relies, and expects to continue to rely, on a small number of vendors to manufacture supplies and raw materials for its development programs. These programs could be adversely affected by a significant interruption in these manufacturing services or the availability of raw materials.

Cash and cash equivalents

The Company considers all highly liquid investments with original maturities of three months or less at date of purchase to be cash equivalents. The Company had no cash equivalents at December 31, 2017 and 2018.

Accounts receivable

The Company makes judgments as to its ability to collect outstanding receivables and provides an allowance for receivables when collection becomes doubtful. Provisions are made based upon a specific review of all significant outstanding invoices and the overall quality and age of those invoices. To date, the Company has not had any write-offs of bad debt, and the Company did not have an allowance for doubtful accounts as of December 31, 2017 and 2018.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Deferred offering costs

The Company capitalizes certain legal, professional accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in shareholders' (deficit) equity as a reduction of proceeds generated as a result of the offering. Should an in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the consolidated statements of operations and comprehensive loss. At December 31, 2018, the Company capitalized $1.6 million of offering costs, which are recorded within other assets in the consolidated balance sheets.

Property and equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization expense is recognized using the straight-line method over the estimated useful lives of the respective assets as follows:

	Estimated Useful Life
Laboratory equipment	3 to 5 years
Leasehold improvements	Lesser of lease term or useful life
Computer equipment	3 years
Furniture and office equipment	5 years

Costs for capital assets not yet placed into service are capitalized as construction-in-progress and depreciated in accordance with the above guidelines once placed into service. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in loss from operations. As of December 31, 2017 and 2018, there have been no significant asset retirements to date. Expenditures for repairs and maintenance are charged to expense as incurred.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. To date, the Company has not recorded any impairment losses on long-lived assets.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Deferred rent

The Company recognizes rent expense on a straight-line basis over the respective lease terms and has recorded deferred rent for rent expense incurred but not yet paid.

Fair value measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1 — Quoted prices in active markets for identical assets or liabilities.
- Level 2 — Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3 — Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The Company's warrant liability is carried at fair value, determined according to the fair value hierarchy described above (Note 3). The carrying values of accounts receivable, research and development incentives receivable, other current assets, accounts payable and accrued expenses and other current liabilities approximate their fair values due to the short-term nature of these assets and liabilities.

Warrant liability

The Company classifies warrants to subscribe for Series A and Series B1 convertible preferred shares (Note 6) as a liability on its consolidated balance sheets as these warrants to subscribe for Series A and Series B1 convertible preferred shares are free-standing financial instruments that may require the Company to transfer assets upon exercise. The warrant liability was initially recorded at fair value upon the date of the warrants' issuance and is subsequently remeasured to fair value at each reporting date. Changes in the fair value of the warrant liability are recognized as a component of other income (expense), net in the consolidated statements of operations and comprehensive loss. Changes in the fair value of the warrant liability will continue to be recognized until the warrants to subscribe for Series A and Series B1 convertible preferred shares are exercised or expire.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Segment and geographic information

Operating segments are defined as components of a business for which separate discrete financial information is available for evaluation by the chief operating decision maker in deciding how to allocate resources and assess performance. The Company and its chief operating decision maker, the Company's Chief Executive Officer, view the Company's operations and manages its business as a single operating segment, which is developing a unique class of chemically synthesized medicines based on its proprietary constrained peptides.

The Company operates in two geographic regions: the United Kingdom and the United States.

Revenue recognition

The Company's revenues are generated primarily through collaborative arrangements and license agreements with pharmaceutical companies. The terms of these arrangements may include (i) performing research and development services using the Company's bicyclic peptide screening platform with the goal of identifying compounds for further development and commercialization, (ii) options to obtain additional research and development services or licenses for additional targets, or to optimize product candidates, upon the payment of option fees, or (iii) the transfer of intellectual property rights (licenses).

The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, upfront license fees; payments for research and development services; fees upon the exercise of options to obtain additional services or licenses; payments based upon the achievement of defined collaboration objectives; future regulatory and sales-based milestone payments; and royalties on net sales of future products.

The Company has adopted ASU 2014-09, *Revenue from Contracts with Customers* (Topic 606) ("ASC 606") and all subsequent amendments using the full retrospective transition method for all periods presented. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, it performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when, or as, the Company satisfies the performance obligations. The Company only applies the five-step model to contracts when it is probable that the entity will collect substantially all of the consideration it is entitled to in exchange for the goods or services it transfers to the customer. As part of the accounting for these arrangements, the Company must make significant judgments, including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each performance obligation.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Once a contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within the contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations.

Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer. The promised goods or services in the Company's contracts with customers primarily consist of license rights to the Company's intellectual property for research and development, research and development services, options to acquire additional research and development services, and options to obtain additional licenses, such as a commercialization license for a potential product candidate. Promised goods or services are considered distinct when: (i) the customer can benefit from the good or service on its own or together with other readily available resources, and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct, the Company considers factors such as the stage of development of the underlying intellectual property, the capabilities of the customer to develop the intellectual property on their own and whether the required expertise is readily available. In addition, the Company considers whether the collaboration partner can benefit from a promise for its intended purpose without the receipt of the remaining promises, whether the value of the promise is dependent on the unsatisfied promises, whether there are other vendors that could provide the remaining promises, and whether it is separately identifiable from the remaining promises.

The Company estimates the transaction price based on the amount of consideration the Company expects to receive for transferring the promised goods or services in the contract. The consideration may include both fixed consideration and variable consideration. At the inception of each arrangement that includes variable consideration, the Company evaluates the amount of the potential payments and the likelihood that the payments will be received. The Company utilizes either the most likely amount method or expected value method to estimate variable consideration to include in the transaction price based on which method better predicts the amount of consideration expected to be received. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

After the transaction price is determined it is allocated to the identified performance obligations based on the estimated standalone selling price. The Company must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the standalone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction, probabilities of technical and regulatory success and the estimated costs. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amounts the Company would expect to receive for each performance obligation.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

The Company then recognizes as revenue in the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time based on the use of an input method.

Licenses of intellectual property: If a license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are combined with other promises, such as research and development services and a research license, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the research and development and licensing agreement.

Research and Development Services: The promises under the Company's collaboration agreements may include research and development services to be performed by the Company on behalf of the partner. Payments or reimbursements resulting from the Company's research and development efforts are recognized as the services are performed and presented on a gross basis because the Company is the principal for such efforts.

Customer Options: The Company evaluates the customer options to obtain additional items (i.e. additional license rights) for material rights, or options to acquire additional goods or services for free or at a discount. Optional future services that reflect their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations and are accounted for as separate contracts. If optional future services include a material right, they are accounted for as performance obligations. The Company determines an estimated standalone selling price of any material rights for the purpose of allocating the transaction price. The Company considers factors such as the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised or expires.

Milestone payments: The Company's collaboration agreements may include development and regulatory milestones. The Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such milestones and any related constraint, and if necessary, adjusts the estimate of the overall transaction price. Any

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue and net loss in the period of adjustment.

Royalties: For sales-based royalties, including milestone payments based on the level of sales, the Company determines whether the sole or predominant item to which the royalties relate is a license. When the license is the sole or predominant item to which the sales-based royalty relates, the Company recognizes revenue at the later of: (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any sales-based royalty revenue resulting from the Company's collaboration agreements.

The Company receives payments from customers based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional, such as when the Company has a contractual right to payment per the terms of the contract.

For a complete discussion of accounting for collaboration revenues, see Note 10, "Significant Agreements"

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, travel, facilities costs, materials and laboratory supplies, and external costs of outside vendors engaged to conduct preclinical development, clinical development activities, as well as to manufacture clinical trial materials. Facilities costs primarily include the allocation of rent, utilities, and depreciation.

Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized until the related goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered.

Research and manufacturing contract costs and accruals

The Company has entered into various research and development and manufacturing contracts, including contracts with respect to preclinical studies and clinical trials, with companies both inside and outside of the United States. These agreements are generally cancelable with 90 days or less notice, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the research and development and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Research and development incentives and receivable

The Company, through its subsidiaries in the United Kingdom, receives reimbursements of certain research and development expenditures as part of a United Kingdom government's research and development tax reliefs program. Under the program, the Company is able to surrender trading losses that arise from qualifying research and development expenses incurred by the Company's subsidiaries in the United Kingdom for a tax credit of up to 14.5% of the surrendable losses.

Management has assessed the Company's research and development activities and expenditures to determine which activities and expenditures are likely to be eligible under the research and development incentive program described above. At each period end, management estimates the reimbursement available to the Company based on available information at the time.

The Company recognizes income from the research and development incentives when the relevant expenditure has been incurred, the associated conditions have been satisfied and there is reasonable assurance that the reimbursement will be received. The Company records these research and development incentives as a reduction to research and development expenses in the statements of operations and comprehensive loss, as the research and development tax credits are not dependent on us generating future taxable income, the Company's ongoing tax status, or tax position. The research and development incentives receivable represent an amount due in connection with the above program. The Company recorded a reduction to research and development expense of $2.9 million and $5.9 million during the years ended December 31, 2017 and 2018, respectively.

Patent costs

All patent-related costs incurred in connection with preparing, filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the consolidated statements of operations and comprehensive loss.

Share-based compensation

The Company measures all equity awards granted to employees and directors based on the fair value on the date of grant. Compensation expense of those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company records the expense for awards with only service-based vesting conditions using the straight-line method. The Company accounts for forfeitures as they occur.

The Company has granted awards with both a service condition that vest over time and a performance condition that will accelerate vesting upon the achievement of a specified collaboration revenue threshold. For equity awards that contain both performance and service conditions, the Company recognizes share-based compensation expense using an accelerated attribution model over the requisite service period when the achievement of a performance-based milestone is probable based on the relative satisfaction of the performance condition as of the reporting date.

For share-based awards granted to non-employee consultants, compensation expense is recognized over the period during which services are rendered by such consultants until completed. At the end of each financial reporting period prior to completion of the service, the fair

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

value of these awards is remeasured using the then-current fair value of the Company's ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model, as applicable.

The fair value of each restricted ordinary share award is based on the fair value of the Company's ordinary shares, less any applicable purchase price. The fair value of each share option is estimated using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the fair value of ordinary shares, the expected share price volatility, the expected term of the award, the risk-free interest rate, and expected dividends.

Given the absence of an active market for the Company's ordinary shares, the board of directors determined the estimated fair value of the Company's equity instruments based on input from management which utilized the most recently available independent third-party valuation, and considering a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector. The third party valuation reports performed utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants' Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of the Company's ordinary shares at each grant date, including the following: (1) prices paid for the Company's convertible preferred shares, which the Company had sold to outside investors in arm's-length transactions, and the rights, preferences, and privileges of the Company's convertible preferred shares and ordinary shares; (2) the Company's stage of development; (3) the fact that the grants of share-based awards involved illiquid securities in a private company; and (4) the likelihood of achieving a liquidity event for the ordinary shares underlying the share-based awards, such as an IPO or sale of the Company, given prevailing market conditions.

Expected volatility is calculated based on reported volatility data for a representative group of publicly traded companies for which historical information was available. The historical volatility is calculated based on a period of time commensurate with the assumption used for the expected term. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption. The Company uses the simplified method, under which the expected term is presumed to be the midpoint between the vesting date and the end of the contractual term. The Company utilizes this method due to the lack of historical exercise data and the plain nature of its share-based awards. The Company uses the remaining contractual term for the expected life of non-employee awards. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on ordinary shares.

The Company classifies share-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' (deficit) equity that result from transactions and economic events other than those with shareholders. The

2. Summary of Significant Accounting Policies (Continued)

Company recorded unrealized gains and losses related to foreign currency translation as a component of other comprehensive loss as of December 31, 2017 and 2018.

Contingencies

Liabilities for loss contingencies arising from claims, assessments, litigation, fines, penalties and other sources are recorded when it is probable that a liability has been incurred and the amount can be reasonably estimated. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential loss range is probable and reasonably estimable under the provisions of the authoritative guidelines that address accounting for contingencies. The Company expenses costs as incurred in relation to such legal proceedings as general and administrative expense within the consolidated statements of operations and comprehensive loss.

Income taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that will more likely than not be realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Net loss per share

The Company follows the two-class method when computing net loss per share as the Company has issued shares that meet the definition of participating securities. The two-class method determines net loss per share for each class of ordinary and preferred securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to ordinary shareholders for the period to be allocated

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

between ordinary and preferred securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net loss per share attributable to ordinary shareholders is computed by dividing the net loss attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period. Diluted net loss attributable to ordinary shareholders is computed by adjusting net loss attributable to ordinary shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net loss per share attributable to ordinary shareholders is computed by dividing the diluted net loss attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares assuming the dilutive effect of ordinary share equivalents.

The Company's convertible preferred shares contractually entitle the holders of such shares to participate in dividends but contractually do not require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss, such losses are not allocated to such preferred securities. In periods in which the Company reports a net loss attributable to ordinary shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive.

Recently adopted accounting pronouncements

In March 2016, the FASB issued ASU No. 2016-09, *Compensation — Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting ("ASU 2016-09")*. ASU 2016-09 addresses several aspects of the accounting for share-based payment transactions, including the accounting for income taxes, forfeitures, and statutory tax withholding requirements, as well as classification in the statement of cash flows. Certain of these changes are required to be applied retrospectively, while other changes are required to be applied prospectively. The Company adopted this standard for all periods presented and its adoption did not have a material impact on the Company's financial position, results of operations or cash flows.

