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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2020.

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 001-38916

BICYCLE THERAPEUTICS PLC
(Exact name of registrant as specified in its charter)

England and Wales (State or Other Jurisdiction of Incorporation or Organization)	**Not Applicable** (I.R.S. Employer Identification No.)
B900, Babraham Research Campus **Cambridge, United Kingdom** (Address of Principal Executive Offices)	**CB22 3AT** (Zip Code)

Registrant's telephone number, including area code **+44 1223 261503**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value £0.01 per share*	n/a	The Nasdaq Stock Market LLC
American Depositary Shares, each representing one ordinary share, nominal value £0.01 per share	BCYC	The Nasdaq Stock Market LLC

* Not for trading, but only in connection with the listing of the American Depositary Shares on the NASDAQ Global Select Market.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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 ☐ Accelerated filer ☐

Non-accelerated filer ☒ 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. ☒

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value (approximate) of the registrant's voting and non-voting common equity held by non-affiliates based on the closing price per American Depositary Share, or ADS, of the registrant's ADSs on The Nasdaq Global Select Market on June 30, 2020 (the last business day of the registrant's most recently completed second fiscal quarter) was $189,962,881.

As of March 5, 2021, the registrant had 23,090,382 ordinary shares, nominal value £0.01 per share, outstanding.

Documents Incorporated by Reference:

Portions of the registrant's definitive proxy statement, or Proxy Statement, for its 2021 Annual General Meeting, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2020, are incorporated by reference into Part III of this Annual Report on Form 10-K.

SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS.

This Annual Report on Form 10-K contains forward-looking statements which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements may be identified by such forward-looking terminology as "may," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue" or variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Any forward-looking statement involves known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by such forward-looking statement. Forward-looking statements include statements, other than statements of historical fact, about, among other things:

- statements regarding the impact of the ongoing COVID-19 pandemic and its effects on our operations, research and development and clinical trials and potential disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business;
- 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 Bicycle Toxin Conjugates®, or BTCs, tumor-targeted immune cell agonist programs, 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;
- costs 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 amount of and our ability to satisfy interest and principal payments under our debt facility with Hercules Capital, Inc., or Hercules;

- 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 Jumpstart Our Business Startups Act, or the JOBS Act;
- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance; and
- other risks and uncertainties, including those listed under the caption “Risk Factors.”

Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, these statements are based on our estimates or projections of the future that are subject to known and unknown risks and uncertainties and other important factors that may cause our actual results, level of activity, performance, experience or achievements to differ materially from those expressed or implied by any forward-looking statement. These risks, uncertainties and other factors are described in greater detail under the caption “Risk Factors” in Part I. Item 1A and elsewhere in this Annual Report on Form 10-K. As a result of the risks and uncertainties, the results or events indicated by the forward-looking statements may not occur. Undue reliance should not be placed on any forward-looking statement.

In addition, any forward-looking statement in this Annual Report represents our views only as of the date of this annual report and should not be relied upon as representing our views as of any subsequent date. We anticipate that subsequent events and developments may cause our views to change. Although we may elect to update these forward-looking statements publicly at some point in the future, we specifically disclaim any obligation to do so, except as required by applicable law. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

RISK FACTOR SUMMARY

The below summary risk factors provide an overview of certain of the risks we are exposed to in the normal course of our business activities. The below summary risk factors do not contain all of the information that may be important to investors, and investors should read the summary risk factors together with the more detailed discussion of risks set forth in Part I, Item 1A, "Risk Factors," of this Annual Report.

- 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 may 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.
- Raising additional capital may cause dilution to our existing shareholders or holders of our American Depositary Shares, or ADSs, restrict our operations or cause us to relinquish valuable rights.
- Our failure to comply with the covenants or payment obligations under our existing term loan facility with Hercules Capital, Inc., or Hercules, could result in an event of default, which may result in increased interest charges, acceleration of our repayment obligations or other actions by Hercules, any of which could negatively impact our business, financial condition and results of operations.
- 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 are substantially dependent on the success of our internal development programs and of our product candidates from our Bicycle Toxin Conjugates, or BTCs, Bicycle tumor-targeted immune cell agonist™, or TICA™, programs, which may not successfully complete clinical trials, receive regulatory approval or be successfully commercialized.
- 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.
- Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.
- 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, or IND, that could halt their clinical development, prevent their marketing approval, limit their commercial potential or result in significant negative consequences.
- We may be delayed or not be successful in our efforts to identify or discover additional product candidates.
- 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.
- We may seek designations for our product candidates with the U.S. Food and Drug Administration, or 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.
- 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 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.
- 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.
- 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.
- 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.
- 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, could limit our ability to market those products and decrease our ability to generate revenue.
- Healthcare legislative reform measures may have a negative impact on our business and results of operations.
- We rely on third parties, including independent clinical investigators and clinical research organizations, or 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 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.
- 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
- As a company based outside of the United States, we are subject to economic, political, regulatory and other risks associated with international operations.
- COVID-19 could impact our business.
- The market price of our ADSs is highly volatile, and holders of our ADSs may not be able to resell their ADSs at or above the price at which they purchased their ADSs.

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PART I

ITEM 1. 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 facilitates target binding with high affinity and selectivity, making *Bicycles* attractive candidates for drug development. *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. The relatively large surface area presented by *Bicycles* allow targets to be drugged that have historically been intractable to non-biological approaches. *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.

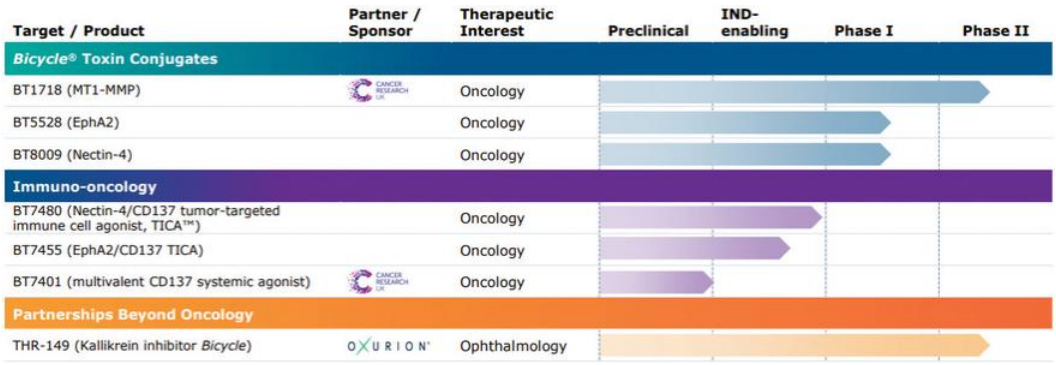
We have a novel and proprietary phage display screening platform which we use to identify *Bicycles* in an efficient manner. The platform initially displays linear peptides on the surface of engineered bacteriophages, or phages, before "on-phage" cyclization with a range of small molecule scaffolds which 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 candidates, BT1718, BT5528 and BT8009, are Bicycle Toxin Conjugates®, or BTCs. These *Bicycles* are chemically attached to a toxin that when administered is cleaved from the *Bicycle*® and kills the tumor cells. BT1718 targets tumors that express Membrane Type 1 matrix metalloproteinase, or MT1-MMP, and is currently in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Cancer Research UK Centre for Drug Development, or Cancer Research UK, to evaluate its safety, tolerability and efficacy. We are also evaluating BT5528, a second-generation BTC targeting Ephrin type A receptor 2, or EphA2, in a company-sponsored Phase I/II clinical trial as a monotherapy and in combination with nivolumab, and BT8009, a second-generation BTC targeting Nectin-4, in a company-sponsored Phase I/II clinical trial. Our discovery pipeline in oncology includes *Bicycle*-based systemic immune cell agonists and Bicycle tumor-targeted immune cell agonists, or TICAs.