In March 2018, the FASB issued ASU No. 2018-05, *Income Taxes (Topic 740): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 118* ("ASU 2018-05"). ASU 2018-05 amends SEC paragraphs in ASC 740 to reflect SEC Staff Accounting Bulletin (SAB) No.118. When the 2017 Tax Cuts and Jobs Act (the "Act") was signed into law, the SEC staff released SAB 118 for applying Topic 740 as it relates to the Act. SAB 118 outlines the approach companies may take if they determine that the necessary information is not available (in reasonable detail) to evaluate, compute, and prepare accounting entries to recognize the effect(s) of the Act by the time the financial statements are required to be filed. Companies may use this approach when the timely determination of some or all of the income tax effect(s) from the Act is incomplete by the due date of the financial statements. SAB 118 also prescribes disclosures that reporting entities must provide in these circumstances. The amendments to the Accounting Standards Codification ("ASC") became effective upon issuance. During the year ended December 31, 2018, the Company did not make any adjustments to the provisional amounts recorded as a result of the Act in the year ended December 31, 2017 and the Company considers the accounting related to the Act to be final.

In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes ("ASU 2015-17")*. ASU 2015-17 requires deferred tax liabilities

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

and assets to be classified as non-current in the consolidated balance sheet. The Company adopted ASU 2015-17 retrospectively to all periods presented as of December 31, 2016, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In November 2014, the FASB issued ASU No. 2014-16, *Determining Whether the Host Contract in a Hybrid Financial Instrument Issued in the Form of a Share Is More Akin to Debt or to Equity ("ASU 2014-16")*. The guidance requires an entity to determine the nature of the host contract by considering all stated and implied substantive terms and features of the hybrid financial instrument, weighing each term and feature on the basis of the relevant facts and circumstances (commonly referred to as the whole-instrument approach). The Company adopted ASU 2014-16 as of the required effective date of January 1, 2016 and reflected the adoption on a retrospective basis, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15"), to address diversity in practice in how certain cash receipts and cash payments are presented and classified in the consolidated statements of cash flows. The Company adopted ASU 2016-15 retrospectively to all periods presented, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash ("ASU 2016-18")*. ASU 2016-18 requires that the statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Entities will also be required to reconcile such total to amounts on the balance sheet and disclose the nature of the restrictions. For public entities, this guidance is effective for annual reporting periods beginning after December 15, 2017 and interim periods within those fiscal years. As early adoption was permitted, the Company adopted this standard retrospectively as of January 1, 2016. The Company does not have any restricted cash, and as such the adoption of this standard had no impact on the Company's financial position, results of operations or cash flows.

In May 2017, the FASB issued ASU 2017-09, *Compensation — Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU 2017-09"). The amendments in ASU 2017-09 clarify that modification accounting is required only if the fair value, the vesting conditions, or the classification of the awards (as equity or liability) changes as a result of the changes in terms or conditions. This guidance is effective for all entities for annual reporting periods beginning after December 15, 2017 and interim periods within those fiscal years. As early adoption was permitted, the Company adopted this standard as of January 1, 2016. The adoption of this guidance had no impact on the Company's financial position, results of operations or cash flows.

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"). This guidance revises existing practice related to accounting for leases under ASC Topic 840 Leases ("ASC 840"). ASU 2016-02 will require lessees to recognize most leases on their balance sheet as a right-of-use asset and a lease liability. The lease liability will be equal to the present value of lease payments and the right-of-use asset will be based on the lease liability, subject to adjustment such as for initial direct costs. For income statement purposes, the new standard retains

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

a dual model similar to ASC 840, requiring leases to be classified as either operating or finance. For lessees, operating leases will result in straight-line expense (similar to current accounting by lessees for operating leases under ASC 840). In July 2018, the FASB issued ASU 2018-11, *Leases (Topic 842) Targeted Improvements*, which provides an additional transition method that allows entities to initially apply the new standard at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption without restating prior periods. The guidance is effective for annual reporting periods beginning after December 15, 2018 and interim periods within those fiscal years, and early adoption is permitted. The Company intends to adopt the requirements of the new standard via a cumulative-effect adjustment without restating prior periods. The Company is evaluating the impact that this standard has on the lease of its corporate headquarters in the U.K., the lease of its office and laboratory space in Lexington, MA, and is currently in the process of reviewing its clinical material manufacturing contracts for any embedded leases.

In June 2016, the FASB issued ASU 2016-13, Financial Instruments — Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments ("ASU 2016-13"). ASU 2016-13 provides for a new impairment model that requires measurement and recognition of expected credit losses for most financial assets and certain other instruments, including but not limited to accounts receivable and available for sale debt securities. ASU 2016-13 is effective for the Company for fiscal years beginning after December 15, 2019, and interim periods within those years, with early adoption permitted. The Company is currently evaluating the impact of this guidance on its consolidated financial statements and disclosures.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation — Stock Compensation: Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07") to simplify the accounting for share-based payments to non-employees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The new guidance expands the scope of ASC 718, *Compensation — Stock Compensation*, to include share-based payments granted to non-employees in exchange for goods or services used or consumed in an entity's own operations and supersedes the guidance in ASC Topic 505-50, *Equity-Based Payments to Non-Employees*. The guidance is effective for public business entities in annual periods beginning after December 15, 2018 and interim periods within those years. Early adoption is permitted. The Company is currently evaluating the effect of this guidance on the Company's consolidated financial statements and disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820)*, which modifies, removes and adds certain disclosure requirements on fair value measurements based on the FASB Concepts Statement, *Conceptual Framework for Financial Reporting — Chapter 8: Notes to Financial Statements*. The ASU is effective for all entities for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2019. The amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all periods presented upon their effective date. Early adoption is permitted. The Company is in the process of evaluating the impact of the adoption of the ASU on its consolidated financial statements and disclosures.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

3. Fair value of financial assets and liabilities

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis (in thousands):

	Fair Value Measurement as of December 31, 2017 using:			
	Level 1	Level 2	Level 3 (as restated)	Total (as restated)
Liabilities:				
Warrant liability	$ —	$ —	$ 4,411	$ 4,411
	$ —	$ —	$ 4,411	$ 4,411

	Fair Value Measurement as of December 31, 2018 using:			
	Level 1	Level 2	Level 3	Total
Liabilities:				
Warrant liability	$ —	$ —	$ 4,804	$ 4,804
	$ —	$ —	$ 4,804	$ 4,804

The warrant liability was initially recorded at fair value upon the date of the warrants' issuance and is subsequently remeasured to fair value at each reporting date (Note 7).

During the years ended December 31, 2017 and 2018, there were no transfers between levels.

4. Property and equipment, net

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2017	2018
Laboratory equipment	$ 2,415	$ 3,356
Leasehold improvements	67	75
Computer equipment	193	221
Furniture and office equipment	26	99
	2,701	3,751
Less: Accumulated depreciation and amortization	(1,339)	(1,933)
	$ 1,362	$ 1,818

Depreciation expense was $0.3 million and $0.7 million for the years ended December 31, 2017 and 2018, respectively.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

5. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31,	
	2017	2018
Accrued employee compensation and benefits	$ 1,045	$ 1,610
Accrued external research and development expenses	1,995	3,814
Income taxes payable	94	15
Accrued professional fees	123	1,494
Other	148	99
	$ 3,405	$ 7,032

6. Convertible preferred shares

The Company has issued Series A convertible preferred shares ("Series A Preferred Shares"), Series B1 convertible preferred shares ("Series B1 Preferred Shares"), and Series B2 convertible preferred shares ("Series B2 Preferred Shares") (collectively the "Preferred Shares").

On May 26, 2017 the Company completed the issue of 3,562,583 Series B1 Preferred Shares at a price per share of £11.2278, for gross cash proceeds of $51.9 million. In addition, on October 27, 2017, an additional unaffiliated investor subscribed for a further 384,615 Series B1 Preferred Shares at a price per share of £13, for gross cash proceeds of $6.6 million. These two transactions are collectively referred to as "the Series B1 Financing". In conjunction with the Series B1 Financing, the Company also issued warrants to subscribe for 743,287 Series B1 Preferred Shares to the subscribers of the Series B1 Preferred Shares (Note 7). The Company allocated a portion of the proceeds equal to the fair value of the warrants at the date of grant to the warrant liability, and the remaining amount was allocated to the Series B1 Preferred Shares.

On December 20, 2018, the Company completed the issue of 1,323,248 Series B2 preferred shares at a price per Series B2 preferred share of £15.55, for gross cash proceeds of $26.1 million (the "Series B2 Financing"). In conjunction with the Series B2 Financing, the existing holders of warrants to subscribe for Series B1 preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 preferred shares and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 preferred shares to the new investor. In conjunction with the Series B2 Financing, the Company designated all previously outstanding Series B preferred shares as Series B1 preferred shares.

The rights, preferences, and privileges of the Preferred Shares are described below:

Voting rights

The holders of Preferred Shares are entitled to vote, together with the holders of ordinary shares, on all matters submitted to shareholders for a vote, except as required by law. Each preferred shareholder is entitled to the number of votes equal to the number of ordinary shares into which each preferred share is convertible as of the date of the vote.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

6. Convertible preferred shares (Continued)

Liquidation preferences

In the event that the Company liquidates, dissolves or winds up, whether voluntarily or involuntarily, the Company sells all or substantially all of its assets or businesses, or the Company sells the whole or any part of the issued share capital of a subsidiary, the shareholders of the Company sell a controlling interest in the Company, or if certain events deemed to be a liquidation occur, then the holders of the Series B2 Preferred Shares are entitled to receive in preference to the holders of the Series B1 Preferred Shares, the Series A Preferred Shares and the ordinary shares an amount per share equal to the original purchase price of the Series B2 Preferred Shares, plus any dividends, if declared but unpaid thereon. In addition, following payment of the preference to the holders of Series B2 Preferred Shares, the holders of the Series B1 Preferred Shares are entitled to receive in preference to the holders of the Series A Preferred Shares and the ordinary shares an amount per share equal to the original purchase price of each respective Series B1 Preferred Share, plus any dividends, if declared but unpaid thereon. In addition, following payment of the preference to the holders of Series B1 Preferred Shares, the holders of the Series A Preferred Shares are entitled to receive in preference to the holders of the ordinary shares, an amount per share equal to the original purchase price of each respective Series A Preferred Share, plus any dividends, if declared but unpaid thereon. Following all preferential payments to holders of the Preferred Shares, as required, any remaining undistributed assets are shared ratably with the holders of the ordinary shares and the convertible preferred shares with the latter's share number being determined on an "as-if-converted" basis.

Dividends

The holders of the Preferred Shares rank pari passu in all respects as to dividends with the holders of the ordinary shares. The Company may not pay any dividends on ordinary shares of the Company unless the holders of Preferred Shares then outstanding simultaneously receive dividends at the same rate and same time as dividends paid with respect to ordinary shares. Through December 31, 2017 and 2018, no dividends have been declared or paid.

Redemption rights

The Preferred Shares are not redeemable at the option of the holder.

The holders of Preferred Shares have liquidation rights in the event of a deemed liquidation that, in certain situations such as a change in control, are not solely within the control of the Company. Therefore, convertible preferred shares are classified outside of shareholders' (deficit) equity.

Conversion rights

Each Preferred Share is convertible at any time at the option of the shareholder into fully paid ordinary shares. Each Preferred Share will be automatically converted into such number of ordinary shares, at the applicable conversion ratio then in effect, upon either (i) the closing of a firm commitment public offering with at least £50.0 million of gross proceeds and at a price of at least £31.10 per share, subject to appropriate adjustment in the event of any share split, share dividend, combination or other similar recapitalization, or (ii) the vote or written consent of the holders of at

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

6. Convertible preferred shares (Continued)

least a 77% of the outstanding Preferred Shares on an as converted basis, voting together as a single class.

The Preferred Shares are initially convertible to ordinary shares on a one for one basis, subject to adjustment for certain dilutive events and certain capital reorganizations in accordance with the terms of the articles of association of the Company.

Upon issuance of each class of Preferred Shares, the Company assessed the embedded conversion and liquidation features of the securities. The Company determined that each class of Preferred Shares does not require the Company to separately account for the conversion or liquidation features. The Company also concluded that no beneficial conversion features existed upon the issuance date of the Series A Preferred Shares, Series B1 Preferred Shares, or Series B2 Preferred Shares.

7. Warrant liability (restated)

On May 26, 2017, the Company issued 200,000 warrants to subscribe for Series A Preferred Shares at £0.01 each which are exercisable at any time after May 26, 2017 provided that they have not otherwise lapsed in accordance with their terms. The warrants were issued as consideration to amend a royalty arrangement (Note 12) with certain founders of the Company. The Company recorded the fair value of the warrants to subscribe for Series A Preferred Shares to the founders of $0.9 million as research and development expense at the time of issuance in May 2017, as the underlying license rights do not have alternative future use, in accordance with ASC Topic 730, Research and Development.

The warrants to subscribe for Series A Preferred Shares expire upon the earlier of (i) 10 years from their issuance date, or (ii) upon an IPO or exit unless an exercise delay notice is provided by the Series A warrant holder, in which case they will expire 12 months following an IPO or exit.

On May 26, 2017, in conjunction with the issuance of 3,562,583 Series B1 Preferred Shares at a price per share of £11.2278 (Note 6), the Company issued 627,903 warrants to subscribe for Series B1 Preferred Shares with an exercise price of £0.01. In addition, on October 27, 2017, in conjunction with the issuance of 384,615 Series B1 Preferred Shares the Company issued a further 115,384 warrants to subscribe for Series B1 Preferred Shares with an exercise price of £0.01. In conjunction with the Series B2 Financing (Note 6), the existing holders of warrants to subscribe for Series B1 preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 preferred shares and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 preferred shares to the new investor.

The warrants to subscribe for Series B1 Preferred Shares may be exercised from the first to occur of (i) March 31, 2020, (ii) upon notification of an equity fund raise for aggregate proceeds of a minimum amount to be determined by the board of directors of the Company, (iii) the notification of initiation of an IPO, (iv) notification of an exit (being either: (a) a sale or other transfer of the whole or any part of the issued share capital of the Company or any subsidiary on an arm's length basis that results in such person (along with any persons acting in concert) holding a controlling interest in the Company or any subsidiary; or (b) the disposition of all or substantially all of the assets or business of the Company to a third party (either by way of a sale, license and/or other transfer), or (v) upon an unfavorable outcome related to a patent complaint (Note 12). The

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

7. Warrant liability (restated) (Continued)

Series B1 Warrants expire upon five years from becoming exercisable, or immediately prior to an exit (having the meaning set out above in this paragraph), IPO, an equity fund raise (having the meaning set out above in this paragraph), upon a favorable judgment related to a patent complaint (Note 12), or upon the winding up of the Company. The warrants to purchase Series B1 preferred shares contain limitations on their ability to be exercised based on the status of the patent complaint, in accordance with the terms of the warrant agreement.

The warrants to subscribe for Series A and Series B1 Preferred Shares are recorded as a liability and remeasured to fair value at each reporting date (Note 3). Changes in the fair value of the warrant liability are recognized as other expense, net in the consolidated statements of operations and comprehensive loss. The following table provides a roll-forward of the fair values of the Company's warrant liability for which fair value is determined by Level 3 inputs (in thousands):

	Warrant Liability
Fair value at December 31, 2016	$ —
Issuance of warrants to subscribe for Series A convertible preferred shares (as restated)	856
Issuance of warrants to subscribe for Series B1 convertible preferred shares (as restated)	3,254
Change in fair value of warrant liability recorded as other expense (as restated)	119
Impact of exchange rates on translation of warrant liability to USD included in accumulated other comprehensive income (loss) (as restated)	182
Fair value at December 31, 2017 (as restated)	4,411
Change in fair value of warrant liability recorded as other expense	665
Impact of exchange rates on translation of warrant liability to USD included in accumulated other comprehensive income (loss)	(272)
Fair value at December 31, 2018	$ 4,804

In conjunction with the Series B2 Financing (Note 6), the existing holders of warrants to subscribe for Series B1 preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 preferred shares and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 preferred shares to the new investor. The transfer of warrants between investors did not have an impact to the valuation of the warrant liability, as this represents a transaction between shareholders and the Company did not issue any new instruments or change the rights and preferences of the underlying warrants to subscribe for Series B1 preferred shares.

The warrant liability in the table above consisted of the fair value of warrants to subscribe for Series A and Series B1 Preferred Shares (see Note 6) and was based on significant inputs not observable in the market, which represent a Level 3 measurement within the fair value hierarchy. The Company's valuation of the warrants to subscribe for Series A and Series B1 Preferred Shares utilized the Black-Scholes option-pricing model, which incorporates assumptions and estimates to value the warrant liability. The Company assesses these assumptions and estimates on a quarterly basis as additional information impacting the assumptions is obtained.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

7. Warrant liability (restated) (Continued)

The quantitative elements associated with the Company's Level 3 inputs impacting the fair value measurement of the warrant liability include the fair value per share of the underlying Series A and Series B1 preferred shares into which the warrant is exercisable, the remaining contractual term of the warrants, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares.

The most significant assumption in the Black-Scholes option-pricing model impacting the fair value of the warrant liability is the fair value of the Series A and Series B1 preferred shares into which the warrant is exercisable as of each remeasurement date. Given the absence of an active market for the Company's equity securities, Company determines the fair value per share of the convertible preferred shares underlying the warrants by taking into consideration the implied value derived from an independent third-party valuation of the Company's ordinary shares (Note 1), adjusted for certain restrictions on the exercise of the B1 warrants per their contractual terms. Assumptions related to the remaining term, free interest rate, expected dividend yield and expected volatility do not have an impact to the fair value of the warrants because the exercise price of the warrants is £0.01, and the fair value of the warrant is equal to the difference between the exercise price and the fair value regardless of the assumptions. The Company historically has been a private company and lacks company-specific historical and implied volatility information of its shares. Therefore, it estimates its expected share volatility based on the historical volatility of publicly traded peer companies for a term equal to the remaining contractual term of the warrants. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the remaining contractual term of the warrants. The Company has estimated a 0% dividend yield based on the expected dividend yield and the fact that the Company has never paid or declared dividends. The following table presents the unobservable inputs to the fair value measurement of the warrant liability:

	December 31, 2017		December 31, 2018	
	Series A Warrants	Series B1 Warrants	Series A Warrants	Series B1 Warrants[(1)]
Risk free rate				
Expected dividend yield	—%	—%	—%	—%
Expected term (years)	9.4	7.25	8.4	6.25
Expected volatility	71.4%	70.5%	75.4%	79.6%
Exercise price	£ 0.01	£ 0.01	£ 0.01	£ 0.01
Fair value preferred share underlying the warrant	$ 4.68	$ 4.68	$ 8.61	$ 4.15

(1) The fair value of the Series B1 preferred shares underlying the warrants to purchase Series B1 preferred shares at December 31, 2018 includes a 50% probability that the warrants will be not be exercisable prior to the IPO, based on their contractual terms.

In connection with the December 31, 2018 year-end financial statement close process, the Company identified misstatements in the historical consolidated financial statements, related to the fair value determination of (i) the warrant liability and (ii) ordinary shares utilized to calculate share based compensation expense. The fair value of the warrant liability and ordinary shares, which was derived from an independent third-party valuation report, included an error in an input to the

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

7. Warrant liability (restated) (Continued)

valuation model related to the payment that would be made to the Series A and Series B1 warrant holders in a sale liquidity event, following their exercise. Specifically, the payment to the warrant holders in a sale liquidity event, which is one of the exit scenarios in the valuation, is equal to the purchase price paid of £0.01 for each respective share, whereas it had previously utilized the original issuance price of the Series A Preferred shares of £10, and £11.2278 and £13.00 for the Series B1 preferred shares. The Company has corrected the misstatement by recording a decrease in the warrant liability, and the related impacts on the Series B1 convertible preferred shares carrying value, share-based compensation, additional paid-in-capital, benefit from income taxes and deferred tax assets for the impact of the revised valuation on the fair value of ordinary shares and the warrant liability for the periods that the warrants were outstanding (Note 1).

On March 7, 2019, the holders of the Series B1 warrants to subscribe for Series B1 Preferred Shares agreed that 50% of the warrants will be exercised in conjunction with the IPO and 50% of the warrants will expire.

8. Ordinary shares

Each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. As of December 31, 2017 and 2018, the Company has not declared any dividends.

As of December 31, 2017, the Company's authorized capital share capital consisted of 8,905,805 ordinary shares with a nominal value of £0.01 per share. As of December 31, 2018, the Company's authorized capital share capital consisted of 10,813,450 ordinary shares with a nominal value of £0.01 per share.

9. Share-based compensation

Employee incentive pool

The Company is authorized to issue ordinary shares, as well as options and other securities exercisable for or convertible into ordinary shares, as incentives to its employees, consultants, and members of its board of directors. To the extent such incentives are in the form of share options, the options may have been granted pursuant to a potentially tax-favored Enterprise Management Incentive, or EMI, scheme available to U.K. employees, directors and consultants of the Company. The issuance of share options and ordinary shares is administered by the board of directors using standardized share option and share subscription agreements.

As of December 31, 2017, the Company was authorized to issue a total of 1,107,214 ordinary shares under a reserve set aside for equity awards. As of December 31, 2018, the Company was authorized to issue a total of 1,611,226 ordinary shares under a reserve set aside for equity awards. As of December 31, 2017 and 2018, there were 168,398, and 485,985 ordinary shares available for future issuance to the Company's employees, consultants and members of the board of directors. Awards of restricted ordinary shares, which are referred to as employee shares, are subject to vesting. Unvested employee shares are subject to repurchase upon termination of employment.

Options granted, as well as restricted shares granted as employee incentives, typically vest over a four-year service period with 25% of the award vesting on the first anniversary of the commencement date and the balance thereafter in 36 equal monthly instalments, and expire no later than 10 years from the date of grant.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

9. Share-based compensation (Continued)

Certain equity awards were issued in 2017 for which 20% of the award vests upon the first anniversary of the vesting start date, 60% vests thereafter in 36 equal monthly installments, and 20% vest upon the earlier of the fourth anniversary of the vesting start date, or the achievement of a specified revenue threshold from the Company's collaboration arrangements. Options granted generally expire 10 years from the date of grant.

Options issued to U.K. employees have an exercise price of £0.01 per share. The exercise price for share options granted to U.S. employees, which are not subject to the EMI schemes, have an exercise price that is not less than the fair value of ordinary shares as determined by the board of directors as of the date of grant. The Company's board of directors values the Company's ordinary shares based on input from management, considering the most recently available valuation of ordinary share performed by an independent third-party valuation firm as well as additional factors which may have changed since the date of the most recent contemporaneous valuation through the date of grant.

On December 17, 2018, each of the U.K. employees that were holders of share options, each with an exercise price of £0.01 per share, surrendered all of their issued share options that had not lapsed or been exercised. Thereafter, such persons: (a) subscribed for ordinary shares equal to such number of ordinary shares as were vested under their surrendered option agreement at a subscription price of £0.01 per ordinary share; and (b) were granted options to subscribe for ordinary shares equal to such number of ordinary shares as were unvested under their surrendered option agreement at a subscription price of £0.01 per ordinary share, and with identical vesting terms as the original awards. In conjunction with the surrender of 238,443 vested share options, the Company issued 238,443 ordinary shares. The Company evaluated the surrender of share options and issuance of vested ordinary shares and unvested share options as a modification in accordance with ASU 2017-09. The modification did not have any accounting impact as there were no changes in the fair value, vesting conditions, or the classification of the awards (as equity or liability) in conjunction with the surrender of share options and issuance of vested ordinary shares and unvested share options.

Share-based compensation

The Company recorded share-based compensation expense in the following expense categories of its consolidated statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,	
	2017	2018
	(as restated)	
Research and development expenses	$ 241	$ 513
General and administrative expenses	274	510
	$ 515	$ 1,023

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

9. Share-based compensation (Continued)

Share options

The following table summarizes the Company's option activity since December 31, 2017:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2017 (as restated)	674,999	$ 0.99	8.95	$ 1,855
Granted	198,038	1.17		
Exercised	(6,552)	0.01		
Forfeited	(23,598)	1.14		
Surrendered of share options for subscription to vested shares	(238,443)	0.01		
Outstanding as of December 31, 2018	604,444	$ 1.44	8.75	$ 3,292
Vested and expected to vest as of December 31, 2018	604,444	$ 1.44	8.75	$ 3,292
Options exercisable as of December 31, 2018	149,130	$ 2.23	8.51	$ 693

The weighted average grant-date fair value of share options granted during the years ended December 31, 2017 (restated) and 2018 was $2.55 per share and $5.27 per share, respectively.

For the years ended December 31, 2017 and 2018, the Company recorded share-based compensation expense for share options granted of $0.4 million and $0.8 million, respectively. Expense for non-employee consultants for the years ended December 31, 2017 and 2018, was immaterial.

The aggregate intrinsic value of share options is calculated as the difference between the exercise price of the share options and the fair value of the Company's ordinary shares. The aggregate intrinsic value of share options exercised during the years ended December 31, 2017 and 2018 was $7,000 and $23,000 respectively.

During the year ended December 31, 2017 and 2018, the Company granted options for the purchase of an aggregate of 474,888 and 49,600 ordinary shares, respectively, for which 20% of the award vests upon the first anniversary of the vesting start date, 60% vests thereafter in 36 equal monthly installments, and 20% on the earlier of the fourth anniversary of the vesting start date, or the achievement of a specified revenue threshold from the Company's collaboration arrangements. The Company concluded that the accelerated vesting condition was not probable at December 31, 2017. In May 2018, the Company determined that the performance condition became probable of achievement and recorded a cumulative catch-up to reflect the expense as if the vesting condition was probable of achievement at the time of the grant of the award. The Company recorded expense of $0.3 million and $0.7 million, during the year ended December 31, 2017 (restated) and 2018, respectively, related to these awards, which includes the acceleration of vesting expense.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

9. Share-based compensation (Continued)

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of share options granted to employees and directors:

	Year Ended December 31,	
	2017	2018
Risk-free interest rate	2.0%	2.7%
Expected volatility	79.7%	78.6%
Expected dividend yield	—	—
Expected term (in years)	6.07	6.07

As of December 31, 2018, total unrecognized compensation expense related to the unvested employee and director share-based awards was $1.0 million, which is expected to be recognized over a weighted average period of 3.1 year.