Beyond our wholly-owned oncology portfolio, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas in which 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 in immuno-oncology, or I-O, anti-infective, cardiovascular, ophthalmology, dementia 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*. From our founding through December 31, 2020, we have generated substantial intellectual property, including four patent families directed to novel scaffolds, 16 patent families directed to our platform technology, 79 patent families directed to bicyclic peptides and related conjugates, and nine patent families directed to clinical indications and other properties of development assets. 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 biopharmaceutical companies including Amgen, GlaxoSmithKline, Novartis and Pfizer. Our board of directors and scientific advisory board include industry experts and seasoned investors, with extensive experience in I-O.

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:

- ***Progress our most advanced candidates, BT1718, BT5528 and BT8009, through clinical development.*** BT1718 is being investigated in an ongoing Phase I/IIa clinical trial sponsored by Cancer Research UK. Cancer Research UK initiated expansion cohorts in the Phase IIa portion of the Phase I/IIa study in 2020. We are also evaluating BT5528, a second-generation BTC targeting EphA2, in a company-sponsored Phase I/II clinical trial as a monotherapy and in combination with nivolumab, and BT8009, a second-generation BTC targeting Nectin-4, in a company-sponsored Phase I/II clinical trial. We intend to advance development of these candidates across oncology indications based on target expression.

- ***Continue IND-enabling activities for our lead TICA program, BT7480.*** BT7480 is a fully synthetic TICA that contains a *Bicycle* targeting Nectin-4 and a *Bicycle* targeting the costimulatory receptor CD137. BT7480 has been shown in preclinical models to rapidly penetrate tumors, have anti-tumor activity, and induce immune memory specific to the implanted tumor. IND-enabling activities for BT7480 are ongoing, and we are on track to commence the Phase I clinical trial in the second half of 2021.

- ***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, early I-O

discovery efforts have resulted in the identification of TICA candidates targeting natural killer, or NK, cells. We are currently advancing these programs into lead optimization.

- ***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 and TICAs, and we 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-infective, cardiovascular, ophthalmology, dementia 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.

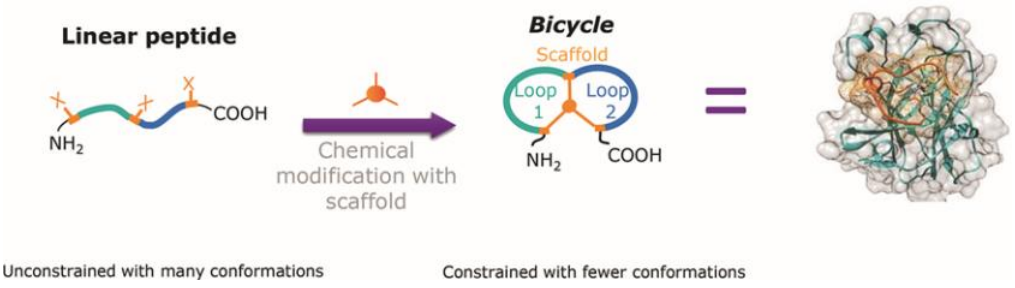
The *Bicycle* Opportunity

Introduction to Bicycles

Bicycles are fully synthetic, short peptides consisting of nine to 20 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^{20} today. We have applied our novel *Bicycle* modality to a growing range of targets, from a single target in 2009 to more than 125 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. We can readily identify *Bicycles* that may 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

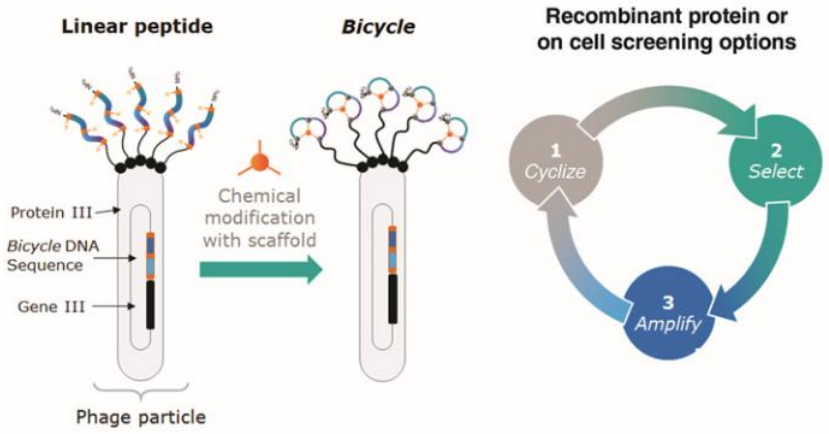
We utilize our novel and proprietary phage display screening platform to identify *Bicycles* that are potentially useful in medicine. We have used this technology to identify our current pipeline and intend to leverage it to develop a broader portfolio of product candidates to address unmet medical needs 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 agonists 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 systemic and tumor-targeted immune cell agonist programs. 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. We can readily identify *Bicycles* that may 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.

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 125 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, ovarian cancer, endometrial cancer, bladder cancer, esophageal cancer)	• Phase I/IIa	• Ongoing Phase I/IIa clinical trial in collaboration with CRUK
BT5528	• High EphA2 expressing tumors (e.g., lung cancer, breast cancer, bladder cancer, gastric cancer, ovarian cancer, esophageal cancer, pancreatic cancer)	• Phase I/IIa	• Ongoing company-sponsored Phase I/IIa clinical trial
BT8009	• High Nectin-4 expressing tumors (e.g. bladder cancer, breast cancer, esophageal cancer, head & neck cancer, lung cancer, ovarian cancer)	• Phase I/IIa	• Ongoing company-sponsored Phase I/IIa clinical trial
***Bicycle* Tumor-targeted Immune Cell Agonists (TICAS™) and Systemic Agonists**			
BT7480 (Nectin-4/CD137 TICA)	• Oncology	• Preclinical	• IND-enabling activities in process
BT7401 (multivalent CD137 agonist)	• Oncology	• Preclinical	• CRUK to fund and sponsor development through a Phase IIa clinical study
BT7455 (EphA2/CD137 TICA)	• Oncology	• Preclinical	• IND-enabling activities in process
Undisclosed	• Oncology	• Discovery	• Collaborating with Genentech
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
Novel anti-bacterials	• Anti-bacterials	• Discovery	• Collaborating with Innovate UK and Small Business Research Initiative
Neurological	• Dementia	• Discovery	• Collaborating with Dementia Discovery Fund and Oxford Drug Discovery Institute

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 cell agonists. 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. 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 tumor-targeted immune cell-engaging *Bicycle* molecules.

Bicycle *Toxin Conjugates*

Within our BTC programs, we are developing BT1718 (carrying a DM1 (mertansine) 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 Cancer Research UK Centre for Drug Development. Patient enrollment in the Phase IIa portion of the Phase I/IIa trial remains ongoing.

We are evaluating BT5528, our first second-generation BTC that targets EphA2 and carries a monomethyl auristatin E, or MMAE, cytotoxin payload, in an ongoing, company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics, and preliminary clinical activity in patients with solid tumors. We are currently enrolling patients in the Phase I portion of the Phase I/II trial of BT5528.

We are also evaluating BT8009, a second-generation BTC that targets Nectin-4 and carries an MMAE cytotoxin payload, in an ongoing company-sponsored Phase I/II clinical trial to assess to assess the safety,

pharmacokinetics, and preliminary clinical activity in patients with Nectin-4 expressing advanced malignancies. Studies have demonstrated that MT1-MMP, EphA2 and Nectin-4 are overexpressed in many cancer types with high unmet medical needs, including lung cancer, breast, gastric, endometrial, sarcoma, pancreatic, 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. Early clinical data from an ongoing clinical trial has shown ten times higher tumor cytotoxin levels than corresponding plasma levels based on clinical tumor biopsies taken 24 hours post-infusion.

- ***Retention in tumors.*** In preclinical studies a tumor antigen targeting *Bicycle* was observed to be retained in the tumor for at least 120 hours after dosing. Preliminary clinical data observed to date from our ongoing clinical trials are consistent with preclinical observations of post-dose tumor retention.

- ***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 to 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.

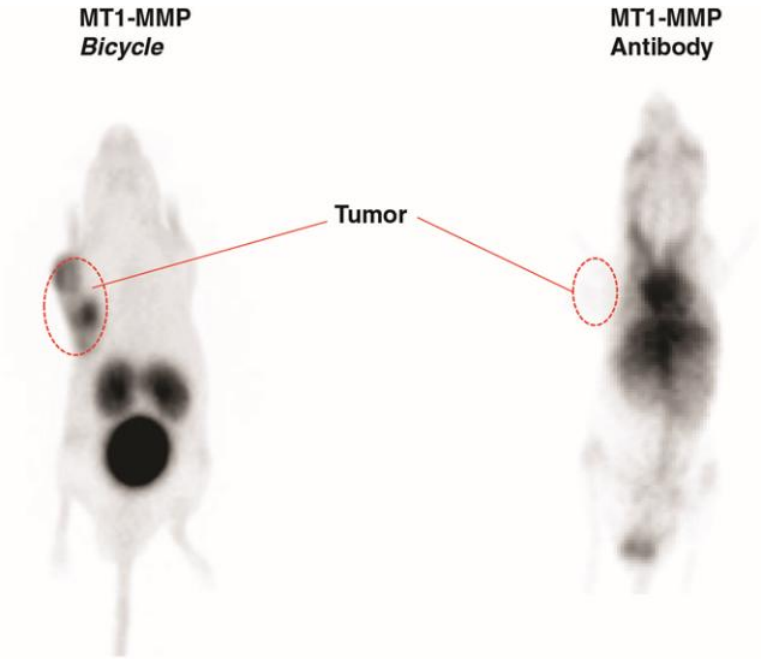
- ***Access to non-expressing tumor cells.*** The toxin in our BTCs is liberated in the extracellular space, enabling cell-killing adjacent cells that do not express the specific target through a toxin bystander effect. In our preclinical studies, we observed activity for BTCs even in tumors that were 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.

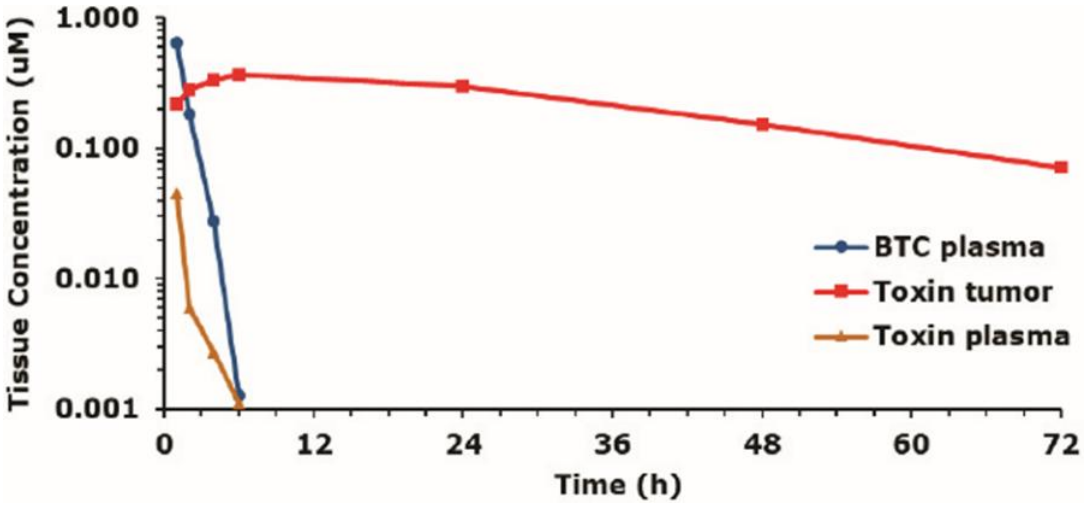
PET Imaging Revealing Payload Delivery in a Mouse Model



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

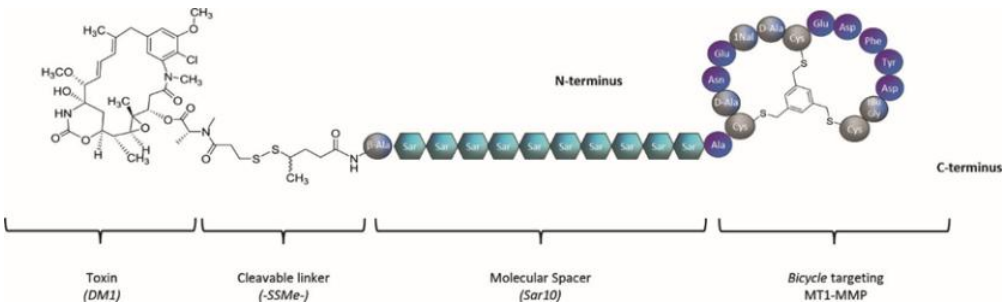


We believe these data demonstrate the potential of BTCs to have long-term sustained activity and to limit the toxicity that is associated with ADCs.

BT1718

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 DM1 cytotoxin payload. We are not aware of any other cytotoxin conjugates in development that target MT1-MMP.

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.

In our preclinical studies, we observed that BT1718 was associated with the greatest anti-tumor effect when membrane expression of MT1-MMP was high (as quantified by fluorescence activated cell sorting, or FACS). 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.

Clinical Development

Ongoing Phase I/IIa First in Human Clinical Trial

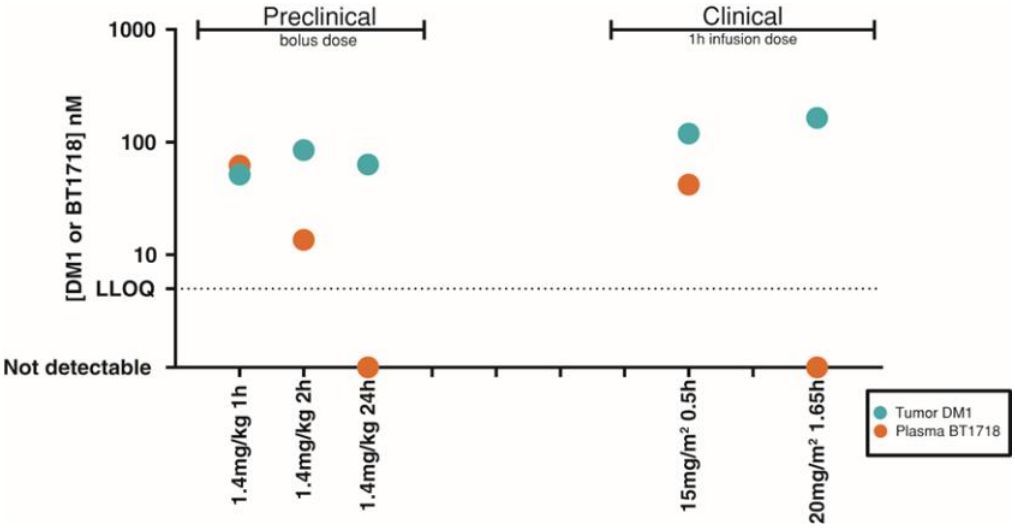
BT1718 is being investigated in an ongoing Phase I/IIa open label dose escalation and expansion clinical trial sponsored by Cancer Research UK. The Phase I part of this trial evaluated up to 40 patients with advanced solid tumors in two dosing regimens at three sites in the United Kingdom. In the Phase I portion of the Phase I/IIa trial, BT1718 was generally well-tolerated. Based on the Phase I trial results, 20 mg/m^2 of BT1718 administered once weekly was selected as the Phase IIa dose. This dose is within the efficacious dose range predicted by preclinical models, in which an equivalent dose level was associated with complete responses, or CRs. With once-weekly dosing, BT1718 appeared tolerable, with manageable adverse events. Though the primary objective of the Phase I portion of the BT1718 trial was evaluating safety and tolerability in an unselected group of patients with advanced solid tumors, some signs of anti-tumor activity were observed: at doses of between 9.6 mg/m^2 and 32.0 mg/m^2 administered once-weekly, 13 out of 24 response evaluable patients at the eight week timepoint exhibited best response of at least stable disease. Ten of these 13 patients had a greater than 10% reduction in at least one target lesion, including a tumor reduction of 68% observed in one patient, a reduction that meets the RECIST Version 1.1 criteria of a partial response.