Restricted shares

The Company has granted restricted shares with service-based vesting conditions. Shares of unvested restricted shares may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. These restricted shares are subject to repurchase rights, for aggregate consideration of £1. Accordingly, the Company has recorded the proceeds from the issuance of restricted shares as a liability in the consolidated balance sheets included as a component of accrued expenses and other current liabilities. The restricted share liability is reclassified into shareholders' (deficit) equity as the restricted shares vest.

The following table summarizes the Company's restricted ordinary share award activity since December 31, 2017:

	Shares	Weighted Average Grant-Date Fair Value
Unvested restricted ordinary shares as of December 31, 2017 (as restated)	113,694	$ 2.62
Issued	20,286	5.75
Forfeited	(8,301)	2.02
Vested	(66,933)	3.52
Unvested restricted ordinary shares as of December 31, 2018	58,746	$ 2.76

For the years ended December 31, 2017 (as restated) and 2018, the Company recorded share-based compensation expense of $0.1 million and $0.2 million, respectively, for unvested restricted shares granted.

The fair value of employee restricted share awards vested during the years ended December 31, 2017 (as restated) and 2018, based on estimated fair values of the ordinary shares

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

9. Share-based compensation (Continued)

underlying the restricted share awards on the day of vesting, was $0.1 million and $0.2 million, respectively.

As of December 31, 2018, total unrecognized compensation cost related to the unvested employee and director restricted share awards was $0.2 million, which is expected to be recognized over a weighted average period of 1.9 years.

10. Significant Agreements

For the years ended December 31, 2017 and 2018, the Company had collaboration agreements with AstraZeneca, Bioverativ, ("Bioverativ"), and Oxurion. The following table summarizes the revenue recognized in the Company's consolidated statements of operations and comprehensive loss from these arrangements (in thousands):

	Year Ended December 31,	
	2017	2018
Collaboration revenues		
AstraZeneca	$ 890	$ 1,386
Bioverativ	355	4,007
Oxurion	815	1,743
Total collaboration revenues	$ 2,060	$ 7,136

AstraZeneca Collaboration Agreement

Summary of Agreement — 2016 Agreement

In November 2016, the Company entered into a Research Collaboration Agreement (the "AstraZeneca Collaboration Agreement") with AstraZeneca. The collaboration is focused on the research and development of Bicycle peptides that bind to up to six biological targets. After discovery and initial optimization of such Bicycle peptides, AstraZeneca will be responsible for all research and development, including lead optimization and drug candidate selection. AstraZeneca has option rights, at drug candidate selection, which allow it to obtain development and exploitation license rights with regard to such drug candidate. The initial research obligation focuses on two targets within respiratory, cardiovascular and metabolic disease. AstraZeneca also has an option to nominate up to four additional targets at any point up to the second anniversary of the agreement ("Additional Four Target Option"). The exercise of this option right results in an option fee payable to the Company of $5.0 million and the research obligations and rights are consistent with the obligations and rights related to the initial two targets discussed below.

Under the AstraZeneca Collaboration Agreement, the Company is obligated to use commercially reasonable efforts to perform research activities on the initial two targets, under mutually agreed upon research plans. The research plans includes two discrete parts, on a research program by research program basis: (i) the Bicycle Research Term, which is focused on the generation of Bicycle peptide libraries using the Company's peptide drug discovery platform, to be screened against selected biological targets and optimization of promising compounds, with the

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

goal of identifying compounds that meet the criteria set by the parties, and (ii) the AZ Research Term, during which AstraZeneca may select certain compounds and continue research activities on those compounds, at its sole expense, with the goal of identifying compounds that satisfy the relevant pharmacological and pharmaceutical criteria for clinical testing. AstraZeneca may, at its sole discretion, approve any compound to be progressed into drug development and, upon the selection of each drug candidate, AstraZeneca is to pay $8.0 million as an option fee, in order to obtain worldwide development and exploitation rights.

Each research program is to continue for an initial period of three years (the "Research Term"), including one year for the Bicycle Research Term and two for the AZ Research Term. AstraZeneca may extend the Research Term for each research program by twelve months (or fifteen months, if needed to complete certain toxicology studies). The Research Term for a specific program can be shorter if it is ceased due to a screening failure, a futility determination, abandonment by AstraZeneca, or upon selection of a drug candidate. AstraZeneca has certain substitution rights should a screening failure or futility determination be reached but is obligated to fund these additional efforts related to substitution.

Under the terms of the AstraZeneca Collaboration Agreement, the Company granted to AstraZeneca, for each research program, a right and license (with the right to sublicense) certain background and platform intellectual property, for the duration of the applicable Research Term, to the extent necessary or useful for AstraZeneca to conduct the activities assigned to it in the applicable research plan, but for no other purpose.

The activities under the AstraZeneca Collaboration Agreement are governed by a joint steering committee ("JSC") formed by an equal number of representatives from the Company and AstraZeneca. The JSC oversees and reviews each research program. Among other responsibilities, the JSC monitors and reports on research progress and ensure open and frequent exchange between the parties regarding research program activities.

AstraZeneca is obligated to fund two full time equivalents ("FTE") during the Bicycle Research Term, for each research program, based on an agreed upon FTE reimbursement rate. Payment is made quarterly in advance of services being provided.

AstraZeneca has the option to obtain development and commercialization licenses associated with each designated drug candidate in return for a fee of $8.0 million per drug candidate. In addition, AstraZeneca is required to make certain milestone payments to the Company upon the achievement of specified development, regulatory and commercial milestones. More specifically, for each research program, the Company is eligible to receive up to $29.0 million in development milestone payments and up to $23.0 million in regulatory milestone payments. The Company is also eligible for up to $110.0 million in commercial milestone payments, on a research program by research program basis. Development milestone payments are triggered upon initiation of a defined phase of clinical research for a drug candidate. Regulatory milestone payments are triggered upon approval to market a product candidate by the United States Food and Drug Administration ("FDA") or other global regulatory authorities. Commercial milestone payments are triggered when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee. In addition, to the extent any of the product candidates covered by the licenses conveyed to AstraZeneca are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Royalty payments are subject to certain

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Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

reductions, including in certain countries where AstraZeneca faces generic competition. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from AstraZeneca.

Either party may terminate the AstraZeneca Collaboration Agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. Either party may terminate the AstraZeneca Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. AstraZeneca may terminate the AstraZeneca Collaboration Agreement, entirely or on a licensed product by licensed product or country by country basis, for convenience.

Accounting Analysis

The Company has identified the following performance obligations:

(i) research license and the related research and development services during the Bicycle Research Term for the first target (the "Target One Research License and Related Services"),

(ii) research license and the related research and development services during the Bicycle Research Term for the second target (the "Target Two Research License and Related Services").

The Company concluded that the Additional Four Target Option is not a material right, as the option does not provide a discount that AstraZeneca otherwise would not have received. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract. The Company has concluded that the research license is not distinct from the research and development services during the Bicycle Research Term as AstraZeneca cannot obtain the benefit of the research license without the Company performing the research and development services. The services incorporate proprietary technology and unique skills and specialized expertise, particularly as it relates to constrained peptide technology that is not available in the marketplace. As a result, for each research program, the research license has been combined with the research and development services into a single performance obligation.

The total transaction price was initially determined to be $1.2 million, consisting solely of research and development funding. The Company utilizes the most likely amount method to determine the amount of research and development funding to be received. Additional consideration to be paid to the Company upon the exercise of the license options by AstraZeneca or upon reaching certain milestones is excluded from the transaction price as they relate to option fees and milestones that can only be achieved subsequent to the option exercise or are outside of the initial contact term.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for the Target One and Target Two Research License and Related Services is primarily based on the nature of the services to be performed and estimates of the associated effort and

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

costs of the services, adjusted for a reasonable profit margin what would be expected to be realized under similar contracts. The transaction price allocated to each performance obligation was initially $0.6 million.

The Company will recognize revenue related to amounts allocated to the Research License and Related Services as the underlying services are performed over the one year Research Term using a proportional performance model over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected and will remeasure its progress towards completion at the end of each reporting period, which best reflects the progress towards satisfaction of the performance obligation.

In October 2017, AstraZeneca selected a replacement target for the first target, and as such a new Research Term was started related to the Target One Research License and Related Services. In addition, both programs were extended. The total transaction price under the arrangement increased to $1.9 million for the additional research and development funding to be received.

For the years ended December 31, 2017 and 2018, the Company recognized $0.9 million and $1.0 million, respectively, of collaboration revenue related to the Target One and Target Two Research License and Related Services for its Collaboration Agreement with AstraZeneca. As of December 31, 2017 and 2018, the Company recorded no deferred revenue and $8,000 of deferred revenue, respectively, in connection with the 2016 AstraZeneca Collaboration Agreement.

May 2018 AstraZeneca Option Exercise — Additional Four Targets

Under the AstraZeneca Collaboration Agreement, AstraZeneca was granted an option to nominate up to four additional targets at any point up to the second anniversary of the agreement ("Additional Four Target Option"). In May 2018, AstraZeneca made an irrevocable election to exercise the Additional Four Target Option. As a result, AstraZeneca is entitled to obtain research and development services with respect to Bicycle peptides that bind to up to four additional targets, along with license rights to those selected targets, in exchange for an option fee of $5.0 million to be paid by AstraZeneca to the Company no later than January 31, 2019. AstraZeneca is obligated to fund two FTEs during the Bicycle Research Term, for each research program, based on an agreed upon FTE reimbursement rate. Payment is made quarterly in advance of services being provided. AstraZeneca has the option to obtain worldwide development and commercialization licenses associated with each designated drug candidate in return for a fee of $8.0 million per drug candidate, upon the selection of such drug candidate, after which AstraZeneca would be required to fund development and commercialization costs, and to pay regulatory and commercial milestone payments and royalties to BicycleTX as for the other products developed under the AstraZeneca Collaboration Agreement.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

Accounting Analysis

Upon the execution of the agreement, the Company has identified the following five performance obligations associated with the AstraZeneca May 2018 Agreement:

(i) Research license and the related research and development services during the Bicycle Research Term for the third target (the "Target Three Research License and Related Services "),

(ii) Material right associated with the development and exploitation license option for the third target ("Target Three Material Right"),

(iii) Material right associated with the research services option, including the underlying development and exploitation license option for the fourth target ("Target Four Material Right"),

(iv) Material right associated with the research services option, including the underlying development and exploitation license option for the fifth target ("Target Five Material Right"), and

(v) Material right associated with the research services option, including the underlying development and exploitation license option for the sixth target ("Target Six Material Right").

The Company concluded that the fourth, fifth and sixth targets available for selection are options. Upon exercise, AstraZeneca will obtain a research license and the related research and development services and an option to a development and exploitation license. The Company has concluded that the research services option, including the underlying development and exploitation license options related to each respective target results in a material right as the option exercise fee related to the development and exploitation license contains a discount that AstraZeneca would not have otherwise received.

The research license and the related research and development services related to the fourth, fifth and sixth targets are not performance obligations, as they are optional services that will be performed if AstraZeneca selects additional targets and they reflect their standalone selling prices and do not provide the customer with material rights. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract.

The total transaction price was determined to be $5.7 million, consisting of the $5.0 million option exercise fee and research and development funding of an estimated $0.7 million. The research and development funding is being provided based on the costs that are incurred to conduct the research and development services. The Company utilizes the most likely amount method to determine the amount of research and development funding to be received. Additional consideration to be paid to the Company upon the exercise of the license options by AstraZeneca or upon reaching certain milestones are excluded from the transaction price as they relate to option fees and milestones that can only be achieved subsequent to the license option exercise or are outside of the initial contact term.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

selling prices for each Research License and Related Services obligation is primarily based on the nature of the services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees AstraZeneca would pay to exercise the license options, the estimated value of the License Option using comparable transactions, and the probability that (i) AstraZeneca would opt into the target development, and (ii) the license options would be exercised by AstraZeneca. Based on the relative standalone selling price, the allocation of the transaction price to the separate performance obligations is as follows (in thousands):

Performance Obligations	Allocation of Transaction Price
Target Three Research License and Related Services	$ 650
Target 3 Material Right	1,504
Target 4 Material Right	1,204
Target 5 Material Right	1,165
Target 6 Material Right	1,127
	$ 5,650

The Company will recognize revenue related to amounts allocated to the Target Three Research License and Related Services as the underlying services are performed using a proportional performance model over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company will commence revenue recognition upon exercise of or upon expiry of the option.

For the year ended December 31, 2018, the Company recognized $0.4 million of revenue related to the Target Three Research License and Related Service related to the May 2018 AstraZeneca Option Exercise. As of December 31, 2018, the Company recorded $4.7 million of deferred revenue in connection with the AstraZeneca Collaboration.

Bioverativ Collaboration Agreement

Summary of Agreement

In August 2017, the Company entered into a Collaboration Agreement (the "Bioverativ Collaboration Agreement") with Bioverativ. Under the Bioverativ Collaboration Agreement the Company will provide for research and development services focused on up to three collaboration programs; (i) Sickle cell disease, (ii) Hemophilia, and (iii) and a third program ("Program 3"), which is an optional program, to be defined. The Company will use its bicyclic peptide screening platform to perform research and development services for the programs and Bioverativ has the ability to select a collaboration product for each program and obtain a license to develop and exploit the selected collaboration product for an additional option fee.