The Phase IIa part of the trial, which commenced in 2020, is evaluating BT1718 in patients with tumors that express MT1-MMP at the recommended Phase II dose of 20 mg/m^2, based on the findings from the Phase I part of the trial. To determine tumor types of interest, a clinically validated MT1-MMP immunohistochemistry, or IHC, assay, developed in collaboration with Cancer Research UK, was used to screen tumor tissue microarrays, or TMA, from multiple tumor types selected based on literature reports of high expression of MT1-MMP, including breast, lung, sarcoma, gastric, ovarian, endometrial, bladder, and esophageal cancers. To date, the percentage of patients determined to be MT1-MMP-positive at the pre-specified cutoff is consistent with previous translational research findings. Enrollment is ongoing at four clinical sites, with additional sites expected to begin enrolling patients during the first half of 2021. Patients are currently being enrolled into two solid tumor cohorts, one in squamous non-small cell lung cancer, or NSCLC, and the other in an all-comers “basket” cohort. Depending on results from these first two cohorts, Cancer Research UK may initiate up to two additional cohorts. Each cohort will evaluate 16 patients with a specified tumor type determined using the results of the MT1-MMP IHC TMA analysis.

The endpoints for the Phase IIa part of this clinical trial are safety and preliminary efficacy in patients with tumors expressing MT1-MMP. Archived or fresh tumor samples from all patients are collected and tested for MT1-MMP expression using the clinically validated IHC and associations with tumor and stromal expression and clinical response will be explored. Biopsies of tumors will be mandatory in a subset of patients in this part of the trial in order to evaluate tumor PK and pharmacodynamic biomarkers of response to BT1718.

DM1 delivery has been demonstrated in tumor biopsies at early timepoints (2 out of 3 patients). Concentrations of DM1 in the clinical tumor biopsy samples are consistent with preclinical data obtained at doses that gave partial (4.2 mg/m^2) and full (14.4 mg/m^2) tumor regression in mouse xenograft models. In the phase IIa part of the study, additional tumor biopsies will be taken at later timepoints to further evaluate DM1 retention.

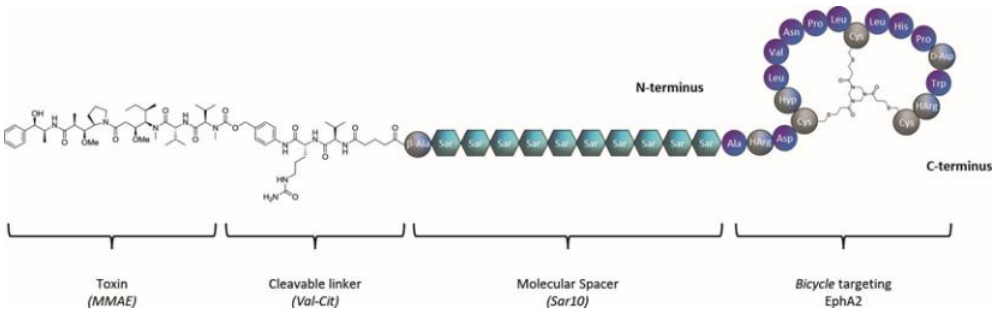
DM1 Levels in Clinical and Preclinical Tumor Samples



BT5528

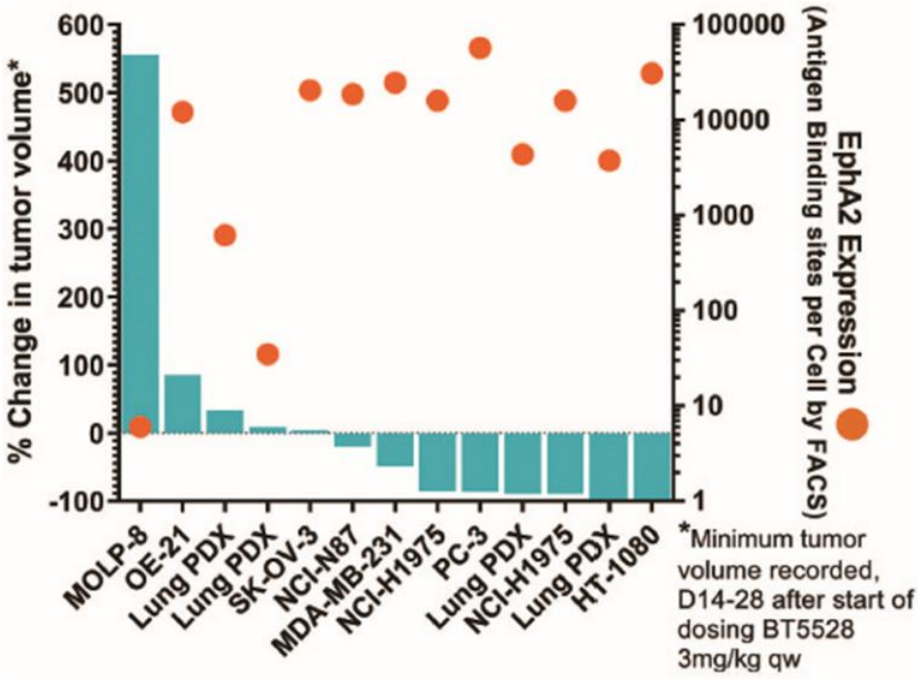
BT5528 is a BTC designed to target EphA2. The molecule is comprised of our EphA2 targeting *Bicycle*, a valine-citrulline, or val-cit, cleavable linker and a cytotoxin MMAE payload.

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, esophageal, pancreatic, and glioma. In both cell-derived and patient-derived preclinical models, we observed anti-tumor activity signals following administration of our EphA2 toxin conjugates, which correlated with EphA2 expression, as determined by FACS studies.

Effect of EphA2 Expression on BT5528 Activity Across Preclinical Xenograft Models



EphA2 has previously been pursued by other companies utilizing antibody drug conjugates, or 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. Similar to the strategy for selecting indications for BT1718, we are screening tumor TMAs using a clinically validated EphA2 IHC, in a CAP accredited and CLIA certified laboratory, to prioritize those indications with high EphA2 protein expression for clinical investigation.

BT5528 was 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 150-fold higher than the clinical dose of an ADC with the same amino acid sequence and with the same linker-toxin combination and average drug/antibody ratio as MEDI-547 used in patients.

Clinical Development

BT5528 is currently being evaluated in the dose escalation, Phase I portion of a company-sponsored Phase I/II clinical trial of patients with advanced solid tumors associated with EphA2 expression. BT5528 has been dosed up to 8.5 mg/m^2 weekly, which we believe, based on pre-clinical studies, is toward the top of the therapeutic range, with transient neutropenia observed at that dose. Dose finding for the Phase II portion of the trial remains ongoing, and additional weekly and every other week doses are currently being explored. Currently administered doses are in the predicted therapeutic range, delivering over 15 times more toxin than MedImmune's EphA2 ADC MEDI-547. In addition, and in contrast to the adverse events observed with MEDI-547, we have observed no signs of coagulopathy to date.

The clinical pharma profile of BT5528 is consistent with preclinical predictions. Early data received from tumor biopsies reveal that 24 hours after infusion of BT5528, tumor levels of the MMAE cytotoxin payload are approximately ten times higher than the corresponding plasma levels. Emerging, qualitative metabolite identification data from the clinical trial supports the hypothesis that BTCs undergo reduced hepatic metabolism and are eliminated renally.

Although dosing continues to be refined, we have observed preliminary findings consistent with anti-tumor activity. An EphA2 IHC assay was deployed during 2020, enabling pre-selection of patients in the Phase I portion of the trial. Since implementation of the IHC assay, patients are prospectively screened and are eligible for enrollment based on a prespecified H-score.