Under the Bioverativ Collaboration Agreement, the Company is obligated to perform research activities on the initial two named collaboration programs, under mutually agreed upon research

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

plans. The research and development services for each program consist of two stages. The first is an initial stage of screening for high affinity binders and affinity maturation of such binders to identify lead compounds led by the Company (the "BV Bicycle Research Term"). Upon the conclusion of the BV Bicycle Research Term, Bioverativ can, at is sole discretion, select a certain number of collaboration compounds to move forward into the Joint Research Term. Upon selection of the collaboration compounds, Bioverativ is required to pay an option fee. During the Joint Research Term, the Company and Bioverativ will jointly conduct research and development activities which will include lead optimization of lead compounds, in preparation for lead collaboration product nomination ("Joint Research Term"). Bioverativ may, at its sole discretion, approve any compound to be progressed into drug development and upon the selection of each collaboration product candidate, Bioverativ shall pay $5.0 million as an option fee, in order to obtain worldwide development and exploitation rights for that collaboration product.

Each research program shall continue for an initial period of three years (the "Research Term") unless a program is abandoned by Bioverativ or extended for up to one year. The first year of each Research Term shall be the BV Bicycle Research Term and the remaining part of the Research Term, including any extensions of the Research Term, shall be the Joint Research Term.

Under the terms of the Bioverativ Collaboration Agreement, the Company granted to Bioverativ, for each collaboration program, a non-exclusive, sublicensable (through multiple tiers), worldwide license under certain intellectual property of the Company to conduct the activities assigned to Bioverativ in the applicable research plan for the duration of the applicable Research Term, but for no other purpose.

The activities under the Bioverativ Collaboration Agreement will be governed by a joint steering committee ("JSC") formed by an equal number of representatives from the Company and Bioverativ. The JSC will oversee, review and recommend direction of each collaboration program and variations of or modifications to the research plans.

Under the terms of the Bioverativ Collaboration Agreement, the Company received a $10.0 million up-front cash payment. Additionally, prior to the initiation of the research plan for each collaboration program, Bioverativ made a non-refundable payment of $1.4 million for the Sickle cell program and $2.8 million for the Hemophilia program as payment for the Company's services during the BV Bicycle Research Term. During the Joint Research Term, Bioverativ is obligated to fund a minimum of two FTE's based on an agreed upon FTE reimbursement rate and fund certain external costs incurred by the Company. Bioverativ has the option to obtain development and commercialization licenses associated with each designated collaboration product candidate in return for a fee of $5.0 million per drug candidate. In addition, Bioverativ would be required to make certain milestone payments to the Company upon the achievement of specified development, regulatory and commercial events. More specifically, for each collaboration program, the Company is eligible to receive between $47.5 million and $67.0 million in development milestone payments for the Sickle Cell and Hemophilia programs, respectively, and up to $104.0 million in regulatory milestone payments for each program. In addition, the Company is eligible for up to $55.0 million in commercial milestone payments, on a research program by research program basis. Development milestone payments are triggered upon initiation of a defined phase of clinical research for a collaboration product. Regulatory milestone payments are triggered upon approval to market a product candidate by the FDA or other global regulatory authorities. Commercial milestone

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

payments are triggered when an approved collaboration product reaches certain defined levels of net sales by the licensee. In addition, to the extent any of the collaboration products covered by the licenses conveyed to Bioverativ are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits to low double digits based on a percentage of net sales. Royalty payments are subject to certain reductions, including for instances where Bioverativ faces generic competition in certain countries. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from BioVerativ.

Under the terms of the Collaboration Agreement, Bioverativ was also provided with an option to obtain screening services on the additional Program 3 target upon making an option fee payment of $5.0 million in addition to a non-refundable payment of $1.4 million as payment for the Company's services related to Program 3 during the BV Bicycle Research Term. The option expired in November 2018 unexercised.

Either party may terminate the Bioverativ Collaboration Agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. Either party may terminate the Bioverativ Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. Bioverativ may terminate the Bioverativ Collaboration Agreement, entirely or on a program by program, licensed product by licensed product or country by country basis, for convenience upon not less than 30 days prior written notice to the Company.

Accounting Analysis

The Company has identified the following four performance obligations associated with the Bioverativ Collaboration Agreement:

(i) Research License and the related research and development services during the BV Bicycle Research Term for Sickle cell program (the "Sickle Cell Research License and Related Services "),

(ii) Research License and the related research and development services during the BV Bicycle Research Term for Hemophilia program (the "Hemophilia Research License and Related Services "),

(iii) Material right associated with the sickle cell program development and exploitation license option ("Sickle Cell License Option Material Right"), and

(iv) Material right associated with the hemophilia program development and exploitation license option ("Hemophilia License Option Material Right").

The Company concluded that the option to obtain screening services on the additional Program 3 target is not a material right, as the option does not provide a discount that Bioverativ otherwise would not have received. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract. Research license and the related research and development services related to the Joint Research Term are not performance

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

obligations at the inception of the arrangement, as they are optional services that will be performed if BioVerativ selects collaboration compounds for lead optimization. The amount paid by BioVerativ for the services during the Joint Research Team do not reflect a discount that the customer would otherwise receive and do not provide the customer with material rights.

The total transaction price was determined to be $14.2 million, consisting of the $10.0 million upfront payment and non-refundable research and development funding of $4.2 million. The Company may receive reimbursement of FTE costs and external costs associated with work under the Joint Research Term, milestone payments during the Joint Research Term, as well as upon exercise of the license options. These variable amounts are excluded from the transaction price as they relate to fees and milestones that can only be achieved subsequent to the exercise of an option.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for the Research License and Related Services is primarily based on the nature of the services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees Bioverativ would pay to exercise the license options, the estimated value of the license option using comparable transactions, and the probability that the license options would be exercised by Bioverativ. Based on the relative standalone selling price, the allocation of the transaction price to the separate performance obligations is as follows (in thousands):

Performance Obligations		Allocation of Transaction Price
Sickle Cell Research License and Related Services	$	1,405
Hemophilia Research License and Related Services		2,811
Sickle Cell License Option Material Right		5,286
Hemophilia License Option Material Right		4,698
	$	**14,200**

The Company will recognize revenue related to amounts allocated to the Sickle Cell and Hemophilia Research License and Related Services obligations as the underlying services are performed using a proportional performance model, over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company will commence revenue recognition when the underlying option is exercised or upon expiry of the option.

For the years ended December 31, 2017 and 2018, the Company recognized $0.4 million and $4.0 million, respectively, of collaboration revenue related to its collaboration with Bioverativ. As of December 31, 2017 and 2018, the Company recorded deferred revenue of $14.5 million and $9.9 million, respectively, related to its collaboration with Bioverativ, respectively.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

Oxurion Collaboration Agreement

Summary of Agreement

In August 2013, the Company entered into a Research Collaboration and License Agreement (the "Oxurion Collaboration Agreement") with Oxurion . Under the Oxurion Collaboration Agreement, the Company is responsible for identifying Bicycle peptides related to the collaboration target, plasma kallikrein, for use in various ophthalmic indications. Oxurion is responsible for further development and product commercialization after the defined research screening is performed by the Company.

Under the Oxurion Collaboration Agreement, the Company is obligated to perform specified research activities in accordance with the research plan, which includes two stages. Stage I, now completed, focused on the screening of targets using the Company's Bicycle peptide discovery platform with the goal of identifying compounds that meet the criteria set by the parties, and Stage II, now underway, during which Oxurion has continued research activities on selected Bicycle peptides with the goal of identifying compounds for further development and commercialization. The Company is not obligated or expected to perform any research services during Stage II of the research plan.

The Company granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Oxurion Collaboration Agreement provided for an upfront payment of €1.0 million and potential additional R&D funding, at an agreed upon FTE rate, should the research effort require more than one FTE or the research plan be amended or extended by Oxurion. In addition, Oxurion is required to make certain milestone payments to the Company upon the achievement of specified research, development, regulatory and commercial events. More specifically, for each collaboration program, the Company is eligible to receive up to €8.3 million in research and development milestones of which €1.8 million has been received as of December 31, 2018. In addition, the Company is eligible to receive up to €16.5 million upon achievement of certain regulatory milestone payments (e.g. €5 million for granting first regulatory approval in either the United States or EU for the first indication). In addition, to the extent any of the collaboration products covered by the licenses granted to Oxurion are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from Oxurion.

Either party may terminate the Oxurion Collaboration Agreement if the other party has materially breached any of its material obligations and such breach continues after the specified cure period. Either party may terminate the Oxurion Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. Oxurion may terminate the Oxurion Collaboration Agreement, entirely or on a program by program, licensed product by licensed product or country by country basis, for convenience upon not less than 90 days prior written notice to the Company.

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Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

In November 2017, the parties executed the First Deed of Amendment to the Oxurion Collaboration Agreement ("First Amendment"). The First Amendment confirms that THR-149 has been selected as a development compound under the Oxurion Collaboration Agreement and that Stage II of the research plan has been completed. The First Amendment provided for additional research services to be performed by the Company related to the identification of two additional compounds for Oxurion, in its discretion, to select as development compounds. As for the work under the Oxurion Collaboration Agreement, the Company will perform the work under Stage I of the research plan which will be funded at a specified FTE rate, plus any direct out of pocket expenses, and Oxurion will be responsible for Stage II research and any development after the selection of a development compound. Additional milestones and royalties were added for the potential additional licensed compounds, consistent with those of the initial Oxurion Collaboration Agreement. The Company is not obligated or expected to perform any research services during Stage II of the research plan.

Accounting Analysis

Under the Oxurion Collaboration Agreement, all licenses were granted and research services to be provided by the Company were fully completed and revenue associated with those obligations was fully recognized prior to January 1, 2016. Under the First Amendment, the Company has identified a single performance obligation associated with the performance of research services associated with Stage I of the research plan for which the Company will be reimbursed for its services at a specified FTE reimbursement rate plus out of pocket costs which will be recognized on a proportional performance basis as the associated FTE efforts and costs are incurred, which best reflects the progress towards satisfaction of the performance obligation. None of the unpaid development or regulatory milestones have been included in the transaction price, as all milestone are not considered probable at December 31, 2017 and December 31, 2018.

For the years ended December 31, 2017 and 2018, the Company recognized $0.8 million and $1.7 million, respectively, of revenue related to its agreements with Oxurion. As of December 31, 2018, the research services under the First Amendment were complete. The revenue recognized for the twelve months ended December 31, 2017 and 2018 includes $0.8 million and $1.2 million, respectively, related to the achievement of developmental milestones during the advancement of the research by Oxurion into a Phase I clinical study. There was no deferred revenue recorded as of December 31, 2017 and 2018 in connection with the agreements with Oxurion.

Summary of Contract Assets and Liabilities

Up-front payments and fees are recorded as deferred revenue upon receipt or when due until such time as the Company satisfies its performance obligations under these arrangements. A contract asset is a conditional right to consideration in exchange for goods or services that the Company has transferred to a customer. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

The following table presents changes in the balances of the Company's contract assets and liabilities (in thousands):

	Balance at Beginning of Period	Additions	Deductions	Impact of Exchange Rates	Balance at End of Period
Period ended December 31, 2017					
Contract assets	$ —	$ —	$ —	$ —	$ —
Contract liabilities:					
Deferred revenue					
Bioverativ collaboration deferred revenue	—	14,200	(355)	622	14,467
Total deferred revenue	$ —	$ 14,200	$ (355)	$ 622	$ 14,467

	Balance at Beginning of Period	Additions	Deductions	Impact of Exchange Rates	Balance at End of Period
Period ended December 31, 2018					
Contract assets	$ —	$ 91	$ (91)	$ —	$ —
Contract liabilities:					
Deferred revenue					
Bioverativ collaboration deferred revenue	14,467	—	(4,006)	(553)	9,908
AstraZeneca collaboration deferred revenue		5,350	(466)	(157)	4,727
Total deferred revenue	$ 14,467	$ 5,350	$ (4,472)	(710)	$ 14,635

The contract assets represents research and development services which have been performed but have not yet been billed, and are reduced when they are subsequently billed.

The Bioverativ deferred revenue balance at December 31, 2018 is comprised of $9.9 million allocated to the Sickle Cell License Option Material Right and Hemophilia License Option Material Right, which will commence revenue recognition when the respective option is exercised at the end of Joint Research Term or when the option expires.

The AstraZeneca deferred revenue balance includes $4.7 million allocated to the Target 3, Target 4, Target 5 and Target 6 Material Rights, which will commence revenue recognition when the respective option is exercised at the end of AZ Research Term or when the option expires. The remaining balance relates to research and development services billed in advance that will be recognized over the Bicycle Research Term.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

During the year ended December 31, 2017 and 2018, the Company recognized the following revenues as a result of changes in the contract asset and the contract liability balances in the respective periods (in thousands):

	Year Ended December 31,	
	2017	2018
Revenue recognized in the period from:		
Revenue recognized based on proportional performance	$ (355)	$ (4,472)

Cancer Research UK

On December 13, 2016, the Company entered into a Clinical Trial and License Agreement with Cancer Research Technology Limited ("CRTL") and Cancer Research UK ("CRUK"). Pursuant to the agreement, as amended in March 2017 and June 2018, CRUK's Centre for Drug Development will sponsor and fund a Phase Ia and Phase IIa clinical trial for the Company's lead product candidate, BT1718, a Bicycle Toxin Conjugate, in patients with advanced solid tumors.