As of January 14, 2021, two EphA2-selected patients have enrolled in the trial, one of whom was response evaluable. In the response evaluable, prospectively screened, EphA2-positive patient, a urothelial patient currently receiving 6.5 mg/m^2 of BT5528 every other week, whose prior lines of therapies included both a PD-1 inhibitor and enfortumab vedotin, we observed a 43% reduction in target lesions at the first radiologic response assessment, constituting a partial response under RECIST version 1.1 criteria. We also observed reductions in non-target lesions, and the patient remains enrolled in the trial.

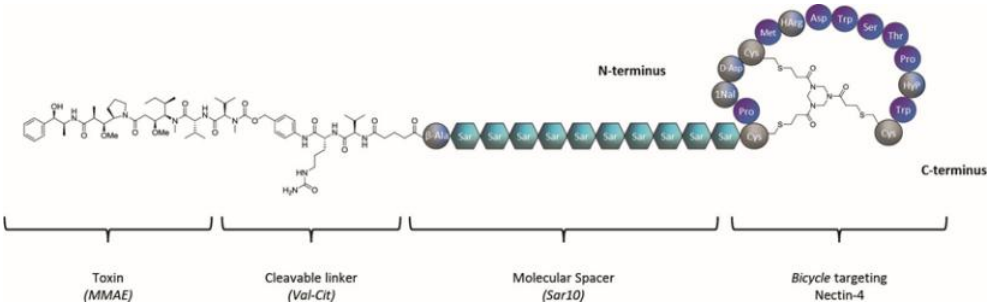
In addition, an ovarian cancer patient, enrolled prior to implementation of the EphA2 assay, currently receiving 4.4mg/m^2 of BT5528 every week, who had been previously treated with chemotherapy, a vascular endothelial growth factor, or VEGF inhibitor, and a poly (ADP ribose) polymerase, or PARP, inhibitor, has achieved an ongoing 25% reduction in target lesions, which constitute stable disease. The patient, first dosed in May 2020, has completed eight cycles of BT5528 and remains enrolled in the trial. We retrospectively analyzed the patient for EphA2 status and determined the patient to be positive but below the current enrollment H-score cutoff.

We are currently enrolling patients in this trial at five active clinical sites, including four in the United States and one in the United Kingdom. We expect that up to five additional sites will open in the first half of this year, primarily in the United Kingdom and Europe. We expect a planned total of up to 17 worldwide sites to be active in 2021, with sites prioritizing the enrollment of eligible EphA2-positive patients in the monotherapy cohorts.

BT8009

BT8009 is a BTC designed to target Nectin-4, a well-validated tumor antigen. 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 are aware of one Nectin-4 ADC program in development, enfortumab vedotin, which is being jointly conducted by Seattle Genetics and Astellas and, in December 2019, received approval from the U.S. Food and Drug Administration, or FDA, as a treatment for patients with locally advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. Similar to our strategy for selecting indications for BT1718 and BT5528, we will screen tumor TMAs using a clinically validated Nectin-4 IHC to prioritize indications with high Nectin-4 protein expression for clinical investigation.

Clinical Experience

BT8009 is advancing in the Phase I portion of the company-sponsored Phase I/II clinical trial. Early clinical data supports a PK profile that is consistent with both preclinical predictions and data to date from our ongoing Phase I trial of BT5528, which utilizes the same linker and toxin payload.

Enrollment in the Phase I/II trial of BT8009 is ongoing at 2 sites in the United States and our first clinical site outside of the United States opened in the first quarter of 2021. We expect up to nine additional sites to open, primarily in Europe and the United Kingdom in the first half of 2021, with further geographic expansion later in 2021. In total, we expect up to 21 clinical sites to be open, with prioritization given to enrolling appropriate Nectin-4-positive patients in the monotherapy cohorts.

Bicycle *Immune Cell Agonist*

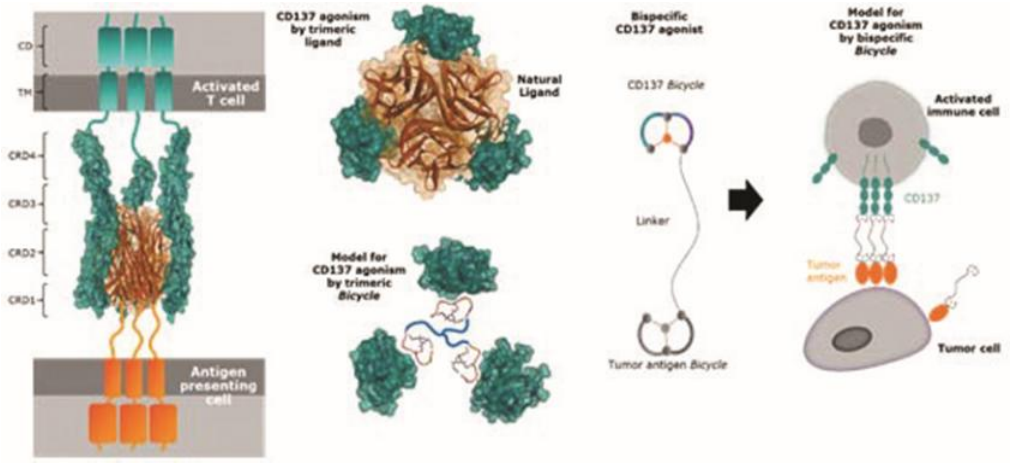
Approaches that activate cytotoxic T-cells and other types of cells used in a body's immune response have been observed to improve outcomes in cancer. However, prolonged immune activation can be toxic and lead to T-cell exhaustion, which is a challenge amplified by the long half-life of antibodies and 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. We are developing immune cell agonists, designed to trigger an immune response to tumors. We have identified potent *Bicycle* agonists 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 small size and PK characteristics of *Bicycles*. Our *Bicycle* immune cell agonists are designed to circumvent the limitations of antibody and biologic therapies, such as liver toxicity and limited efficacy, and to better enable combination therapy. *Bicycle* immune cell agonists can be formed by conjugating multiple copies of a CD137 *Bicycle* to form multimers or by utilizing a bi-specific format in which CD137 *Bicycles* are linked to *Bicycles* that bind to tumor antigens, inhibit checkpoint proteins or otherwise activate the immune system. We believe we are currently the only company that has fully chemically synthetic multivalent or tumor-targeted CD137 agonists.

Properties of Bicycle *Immune Cell Agonists*

In order to agonize the CD137 receptor, cross-linking of a trimeric receptor is required. As a result, we are developing multivalent systemic and tumor-targeted molecules that cross-link the receptor into an active form in a tumor cell independent or dependent manner as shown in the image below.

Schematic of Proposed CD137* Bicycle *Agonists



These *Bicycle* CD137 agonists 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 systemic and tumor-targeted immune cell agonizing *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 multivalent and tumor-targeted *Bicycles* are in the range of approximately 4 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 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 and in combination with other *Bicycles* 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.

- ***Tumor targeting***. Combining CD137-binding *Bicycles* with *Bicycles* that bind to tumor targets potentially affords an additional level of safety as compared to systemically active agonists such as urelumab. The clustering and activation of CD137 occurs only when the tumor-targeting *Bicycle* binds to both the tumor antigen target and CD137. Therefore, we expect the tumor targeted agonists will achieve a higher degree of activation locally in the tumor but will have significantly reduced or no activity in healthy tissues that do not express the tumor antigen.