CRUK is responsible to design, prepare, carry out and sponsor the clinical trial at its cost. The Company is responsible for supplying agreed quantities of GMP materials for the study, the supply of which has been completed. In the event that additional quantities are needed, the Company will provide CRUK with all reasonable assistance to complete the arrangements necessary for the generation and supply of such additional GMP materials but CRUK will be responsible for supplying and paying for such additional quantities of GMP materials.

The Company granted CRUK a license to its and its affiliates' intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial the Company retains the right to continue the development of BT1718 during the clinical trial. Upon the completion of the Phase I/IIa clinical study, the Company has the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and the Company decides to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, the Company will assign or grant to CRTL an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case the Company will receive a mid to high double digit percentage of the net revenue depending on the stage of development when the license is granted). The CRUK agreement contains additional future milestone payments upon the achievement of development and regulatory milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a high double digit percentage on net sales of products developed.

The CRUK agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity generates its revenue from the sale of tobacco products or is an affiliate of such party). CRUK may terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met, in which case, if the study is terminated by CRUK prior to the completion of the Phase 1a dose escalation portion of the study for such reasons or if CRUK refuses release of any

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

10. Significant Agreements (Continued)

additional quantities of GMP materials or if the parties cannot agree upon a plan to supply the additional quantities of GMP materials, the Company will be obligated to refund fifty percent of the costs and expenses incurred or committed by CRUK to perform the clinical trial. If the study is terminated by CRUK for an insolvency event, a material breach by the Company, or if the Company is acquired by an entity that generates its revenue from the sale of tobacco products or is an affiliate of such party, the Company will reimburse CRUK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case where we are acquired by an entity that generates its revenue from the sale of tobacco products or is an affiliate of such party, CRUK will not be obliged to grant a license to the Company in respect of the results of the clinical trial and the Company will assign or grant to CRT an exclusive license to develop and commercialize the product without CRT being required to make any payment to the Company.

The Company concluded that the costs incurred by CRUK is a liability in accordance with ASC 730, Research and Development, as the payment is not based solely on the results of the research and development having future economic benefit. As such, the Company recorded a liability of $0.3 million and $0.8 million at December 31, 2017 and 2018, respectively, which is recorded in other long-term liabilities in the consolidated balance sheets. The liability is recorded as incremental research and development expense in the statements of operations and comprehensive loss.

11. Income Taxes

The components of net loss before tax provision from income taxes are as follows (in thousands):

	Year Ended December 31,	
	2017	2018
	(as restated)	
United Kingdom	$ (16,319)	$ (22,229)
United States	37	(13)
Total	$ (16,282)	$ (22,242)

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

11. Income Taxes (Continued)

The components of the benefit for income taxes are as follows (in thousands):

	Year Ended December 31,	
	2017 (as restated)	2018
Current income tax provision (benefit)		
Federal	$ 75	$ (25)
State	10	7
Total current income tax provision (benefit)	85	(18)
Deferred income tax (benefit) provision		
Federal	(58)	(167)
State	(50)	(211)
Total deferred income tax (benefit)	(108)	(378)
Total benefit from income taxes	$ (23)	$ (396)

A reconciliation of the provision (benefit) for income taxes computed at the statutory income tax rate to the provision (benefit) for income taxes as reflected in the financial statement is as follows:

	Year Ended December 31,	
	2017 (as restated)	2018
Benefit for income taxes at statutory rate	19%	19%
(Decreases) increases resulting from:		
Federal tax credits	0.4%	1.1%
Change in valuation allowance	(9.4)%	(7.2)%
Net losses surrendered for research credit	(6.7)%	(3.7)%
Preferred share warrants	(1.1)%	(0.6)%
Other	(2.1)%	(6.8)%
Effective income tax rate	0.1%	1.8%

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

11. Income Taxes (Continued)

Significant components of the Company's current and deferred tax assets at December 31, 2017 and 2018, were as follows (in thousands):

	Year Ended December 31,	
	2017 (as restated)	2018
Deferred tax assets:		
Operating loss carryforwards	$ 4,209	$ 4,953
Research credit carryforwards	—	197
Accrued expenses and other	247	1,149
Total deferred tax assets	4,456	6,299
Deferred tax liabilities:		
Depreciation & amortization	(143)	(163)
Total deferred tax liabilities	(143)	(163)
Valuation allowance	(4,175)	(5,621)
Net deferred tax assets	$ 138	$ 515

During the years ended December 31, 2017 and 2018, the Company recorded an income tax benefit of $23,000 and $0.4 million, respectively. The Company is subject to United Kingdom corporate taxation. Due to the nature of its business, the Company has generated losses since inception and has therefore not paid United Kingdom corporation tax. The Company's income tax benefit is mainly the result of deferred tax assets benefitted in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement.

On December 22, 2017, the Tax Cuts and Jobs Act (the "TCJA") was signed into United States law. The TCJA included a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from a top marginal tax rate of 35% to a flat rate of 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely). The federal tax rate change resulted in a reduction in the amount of the Company's deferred tax assets and liabilities recorded as of December 31, 2017 of $21,000. As a result, $21,000 of tax expense was recognized as of the enactment date of the TCJA.

On December 22, 2017, the Securities and Exchange Commission issued guidance under Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act directing taxpayers to consider the impact of the U.S. legislation as "provisional" when it does not have the necessary information available, prepared or analyzed (including computations) in reasonable detail to complete its accounting for the change in tax law.

In connection with the initial analysis of the impact of the TCJA, the Company remeasured its deferred tax assets and liabilities based on the rates at which they are expected to reverse in the

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

11. Income Taxes (Continued)

future, which is generally 21% for federal tax purposes. During the year ended December 31, 2018, the Company did not make any adjustments to the provisional amounts recorded as a result of the TCJA of $21,000 recorded in the year ended December 31, 2017 and the Company considers the accounting related to the TCJA to be final.

The Company regularly assesses its ability to realize its deferred tax assets. Assessing the realization of deferred tax assets requires significant judgment. In determining whether its deferred tax assets are more likely than not realizable, the Company evaluated all available positive and negative evidence, and weighed the evidence based on its objectivity. After consideration of the evidence, including the Company's history of cumulative net losses in the U.K., and has concluded that it is more likely than not that the Company will not realize the benefits of its U.K. deferred tax assets and accordingly the Company has provided a valuation allowance for the full amount of the net deferred tax assets in the U.K. The Company has considered the Company's history of cumulative net profits in the United states, estimated future taxable income and concluded that it is more likely than not that the Company will realize the benefits of its United State deferred tax assets and has not provided a valuation allowance against the net deferred tax assets in the United States. The valuation allowance increased for the year ended December 31, 2017 by $1.8 million due to the corresponding increase in UK deferred tax assets, primarily due to operating loss carryforwards generated during the year. The valuation allowance increased in the year ended December 31, 2018 by $1.4 million due to the corresponding increase in UK deferred tax assets, primarily due to operating loss carryforwards generated during the year that were not surrendered for research credit utilization.

The Company recorded a valuation allowance against all of its U.K. deferred tax assets as of December 31, 2017 and 2018.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2017 and 2018 related primarily to the increase in net operating loss carryforwards and research and development tax credit carryforwards in 2017 and 2018 and were as follows (in thousands):

	Year Ended December 31,	
	2017	2018
	(as restated)	
Valuation allowance as of beginning of year	$ 2,402	$ 4,175
Increases recorded to income tax provision	1,773	1,446
Valuation allowance as of end of year	$ 4,175	$ 5,621

The Company intends to continue to maintain a full valuation allowance on its U.K. deferred tax assets until there is sufficient evidence to support the reversal of all or some portion of these allowances. The release of the valuation allowance would result in the recognition of certain deferred tax assets and an increase to the benefit for income taxes for the period the release is recorded. However, the exact timing and amount of the valuation allowance release are subject to change on the basis of the level of profitability that the Company is able to actually achieve.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

11. Income Taxes (Continued)

The benefit for income taxes shown on the consolidated statements of operations differs from amounts that would result from applying the statutory tax rates to income before taxes primarily because of certain permanent expenses that were not deductible, U.K., federal and state research and development credits, as well as the application of valuation allowances against the U.K. deferred tax assets.

As of December 31, 2017, the Company had $24.8 million of U.K. operating loss carryforwards and $0 of federal and state net operating loss carryforwards. As of December 31, 2018, the Company had $29.1 million of U.K. operating loss carryforwards and $0 of U.S. federal and state net operating loss carryforwards. The U.K. operating loss carryforwards have an indefinite life. As of December 31, 2018, the Company had $60,000 and $0.1 million of federal and state research and development credit carryforwards, respectively, that expire at various dates through 2038.

The Company recognizes, in its consolidated financial statements, the effect of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. The Company had no uncertain tax positions during the years ended of December 31, 2017 and 2018. There are no amounts of interest or penalties recognized in the consolidated statement of operations or accrued on the consolidated balance sheet for any period presented. The Company does not expect any material changes in these uncertain tax benefits within the next 12 months.

The Company files income tax returns in the United Kingdom, and in the United States for federal income taxes and in the Commonwealth of Massachusetts for state income taxes. In the normal course of business, the Company is subject to examination by tax authorities in these jurisdictions. The 2017 tax year remains open to examination the by HM Revenue & Customs. The statute of limitations for assessment with the Internal Revenue Service is generally three years from filing the tax return. As such, all years since inception in the U.S. remain open to examination. The Company is currently not under examination by jurisdictions for any tax years.

12. Commitments and Contingencies

In September 2015, the Company entered into a tenancy agreement for space in Building 260 Babraham Research Campus, Cambridge, UK for a period of two years, beginning on October 1, 2015. The annual rent was approximately $0.2 million plus service charges. In October 2017 this agreement was extended until January 2018 with annual rent of approximately $0.2 million.

In January 2017, Bicycle Therapeutics Inc. entered into a lease for office and laboratory space in Cambridge, Massachusetts for the period from February 1, 2017 to December 31, 2017. Rental payments under the lease were $19,500 per month, plus a portion of the landlords operating costs.

In September 2017, Bicycle Therapeutics Inc. entered into a lease agreement for office and laboratory space in Lexington, Massachusetts, which commenced on January 1, 2018 and expires on December 31, 2022. The rent expense, inclusive of the escalating rent payments, is recognized on a straight-line basis over the lease term. Bicycle Therapeutics Inc. has the option to extend the lease agreement for a successive period at a market based rental rate. In conjunction with the lease agreement, Bicycle Therapeutics Inc. paid a security deposit $0.2 million as well as prepaid rent of

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

12. Commitments and Contingencies (Continued)

$0.1 million for the first month of the third, fourth and fifth year of the lease. The deposit and prepaid rent balances are recorded in other assets in the consolidated balance sheets.

In October 2017, the Company entered into a lease agreement for office and laboratory space in Building 900, Babraham Research Campus, Cambridge, UK, which expires on December 21, 2021. The annual rent is approximately $0.5 million. The Company has the right to renew the lease for five years commencing December 21, 2021 which would be subject to a day one rent review. Service charges are also payable based on floor area and are estimated to be approximately $0.1 million per year. In conjunction with the lease agreement, the Company paid a security deposit $0.6 million, which is recorded in other assets in the consolidated balance sheets.

The Company recorded rent expense of $0.5 million and $1.0 million, during the years ended December 31, 2017 and 2018, respectively.

The following table summarizes the future minimum lease payments due under the Company's operating leases as of December 31, 2018 (in thousands):

2019	888
2020	901
2021	915
2022	483
2023	—
	$ 3,187

The Company has entered into various agreements with contract manufacturing organizations to provide clinical trial materials and with vendors for preclinical research studies, synthetic chemistry and other services for operating purposes. These payments are not included in the table of contractual obligations above since the contracts are generally cancelable at any time upon less than 90 days' prior written notice. The Company is not contractually able to terminate for convenience and avoid any and all future obligations to these vendors. Under such agreements, the Company is contractually obligated to make certain minimum payments to the vendors, with the payments in the event of a termination with less than 90 days' notice based on the timing of the termination and the exact terms of the agreement.

Legal proceedings

From time to time, the Company or its subsidiaries may become involved in various legal proceedings and claims, either asserted or unasserted, which arise in the ordinary course of business.

In September 2016, the Company filed a complaint in the District Court of the Hague against Pepscan Systems B.V. ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement we entered into with Pepscan in 2009 and 2010 ("PLA"). In response, Pepscan counterclaimed for injunctive relief and unquantified damages. The Company is vigorously prosecuting its claims and defending against those of Pepscan. The Company does not believe that a loss is probable or estimable at this time, and as such, the Company has not recorded a liability related to the Pepscan litigation as of December 31, 2017 or at December 31, 2018. Should the

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

12. Commitments and Contingencies (Continued)

Company not be successful in maintaining its rights to Pepscan's patent or in the Company's alternative demand that the patent be invalidated, commercialization of the Company's lead product could be delayed. As the Pepscan patent expires prior to the expected commercialization date of the product, the Company does not believe that the legal proceedings could have a material adverse effect on the Company's business and operating results.

Founder Royalty arrangements

At the time BicycleRD Limited was organized, BicycleRD Limited entered into a royalty agreement with its founders and initial investors (the "Founder Royalty Agreement"). Pursuant to the Founder Royalty Agreement, the Company will pay a royalty rate in the low single digit percentages on net product sales to its founders and initial investors, for a period of 10 years from the first commercial sale on a country by country basis. No royalties have been earned or paid under the royalty arrangements to date.