Comparison of the Features of our Bicycle Immune Cell Agonists to Biological Immune 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 multivalent; ~3.5-8 kDa for tumor-targeted immune cell agonists (TICAS) • Linkage through various sites of attachment allows presentation of binder in various orientations • Easy to make tri- and tetrameric molecules • Immunogenicity unlikely—multivalent 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

Multivalent CD137 Immune Cell Agonists

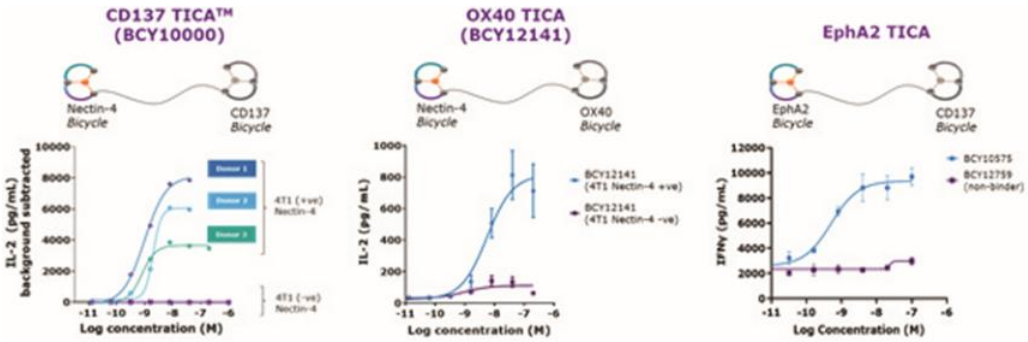
We observed that simple multivalent *Bicycle* CD137 agonists displayed potent activity in preclinical cell-based assays. Several *Bicycle* CD137 agonists displayed comparable or higher fold induction compared to the natural ligand (CD137L) in an engineered reporter cell assay whereby CD137 activation leads to production of a luminescence signal. We also observed *Bicycles* stimulated the release of the cytokine IL-2, a marker of immune response, from primary human T-cells. In additional *in vivo* studies, we observed that CD137-binding *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.

Bicycle *Tumor-Targeted Immune Cell Agonists (TICAs)*

We have linked immune cell receptor binding *Bicycles* to tumor antigen binding *Bicycles* to form TICAs. We have found this approach to be generalizable across tumor antigen and immune cell receptors. We constructed CD137-

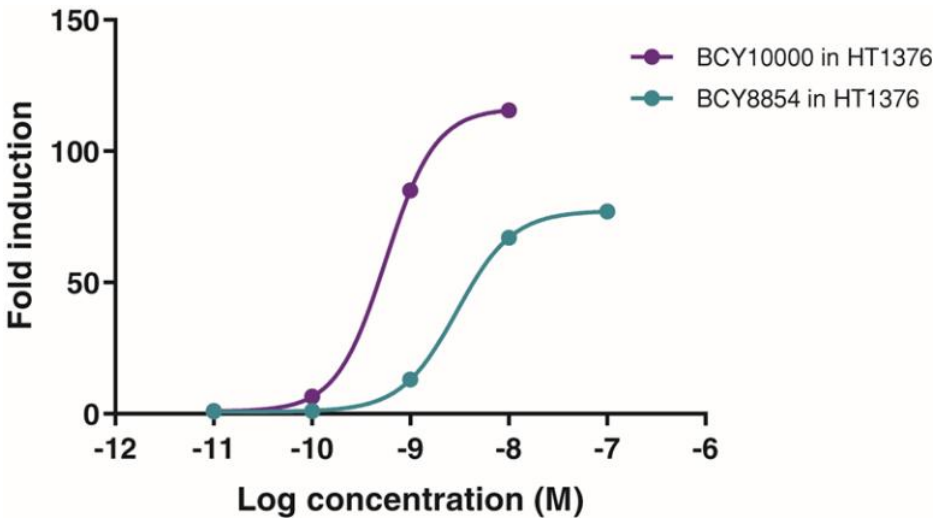
targeting TICA molecules and observed that these bi-specific *Bicycles* agonize the CD137 receptor only in the presence of cells that express the appropriate tumor antigen. Additionally, we have constructed TICA molecules with *Bicycles* that bind to another member of the TNF family of T-cell costimulatory receptors TNFRSF4, also known as OX40. As shown in the figure below, TICA molecules combining our Nectin-4 or EphA2 tumor antigen binding *Bicycles* and CD137 or OX40 binding *Bicycles* stimulated the release of the cytokine IL-2 or IFN from human PBMCs when in co-culture with tumor cells that express appropriate receptor (Nectin-4 or EphA2). In co-culture with cells lacking Nectin-4 expression, or when non-binding *Bicycles* are incorporated (such as BCY12759) there was no activity observed. This is an example of how both the immune cell binding and tumor cell binding *Bicycles* can be readily interchanged in the context of our synthetic TICA molecules to generate novel and targeted immune agonists for further study.

Modularity of TICAs



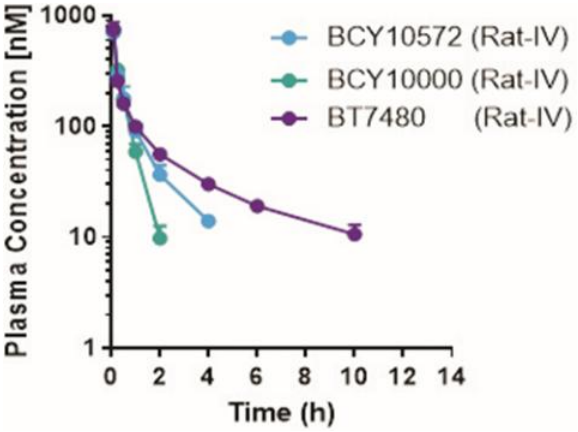
In our preclinical development of TICA molecules, we have observed an ability to tune molecules based on simple chemical changes, which we believe is an inherent advantage of our *Bicycle* platform-based approach to bi-specifics compared to other modalities. As an example of this, activity of two different Nectin-4/CD137 TICA molecules is shown below. BCY10000 was observed to have a higher affinity CD137 binding *Bicycle* than BCY8854, yielding increased activity and potency in a CD137 assay.

Tunable Activity of CD137 TICAs



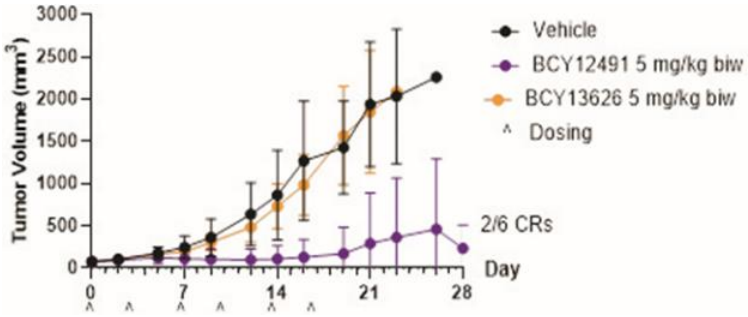
We also observed that the pharmacokinetic properties of TICA molecules can be tuned through chemical changes. The figure below shows the plasma concentrations over time of three Nectin-4/CD137 TICA molecules after intravenous infusion into rats at a dose of 3 mg/kg. BCY11863 demonstrates a longer circulation time than BCY10000 and BCY10572. This data shows that the properties of the TICAs can be modulated to extend the duration of exposure *in vivo*.

Tunable Pharmacokinetics of CD137 TICAs



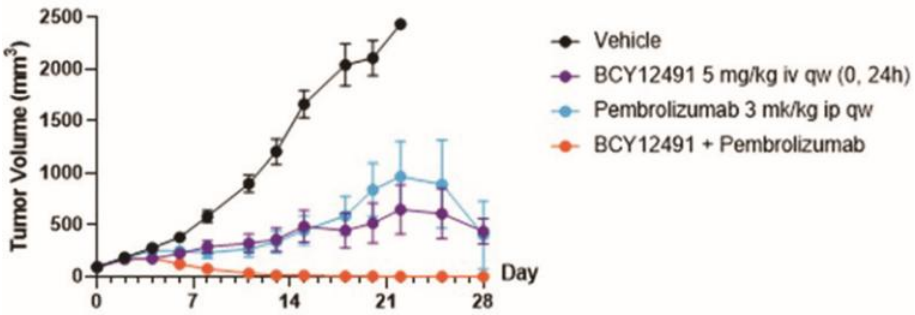
In further studies, we have observed that intermittent dosing of BCY12491, an EphA2/CD137 TICA, leads to a robust anti-tumor activity in syngeneic MC38 mouse model using humanized CD137 (huCD137) C57BL/6 mice. Administration of BCY12491 in six intravenous biweekly doses over a period of 17 days at 5 mg/kg led to substantial tumor regressions, including two out of six CRs. In addition, administration of BCY13626, a non-binding analog of BCY12491 had no impact on tumor growth rates.