In accordance with the terms of the Founder Royalty Agreements, as amended in May 2017, the parties amended the terms of the royalty arrangements to limit the future royalties payments to net sales on future products that could be generated under the collaboration with Oxurion and AstraZeneca, in exchange for the issuance of warrants to subscribe for 200,000 Series A Preferred Shares. The Company recorded the fair value of the warrants to subscribe for Series A Preferred Shares to the founders of $0.9 million as research and development expense during the year ended December 31, 2017, as the licenses do not have alternative future use, in accordance with ASC Topic 730, *Research and Development*.

Indemnification obligations

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has indemnification obligations towards members of its board of directors that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification arrangements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnification obligations. The Company is not aware of any claims under indemnification arrangements, and therefore it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2017 and 2018.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

13. Net loss and unaudited pro forma net loss per share

Net loss per share

Basic and diluted net loss per share attributable to ordinary shareholders was calculated as follows (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2017 (as restated)	2018
Numerator:		
Net loss attributable to ordinary shareholders	$ (16,259)	$ (21,846)
Denominator:		
Weighted average ordinary shares outstanding, basic and diluted	233,134	307,123
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (69.74)	$ (71.13)

The Company's potentially dilutive securities, which include share options, convertible preferred shares and warrants to subscribe for Series A and Series B1 Preferred Shares, and unvested restricted shares, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of ordinary shares outstanding used to calculate both basic and diluted net loss per share attributable to ordinary shareholders is the same. The Company excluded the following potentially dilutive ordinary shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to ordinary shareholders for the periods indicated because including them would have had an anti-dilutive effect:

	Year Ended December 31,	
	2017	2018
Convertible preferred shares (as converted to ordinary shares)	6,747,199	8,070,447
Warrants to subscribe for convertible preferred shares (as converted to ordinary shares)	943,287	943,287
Restricted ordinary shares	113,694	58,746
Options to purchase ordinary shares	674,999	604,444
	8,479,179	9,676,924

Unaudited pro forma net loss per share attributable to ordinary shareholders

The unaudited pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2018 (unaudited) have been prepared to give effect to adjustments arising upon the completion of the proposed IPO as if the IPO had occurred on January 1, 2018. The unaudited pro forma net loss attributable to ordinary shareholders used in the calculation of unaudited pro forma basic and diluted net loss per share attributable to ordinary shareholders does not include the effects the change in fair value of the warrant liability because

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

13. Net loss and unaudited pro forma net loss per share (Continued)

the calculation gives effect to (i) the conversion of all outstanding convertible preferred shares into ordinary shares upon the completion of an IPO and (ii) the exercise of 200,000 warrants to subscribe for Series A convertible preferred shares immediately prior to an IPO, and (iii) the exercise of the warrants to subscribe for 371,645 Series B1 convertible preferred shares (Note 7), as if the proposed IPO had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares and the warrants to subscribe for convertible preferred shares.

	Year Ended December 31, 2018 (unaudited)
Numerator:	
Net loss attributable to ordinary shareholders	$ (21,846)
Change in fair value of preferred stock warrant liability	665
Pro forma net loss attributable to ordinary shareholders	$ (21,181)
Denominator:	
Weighted average ordinary shares outstanding, basic and diluted	307,123
Pro forma adjustment to reflect the weighted average conversion of all outstanding convertible preferred shares into ordinary shares upon the completion of an IPO	6,786,968
Pro forma adjustment to reflect the exercise of warrants to subscribe for convertible preferred shares which expire upon the completion of an IPO	571,645
Pro forma weighted average ordinary shares outstanding, basic and diluted	7,665,736
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.76)

14. Benefit plans

The Company established a defined-contribution savings plan under Section 401(k) of the Code (the "401(k) Plan"). The 401(k) Plan covers all U.S. employees and allows participants to defer a portion of their annual compensation on a pre-tax basis. Matching contributions to the 401(k) Plan may be made at the discretion of the Company's board of directors. During the years ended December 31, 2017 and 2018 the Company made contributions totaling $42,000 and $0.1 million, respectively, to the 401(k) Plan.

The Company provides a pension contribution plan for its employees in the United Kingdom, pursuant to which the Company may match employees contributions each year ("U.K Plan"). During the years ended December 31, 2017 and 2018 the Company made contributions totaling $0.2 million and $0.2 million, respectively, to the U.K. Plan.

15. Related party transactions

The Company has entered into Founder Royalty Agreements with its founders and initial investors (Note 12). No royalties have been earned or paid under the Founder Royalty Agreements to date.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

15. Related party transactions (Continued)

The Chairman of the Company's Board of Directors is associated with 10X Capital Inc., who provided consultancy services to the Company totaling $0.1 million and $0.2 million during the years ended December 31, 2017 and 2018, respectively.

16. Geographic information

The Company operates in two geographic regions: the United States and the United Kingdom. Information about the Company's long-lived assets held in different geographic regions is presented in the table below (in thousands):

	December 31,	
	2017	2018
United States	$ 395	$ 498
United Kingdom	967	1,320
	$ 1,362	$ 1,818

The Company's collaboration revenues are attributed to the operations of the Company in the United Kingdom.

17. Restatement of previously reported financial information

In connection with the December 31, 2018 year-end financial statement close process, the Company identified misstatements in the historical consolidated financial statements, related to the valuation of the warrant liability (Note 7) and ordinary shares. The Company has corrected the misstatement by recording a decrease in the warrant liability and the related impacts on the Series B1 convertible preferred share carrying value, share based compensation expense, additional paid-in capital, benefit from income taxes, and deferred tax assets for the impact of the revised valuation on the fair value of ordinary shares and the warrant liability. The Company has also disclosed the impact as of the adjustments to the previously issued consolidated financial statements as of September 30, 2018 (unaudited) and for the nine month periods ended September 30, 2017 and 2018 (unaudited) (Note 1). The impact of these adjustments to previously reported financial statement footnotes is detailed below.

The financial data and other information disclosed in these notes related to the nine months ended September 30, 2017 and 2018 are unaudited. The unaudited interim consolidated financial information has been prepared on the same basis as the audited annual consolidated financial statements and, in the opinion of management, reflect all adjustments, which include only normal recurring adjustments, necessary for the fair statement of the Company's financial position as of September 30, 2018 and the results of its operations and its cash flows for the nine months ended September 30, 2017 and 2018.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

Fair value of financial assets and liabilities

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis (in thousands):

	Fair Value Measurement as of September 30, 2018 using:			
	Level 1	Level 2	Level 3 (as restated)	Total (as restated)
Liabilities:				
Warrant liability	$ —	$ —	$ 5,721	$ 5,721
	$ —	$ —	$ 5,721	$ 5,721

Warrant liability

The following table provides a roll-forward of the fair values of the Company's warrant liability for which fair value is determined by Level 3 inputs (in thousands):

	Warrant Liability (as restated)
Fair value at December 31, 2017	$ 4,411
Change in fair value of warrant liability recorded as other expense	1,472
Impact of exchange rates on translation of warrant liability to USD included in accumulated other comprehensive income (loss)	(162)
Fair value at September 30, 2018 (unaudited)	$ 5,721

Share-based compensation

The Company recorded share-based compensation expense in the following expense categories of its consolidated statements of operations and comprehensive loss (in thousands):

	Nine Months Ended September 30,	
	2017 (as restated) (unaudited)	2018 (as restated) (unaudited)
Research and development expenses	$ 139	$ 421
General and administrative expenses	132	395
	$ 271	$ 816

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

Share options

The following table summarizes the Company's option activity since December 31, 2017:

		As reported	Adjustments	As restated
	Number of Shares	Aggregate Intrinsic Value	Aggregate Intrinsic Value	Aggregate Intrinsic Value
		(in thousands)	(in thousands)	(in thousands)
Outstanding as of December 31, 2017	674,999	$ 1,135	$ 720	$ 1,855
Granted	49,600			
Exercised	(6,552)			
Forfeited	(1,972)			
Outstanding as of September 30, 2018 (unaudited)	716,075	$ 1,135	$ 720	$ 1,855
Vested and expected to vest as of September 30, 2018 (unaudited)	716,075	$ 1,861	$ 840	$ 2,701
Options exercisable as of September 30, 2018 (unaudited)	353,406	$ 994	$ 415	$ 1,409

The weighted average grant-date fair value of share options granted during the nine months ended September 30, 2017 and 2018 (unaudited) was $1.85 per share and $1.82 per share, respectively.

For the nine months ended September 30, 2017 and 2018 (unaudited), the Company recorded share-based compensation expense of $0.2 million and $0.5 million.

The aggregate intrinsic value of share options exercised during the nine months ended September 30, 2017 and 2018 (unaudited) was $5,000 and $23,000, respectively.

During the year ended December 31, 2017 and 2018, the Company granted options for the purchase of an aggregate of 474,888 and 49,600 ordinary shares, respectively, for which 20% of the award vests upon the first anniversary of the vesting start date, 60% vests thereafter in 36 equal monthly installments, and 20% on the earlier of the fourth anniversary of the vesting start date, or the achievement of a specified revenue threshold from the Company's collaboration arrangements. The Company concluded that the accelerated vesting condition was not probable at December 31, 2017. In May 2018, the Company determined that the performance condition became probable of achievement and recorded a cumulative catch-up to reflect the expense as if the vesting condition was probable of achievement at the time of the grant of the award. The Company recorded expense of $0.2 million during the year ended December 31, 2017, and $0.6 million during the nine months ended September 30, 2018 (unaudited) related to these awards, which includes the acceleration of vesting expense.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

As of September 30, 2018 (unaudited), total unrecognized compensation expense related to the unvested employee and director share based awards was $0.5 million which is expected to be recognized over a weighted average period of 2.5 years.

Restricted shares

The following table summarizes the Company's restricted ordinary share award activity since December 31, 2017:

	Shares	Weighted Average Grant-Date Fair Value
		(As restated)
Unvested restricted ordinary share as of December 31, 2017	113,694	$ 2.62
Issued	6,825	3.60
Vested	(44,826)	2.72
Unvested restricted ordinary share as of September 30, 2018 (unaudited)	75,693	$ 2.65

For the nine months ended September 30, 2017 and 2018 (unaudited), the Company recorded share-based compensation expense for unvested restricted shares granted of $46,000 and $86,000, respectively.

The fair value of employee restricted share awards vested during the nine months ended September 30, 2017 and 2018 (unaudited), based on estimated fair values of the ordinary shares underlying the restricted share awards on the day of vesting, was $37,000 and $0.2 million, respectively.

As of September 30, 2018 (unaudited), total unrecognized compensation cost related to the unvested employee and director restricted share awards was $0.2 million, which is expected to be recognized over a weighted average period of 2.1 years.

Income Taxes

The components of net loss before tax provision from income taxes are as follows (in thousands):

	Nine Months Ended September 30,	
	2017	2018
	(restated) (unaudited)	(restated) (unaudited)
United Kingdom	$ (9,458)	$ (15,525)
United States	(475)	(76)
Total	$ (9,933)	$ (15,601)

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

The components of the benefit for income taxes are as follows (in thousands):

	Nine Months Ended September 30,	
	2017 (restated) (unaudited)	2018 (restated) (unaudited)
Current income tax provision (benefit)		
Federal	$ 75	$ (25)
State	10	7
Total current income tax provision (benefit)	85	(18)
Deferred income tax (benefit) provision		
Federal	(58)	(167)
State	(50)	(211)
Total deferred income tax benefit	(108)	(378)
Total benefit from income taxes	$ (23)	$ (396)

The benefit from income taxes for the nine months ended September 30, 2017 and 2018 (unaudited) is limited to the total tax benefit the Company expects to realize for the respective year, since the Company incurred losses in the respective year to date periods that exceeds the expected annual loss. The effective tax rate would therefore exceed the statutory rate and as such the Company is precluded from using the estimated annual effective tax rate.

A reconciliation of the provision (benefit) for income taxes computed at the statutory income tax rate to the provision (benefit) for income taxes as reflected in the financial statement is as follows:

	Nine Months Ended September 30,	
	2017 (unaudited)	2018 (unaudited)
Benefit for income taxes at statutory rate	19%	19%
(Decreases) increases resulting from:		
Federal tax credits	0.4%	1.1%
Change in valuation allowance	(9.3)%	(6.5)%
Net losses surrendered for research credit	(6.7)%	(3.7)%
Preferred share warrants	(1.1)%	(0.6)%
Other	(2.1)%	(6.8)%
Effective income tax rate	0.2%	2.5%

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

Significant components of the Company's current and deferred tax assets at September 30, 2018 (unaudited), were as follows (in thousands):

	Nine Months Ended September 30, 2018 (restated) (unaudited)
Deferred tax assets:	
Operating loss carryforwards	$ 4,665
Research credit carryforwards	197
Accrued expenses and other	1,148
Total deferred tax assets	6,010
Deferred tax liabilities:	
Depreciation & amortization	(169)
Total deferred tax liabilities	(169)
Valuation allowance	(5,326)
Net deferred tax assets	$ 515

During the nine months ended September 30, 2017 and 2018 (unaudited), the Company recorded an income tax benefit of $23,000 and $0.4 million, respectively.

The valuation allowance increased in the nine months ended September 30, 2018 (unaudited) by $1.2 million due to the corresponding increase in UK deferred tax assets, primarily due to operating loss carryforwards generated during the year that were not surrendered for research credit utilization.

As of September 30, 2018 (unaudited), the Company had $27.4 million of U.K. operating loss carryforwards and $0 of U.S. federal and state net operating loss carryforwards. The U.K. operating loss carryforwards have an indefinite life. As of September 30, 2018 (unaudited), the Company had $60,000 and $0.1 million of federal and state research and development credit carryforwards, respectively, that expire at various dates through 2038.

Bicycle Therapeutics Limited

Notes to Consolidated Financial Statements (Continued)

17. Restatement of previously reported financial information (Continued)

Net loss per share

Basic and diluted net loss per share attributable to ordinary shareholders was calculated as follows (in thousands, except share and per share amounts):

	Nine Months Ended September 30,	
	2017	2018
	(restated) (unaudited)	
Numerator:		
Net loss attributable to ordinary shareholders	$ (9,910)	$ (15,205)
Denominator:		
Weighted average ordinary shares outstanding, basic and diluted	229,431	291,979
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (43.19)	$ (52.08)

18. Subsequent events

The Company evaluated subsequent events through March 22, 2019, the date on which those financial statements were issued.

On January 3, 2019, the Company completed the issue of 80,385 Series B2 preferred shares at a price per Series B2 preferred share of £15.55, for gross cash proceeds of $1.6 million.

On March 7, 2019, the holders of the Series B1 warrants to subscribe for Series B1 Preferred Shares agreed that 50% of the warrants will be exercised in conjunction with the IPO and 50% of the warrants will expire.

American Depositary Shares

Representing Ordinary Shares

Goldman Sachs & Co. LLC **Jefferies** **Piper Jaffray**

Canaccord Genuity

Through and including , 2019 (the 25th day after the date of this prospectus), all dealers effecting transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to a dealer's obligation to deliver a prospectus when acting as an underwriter and with respect to an unsold allotment or subscription.

PART II

Information Not Required in Prospectus

Item 13. Other Expenses of Issuance and Distribution.

The following table sets forth the fees and expenses, other than underwriting discounts and commissions, which are expected to be incurred in connection with our sale of ADSs in this offering. With the exception of the registration fee payable to the SEC, the Nasdaq listing fee and the filing fee payable to FINRA, all amounts are estimates.

SEC registration fee	$
FINRA filing fee	
Nasdaq listing fee	
Printing and engraving expenses	
Legal fees and expenses	
Accounting fees and expenses	
Miscellaneous fees and expenses	
Total	$

Item 14. Indemnification of Directors and Officers.

Subject to the Companies Act, members of the registrant's board of directors and its officers (excluding auditors) have the benefit of the following indemnification provisions in the registrant's Articles of Association:

Current and former members of the registrant's board of directors or officers shall be reimbursed for:

(i) all costs, charges, losses, expenses and liabilities sustained or incurred in relation to his or her actual or purported execution of his or her duties in relation to the registrant, including any liability incurred in defending any criminal or civil proceedings; and

(ii) expenses incurred or to be incurred in defending any criminal or civil proceedings, in an investigation by a regulatory authority or against a proposed action to be taken by a regulatory authority, or in connection with any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company, or collectively the Statutes, arising in relation to the registrant or an associated company, by virtue of the actual or purposed execution of the duties of his or her office or the exercise of his or her powers.

In the case of current or former members of the registrant's board of directors, there shall be no entitlement to reimbursement as referred to above for (i) any liability incurred to the registrant or any associated company,(ii) the payment of a fine imposed in any criminal proceeding or a penalty imposed by a regulatory authority for non-compliance with any requirement of a regulatory nature, (iii) the defense of any criminal proceeding if the member of the registrant's board of directors is convicted, (iv) the defense of any civil proceeding brought by the registrant or an associated company in which judgment is given against the director, and (v) any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company in which the court refuses to grant relief to the director.

In addition, members of the registrant's board of directors and its officers who have received payment from the registrant under these indemnification provisions must repay the amount they received in accordance with the Statutes or in any other circumstances that the registrant may prescribe or where the registrant has reserved the right to require repayment.

The underwriting agreement the registrant will enter into in connection with the offering of ADSs being registered hereby provides that the underwriters will indemnify, under certain conditions, the registrant's board of directors and its officers against certain liabilities arising in connection with this offering.

Item 15. Recent Sales of Unregistered Securities.

In the three years preceding the filing of this Registration Statement, we have issued the following securities that were not registered under the Securities Act:

(a) Issuances of Share Capital

On October 3, 2016, we issued 406,001 Series A preferred shares to seven investors for an aggregate subscription price of £4,060,010.

On May 26, 2017, we issued warrants to subscribe for up to 200,000 Series A preferred shares to five investors with an exercise price of €0.01 per share.

On May 26, 2017, we issued 3,562,583 Series B1 preferred shares to eight investors for an aggregate subscription price of £39,999,969.41.

On May 26, 2017 we issued warrants to subscribe for up to 627,903 Series B1 preferred shares to three investors with an exercise price of €0.01 per share.

On October 27, 2017, we issued 384,615 Series B1 preferred shares to one investor for an aggregate subscription price of £4,999,995.

On October 27, 2017, we issued warrants to subscribe for up to 115,384 Series B1 preferred shares to a new unaffiliated investor with an exercise price of €0.01 per share.

On December 17, 2018, we issued 251,904 ordinary shares to existing employees for an aggregate of £2,519.04.

On December 20, 2018, we issued 1,323,248 Series B2 preferred shares to three investors for an aggregate subscription price of £20,576,506.40.

On January 3, 2019, we issued 80,385 Series B2 preferred shares to one investor for an aggregate subscription price of £1,249,986.75.

The sales of securities described above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act, including Regulation D and Rule 506 promulgated thereunder, as transactions by an issuer not involving a public offering, or pursuant to Regulation S promulgated under the Securities Act in that offers, sales and issuances were not made to persons in the United States and no directed selling efforts were made in the United States. All of the purchasers in these transactions represented to us in connection with their purchase that they were acquiring the securities for investment and not distribution, that they could bear the risks of the investment and could hold the securities for an indefinite period of time. Such purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration or an available exemption from such registration. All of the foregoing securities are deemed restricted securities for the purposes of the Securities Act.

(b) Grants and Exercises of Options and Restricted Share Awards

From December 2016 to December 2018, we issued share options to subscribe for an aggregate of 764,740 ordinary shares, with exercise prices ranging from £0.01 to £2.83 per ordinary share, to employees and directors.

From December 2016 to December 2018, we issued 9,907 ordinary shares to individuals upon exercise of options for an aggregate subscription price of £99.07.

From December 2016 to December 2018, we issued 374,239 ordinary shares to individuals pursuant to share vesting agreements, for an aggregate subscription price of £3,742.39.

The issuances of the securities described above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act or Rule 701 promulgated under the Securities Act as transactions pursuant to compensatory benefit plans, or pursuant to Regulation S promulgated under the Securities Act in that offers, sales and issuances were not made to persons in the United States and no directed selling efforts were made in the United States. The ordinary shares issued upon the exercise of options are deemed to be restricted securities for purposes of the Securities Act.

All certificates representing the securities issued in the transactions described in this Item 15 included appropriate legends setting forth that the securities had not been offered or sold pursuant to a registration statement and describing the applicable restrictions on transfer of the securities. There were no underwriters employed in connection with any of the transactions set forth in this Item 15.

Item 16. Exhibits and Financial Statement Schedules.

(a) Exhibits:

Exhibit number	Description of exhibit
1.1*	Form of Underwriting Agreement.
3.1**	Articles of Association of Bicycle Therapeutics Limited, as currently in effect.
3.2*	Form of Articles of Association of the registrant (to be effective upon the closing of this offering).
4.1*	Form of Deposit Agreement.
4.2*	Form of American Depositary Receipt (included in Exhibit 4.1).
5.1*	Opinion of Goodwin Procter (UK) LLP.
10.1*	Investment Agreement by and among Aquila Investments IV, the Existing Investors, the Founders, Kevin Lee, Other Shareholders, Bicycle Therapeutics Limited, BicycleRD Limited and BicycleTx Limited relating to Bicycle Therapeutics Limited on December 20, 2018.
10.2*	Registration Rights Agreement by and among Bicycle Therapeutics Limited and the Investors listed therein, dated December 20, 2018.
10.3**#	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in England.
10.4**#	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in the United States.
10.5*#	Senior Executive Cash Incentive Bonus Plan.
10.6*#	2018 Employee Stock Purchase Plan.
10.7*#	2019 Share Option and Incentive Plan and forms of award agreements thereunder (to be adopted prior to the effectiveness of this registration statement).

Exhibit number	Description of exhibit
10.8*#	Employment Agreement between the registrant and Kevin Lee, Ph.D., MBA, to be in effect upon the effectiveness of this Registration Statement.
10.9*#	Employment Agreement between the registrant and Lee Kalowski, MBA, to be in effect upon the effectiveness of this Registration Statement.
10.10*#	Employment Agreement between the registrant and Michael Skynner, Ph.D., to be in effect upon the effectiveness of this Registration Statement.
10.11*#	Employment Agreement between the registrant and Maria Koehler, M.D., Ph.D., to be in effect upon the effectiveness of this Registration Statement.
10.12*#	Employment Agreement between the registrant and Nicholas Keen, Ph.D., to be in effect upon the effectiveness of this Registration Statement.
10.13*#	Form of Deed of Indemnity between the registrant and each of its directors and executive officers.
10.14**	Contract for the Sale of Leasehold Land with Vacant Possession, by and between Convergence Pharmaceuticals Limited and BicycleRD Limited, dated October 31, 2017, which is pursuant to the Underlease of Ground and First Floor Premises Building 900 Babraham Research Campus Babraham Cambridge, between Imperial College Thinkspace Limited, Convergence Pharmaceuticals Limited and Biogen Idec Limited, dated March 2, 2017.
10.15**	Lease Agreement, by and between Bicycle Therapeutics Inc. and King 4 Hartwell Place, LLC, dated September 26, 2017.
10.16**+	Clinical Trial and License Agreement, by and between Bicycle Therapeutics Limited, Cancer Research Technology Limited, and Cancer Research UK, dated December 13, 2016, as amended and restated by the Deed of Amendment on March 31, 2017, as further amended by the Second Deed of Amendment on June 29, 2018.
21.1**	Subsidiaries of the registrant.
23.1*	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
23.2*	Consent of Goodwin Procter (UK) LLP (included in Exhibit 5.1).
24.1*	Power of Attorney (included on signature page to this registration statement).

* To be filed by amendment.

** Previously filed.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

\+ Confidential treatment has been requested for portions of this exhibit. These portions have been omitted from the registration statement and filed separately with the United States Securities and Exchange Commission.

(b) Financial Statements Schedules:

Schedules have been omitted because the information required to be set forth therein is not applicable or is shown in the financial statements or notes thereto.

Item 17. Undertakings.

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, or the Act, may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act and is therefore unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

The Registrant hereby undertakes that:

(a) The Registrant will provide to the underwriter at the closing as specified in the underwriting agreement, certificates in such denominations and registered in such names as required by the underwriter to permit prompt delivery to each purchaser.

(b) For purposes of determining any liability under the Securities Act of 1933, as amended, the information omitted from a form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in the form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933, as amended, shall be deemed to be part of this registration statement as of the time it was declared effective.

(c) For the purpose of determining any liability under the Securities Act of 1933, as amended, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant has duly caused this registration statement on Form S-1 to be signed on its behalf by the undersigned, thereunto duly authorized, under the laws and regulations of England and Wales, on .

BICYCLE THERAPEUTICS LIMITED

By: _____

Name: Kevin Lee, Ph.D., MBA
Title: *Chief Executive Officer*

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Kevin Lee, Ph.D., MBA and Lee Kalowski, MBA, and each of them, his or her true and lawful agent, proxy and attorney-in-fact, with full power of substitution and resubstitution, for and in his or her name, place and stead, in any and all capacities, to (i) act on, sign and file with the Securities and Exchange Commission any and all amendments (including post-effective amendments) to this Registration Statement together with all schedules and exhibits thereto and any subsequent registration statement filed pursuant to Rule 462(b) under the Securities Act of 1933, as amended, together with all schedules and exhibits thereto, (ii) act on, sign and file such certificates, instruments, agreements and other documents as may be necessary or appropriate in connection therewith, (iii) act on and file any supplement to any prospectus included in this Registration Statement or any such amendment or any subsequent registration statement filed pursuant to Rule 462(b) under the Securities Act of 1933, as amended, and (iv) take any and all actions which may be necessary or appropriate to be done, as fully for all intents and purposes as he or she might or could do in person, hereby approving, ratifying and confirming all that such agent, proxy and attorney-in-fact or any of his or her substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Act, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
_____ Kevin Lee, Ph.D., MBA	Chief Executive Officer and Director (Principal Executive Officer)	
_____ Lee Kalowski, MBA	Chief Financial Officer and President (Principal Financial and Accounting Officer)	
_____ Pierre Legault, MBA, CPA	Chairman and Director	
_____ Michael Anstey, DPhil	Director	

Signature	Title	Date
Catherine Bingham, MBA	Director	
Deborah Harland, Ph.D., MBA	Director	
Anja König, Ph.D.	Director	
Eashwar Krishnan	Director	
Carolyn Ng, Ph.D.	Director	
Jason Rhodes, MBA	Director	
Sir Gregory Winter, FRS	Director	
Lee Kalowski	Authorized Representative in the United States	