Activity of EphA2 TICA in vivo



We have also observed that intermittent dosing of TICA BCY12491 leads to an increase in immune cell infiltration and an increase in the expression of checkpoint inhibitor genes in tumors of a syngeneic MC38 mouse model using humanized CD137, or huCD137, C57BL/6 mice. In other studies, we have observed that when BCY12491 is dosed in combination with pembrolizumab, a PD1 checkpoint inhibitor, there is an increased antitumor effect as shown in the figure below. Administration of BCY12491 in eight intravenous doses at 5 mg/kg (dosed on days 0, 1, 7, 8, 14, 15, 21 and 22) in combination with 4 intraperitoneal doses of pembrolizumab at 3 mg/kg (dosed on days 0, 7, 14 and 21) lead to substantial tumor regressions, including ten out of ten CRs. We observed that dosing BCY12491 or pembrolizumab alone using the same dose and schedule led to only two and three out of ten complete regressions respectively.

Activity of NK TICAs and PD1 Inhibitor in vivo

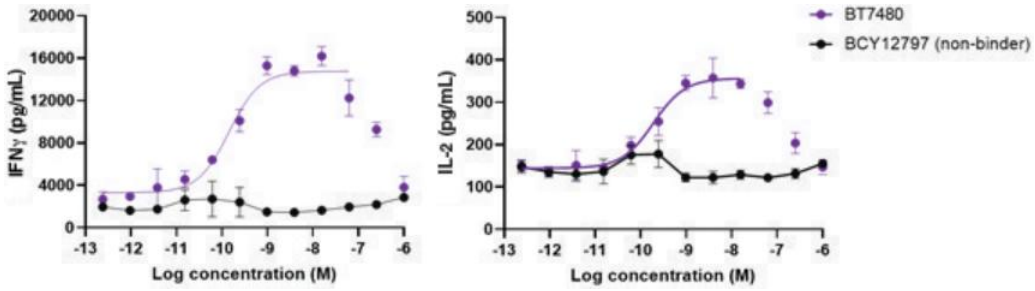


We believe that our ability to rapidly generate and test TICA molecules and their simple molecular format may form the basis of additional programs in the future. In addition to the immune cell and tumor targets that we have already investigated, we are screening for *Bicycles* that target NK cell receptors as well as additional immune cell and tumor specific antigens. We have identified TICA candidates that target and activate NK cells as shown in the figure below. We have observed that treatment of primary human NK cells in co-culture with target-positive tumor cells with NK TICA1 or NK TICA2 results in increased surface levels of CD107a, a marker of NK cell functional activity.

BT7480

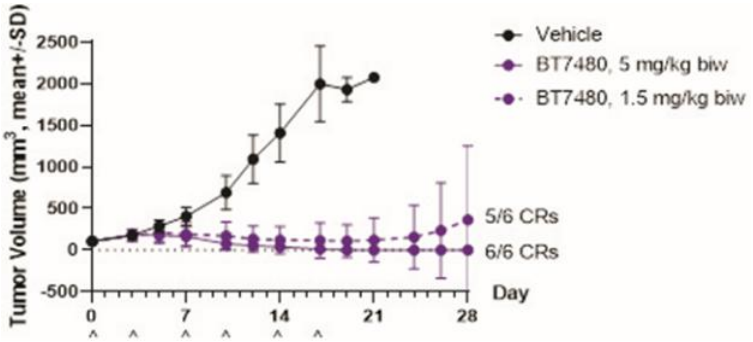
BT7480 is a TICA that targets CD137 and Nectin-4. BT7480 exhibits potent CD137 agonism in an engineered CD137 reporter assay system that correlates with Nectin-4 surface expression on the co-cultured tumor cells. In addition, BT7480 induces robust production of interleukin-2, or IL-2, and interferon gamma, or IFN, in primary PBMC/tumor cell co-culture assays. This activity is strictly dependent on the tumor cells expressing Nectin-4 and on the ability of the TICA to bind to both of its targets, Nectin-4 and CD137. In the figure below, BT7480 induces IL-2 and IFN at sub nanomolar concentrations when incubated with human PBMCs and the Nectin-4 expressing human tumor cell line HT1376.

BT7480 produces IL-2 and IFN in coculture with PBMC and HT1376



Additionally, we have observed that intermittent dosing of BT7480 leads to a robust anti-tumor activity in syngeneic MC38 mouse model, engineered to overexpress Nectin-4, using huCD137 C57BL/6 mice. Administration of BT7480 in six intravenous biweekly doses over a period of 17 days at 1.5 or 5 mg/kg led to substantial tumor regressions, including five out of six complete responses at 1.5 mg/kg and six out of six CRs at 5 mg/kg. In addition, animals that were complete responders in the experiment were subsequently re-challenged with the same tumor cell implantation and no tumor growth was observed, implying development of immunogenic memory.

Effect of BT7480 on Tumor Volume in a Preclinical Syngeneic Model with Nectin-4 Expressing MC38 Tumors in C57BL/6 Mice



Our IND-enabling activities for BT7480 are ongoing, and we expect to initiate a Phase I clinical trial in the second half of 2021.

BT7455

BT7455 is a TICA targeting EphA2 and CD137. In preclinical studies, BT7455 was observed to potentiate cytokine production by pre-activated PBMCs in co-culture with EphA2-expressing cancer cell lines and was associated with tumor growth inhibition and formation of immunologic memory in mice bearing subcutaneous MC38 tumors. IND-enabling studies for BT7455 are currently ongoing.

Genentech Collaboration

In February 2020, we entered into a strategic early discovery collaboration agreement with Genentech, Inc., a member of the Roche Group, or Genentech, to discover, develop and commercialize novel *Bicycle*-based immuno-oncology therapies. Under the collaboration, we will explore the application of our technology to a wider range of immuno-oncology targets, combining the expertise of both companies.

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 multi-targeted research collaboration agreement with AstraZeneca AB, or AstraZeneca, with a focus on targets within respiratory, cardiovascular and metabolic 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 was completed in July 2019. The Phase I clinical trial, conducted by Oxurion, was an open-label, multi-center, non-randomized study to evaluate the safety of a single intravitreal injection of THR-149 at three ascending dose levels in 12 subjects with visual impairment due to center-involved DME. The study also investigated changes to patients' best corrected visual acuity (BCVA). A rapid onset of action was observed from Day 1, with an increasing average improvement in BCVA of up to 7.5 letters at Day 14. This activity was maintained with an average improvement in BCVA of 6.5 letters at Day 90 following a single injection of THR-149. In September 2020, we announced that the first patient had been dosed in Oxurion's Phase II study of THR-149. The Phase II trial is expected to include approximately 122 patients with central involved DME who do not respond adequately to anti-VEGF therapy.

Our Collaborations

Cancer Research UK

BT1718

In December 2016, we entered into a clinical trial and license agreement with Cancer Research UK and Cancer Research Technology Ltd., a wholly owned subsidiary of Cancer Research UK that Cancer Research UK's commercial activities operate through, or the Cancer Research UK Agreement. Pursuant to the agreement, as amended in March 2017 and June 2018, Cancer Research UK 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.

Cancer Research UK 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 Cancer Research UK with all reasonable assistance to complete the arrangements necessary for the generation and supply of such additional GMP materials but Cancer Research UK will be responsible for supplying and paying for such additional quantities of GMP materials.

We granted to Cancer Research UK 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, Cancer Research Technology Limited may elect to receive an assignment and 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 Cancer Research UK 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 Cancer Research UK 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). Cancer Research UK 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 Cancer Research UK prior to the completion of the Phase I dose escalation part of the study for such reasons, or if Cancer Research UK 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 Cancer Research UK to perform the clinical trial. If the study is terminated by Cancer Research UK 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 Cancer Research UK 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, Cancer Research UK 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.

BT7401

In December 2019, we entered into a clinical trial and license agreement with Cancer Research Technology Limited and Cancer Research UK. Pursuant to the agreement, Cancer Research UK Centre for Drug Development will fund and sponsor development of BT7401 from current preclinical studies through the completion of a Phase IIa trial in patients with advanced solid tumors.

We granted to Cancer Research UK a license to our intellectual property in order for Cancer Research UK to design, prepare for, sponsor, and carry out the clinical trial and all necessary preclinical activities to support the trial. We retain the right to continue the development of BT7401 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 contain BT7401 or all the pharmaceutically active parts of BT7401, 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 55% to 80% of the net revenue depending on the stage of development when the license is granted) less certain costs, as defined in the agreement. The BT7401 Cancer Research UK agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash, with an aggregate total value of up to $60.3 million for each licensed product, as well as royalty payments based on a single digit percentage on net sales of products developed, and sublicense royalties to the Cancer Research UK in the low double digit percentage of sublicense income depending on the stage of development when the license is granted.

The BT7401Cancer Research UK 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 upon written notice by either party prior to the last cycle of treatment has been completed under the clinical trial. If the study is terminated by us prior to the filing of a clinical trial authorization, or by the Cancer Research UK for an insolvency event or a material breach by us prior to the start of a clinical trial, we will reimburse Cancer Research UK for certain costs paid or committed prior to the start of the clinical trial. In such case where we are acquired by an entity that generates its revenue from the sale of tobacco products, Cancer Research UK 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.

Genentech

On February 21, 2020, we entered into a Discovery Collaboration and License Agreement with Genentech. The collaboration is focused on the discovery and development of *Bicycle* peptides directed to biological targets selected by Genentech and aimed at developing up to four potential development candidates against multiple I-O targets suitable for Genentech to advance into further development and commercialization.

Under the terms of the Genentech Collaboration Agreement, we received a $30.0 million upfront, non-refundable payment. The initial discovery and optimization activities will focus on utilizing our phage screening technology to identify product candidates aimed at two I-O targets, or Genentech Collaboration Programs, which may also include additional discovery and optimization of *Bicycles* as a targeting element for each Genentech Collaboration Program, or each a Targeting Arm. Genentech has the option to nominate up to two additional I-O targets, or each an Expansion Option, which may also include an additional Targeting Arm for each Expansion Option, as additional Genentech Collaboration Programs during a specified period following completion of certain activities under an agreed research plan. If Genentech exercises one or more Expansion Options, Genentech will pay us an expansion fee of $10.0 million per Expansion Option. Genentech also has rights, under certain limited circumstances, to select an alternative target to be the subject of a Genentech Collaboration Program, in some cases subject to payment of an additional target selection fee.

If Genentech elects for us to perform discovery and optimization services for certain Targeting Arms, we will be entitled to receive an additional advance payment for the additional research services. Genentech exercised its right to select a Targeting Arm for one of the initial Genentech Collaboration Programs at the inception of the arrangement, which entitled us to an additional $1.0 million payment. If a Targeting Arm achieves specified criteria in accordance with the research plan, Genentech will be required to pay a further specified amount in the low single digit millions for each such Targeting Arm as consideration for the additional services to be provided.

We granted to Genentech a non-exclusive research license under our intellectual property solely to enable Genentech to perform any activities under the agreement. The activities under the Genentech Collaboration Agreement

are governed by a joint research committee, or JRC, with representatives from each of Bicycle and Genentech. The JRC will oversee, review and recommend direction of each Genentech Collaboration Program, achievement of development criteria, and variations of or modifications to the research plans.

After we perform the initial discovery and optimization activities in accordance with an agreed research plan and achieves specified criteria, Genentech will have the option to have us perform initial pre-clinical development and optimization activities in exchange for an additional specified milestone payment in the mid-single digit millions for each Genentech Collaboration Program, or the LSR Go Option. Upon completion of such initial pre-clinical development and optimization activities for each Genentech Collaboration Program, Genentech will have the option to obtain an exclusive license to exploit any compound developed under such Genentech Collaboration Program in exchange for an additional specified payment in the mid to high single digit millions for each of the initial two Genentech Collaboration Programs and each of the two Expansion Option Genentech Collaboration Programs, or the Dev Go Option.

On a Genentech Collaboration Program by Genentech Collaboration Program basis, if Genentech elects to obtain exclusive development and commercialization rights and pays the applicable LSR Go Option and Dev Go Option fees, Genentech will be required to make milestone payments to us upon the achievement of specified development, regulatory, and initial commercialization milestones for products arising from each collaboration program, totaling up to $200.0 million. Specifically, we are eligible for additional development milestones totaling up to $65.0 million, as well as regulatory milestones of up to $135.0 million for each collaboration program. In addition, we are eligible to receive up to $200.0 million in sales milestone payments on a Genentech Collaboration Program-by-Genentech Collaboration Program basis. In addition, to the extent any of the product candidates covered by the licenses conveyed to Genentech are commercialized, we would be entitled to receive tiered royalty payments on net sales at percentages ranging from the mid-single to low double-digits, subject to certain standard reductions and offsets. Royalties will be payable, on a product by product and country by country basis, until the later of the expiration of specified licensed patents covering such product in such country, or ten years from first commercial sale of such product in such country.

Dementia Discovery Fund

In May 2019, we entered into a collaboration with the Dementia Discovery Fund, or DDF, to use *Bicycle* technology for the discovery and development of novel therapeutics for dementia. DDF is a specialized venture capital fund focused on discovering and developing novel therapies for dementia. In October 2019, the collaboration with DDF was expanded to include Oxford University's Oxford Drug Discovery Institute (ODDI). Under the terms of the agreement, Bicycle and DDF will collaborate to identify *Bicycles* that bind to clinically validated dementia targets. ODDI will then profile these *Bicycles* in a range of target-specific and disease-focused assays to assess their therapeutic potential. If promising lead compounds are identified, DDF, ODDI and Bicycle will establish a jointly-owned new company to advance the compounds through further development towards commercialization. The jointly-owned company will receive a royalty and milestone-bearing assignment and license of intellectual property from Bicycle for this purpose.

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 $8.0 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 $8.0 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. For each research program, we are eligible to receive, in addition to the milestone fee described above, up to $162.0 million in development, regulatory and commercial milestones on a research program by research program basis, for a total of up to $170.0 million in milestone payments per research program. We are eligible to receive these milestone payments for up to six research programs under the arrangement. 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.

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 that was paid by AstraZeneca to us in January 2019. In October 2020, AstraZeneca terminated two research programs. As of December 31, 2020, three research programs were in the AZ Research Term, and one program was in the Bicycle Research Term. A third program was terminated in March 2021.

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 provides for 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, 2020, in connection with the development of THR-149, and up to €16.5 million in regulatory milestone payments (e.g., €5 million for granting of first regulatory approval in either the United States or the European Union for the first indication). 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.

Founder Royalty Arrangements

We have entered into two royalty agreements with our founders, Christian Heinis, John Tite, and Sir Greg 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. As of December 31, 2020, we had four patent families directed to novel scaffolds, and 15 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. As of December 31, 2020, we had 74 patent families directed to bicyclic peptides and related conjugates, and ten patent families directed to methods of using certain bicyclic peptide conjugates for treating various indications. For example, we have (i) at least two patent families directed to the composition of matter of one of our product candidates, BT1718, and methods of use for treating cancer, which are pending in certain jurisdictions, and if issued, would expire in 2035 and 2037, respectively; (ii) at least two patent families directed to the composition of matter our product candidate, BT5528, and methods of use for treating cancer, which are pending in certain jurisdictions, and if issued, would expire in 2038 and 2040, respectively; and (iii) at least two patent families directed to the composition of matter our product candidate, BT8009, and methods of use for treating cancer, which are pending in certain jurisdictions, and if issued, would expire in 2039 and 2041, 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, or USPTO. 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.

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 report are the property of their respective holders. Solely for convenience, the trademarks and trade names in this report may be referred to without the ®,™ or © 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.

Company-Owned Intellectual Property

As of December 31, 2020, our patent portfolio included four patent families directed to novel scaffolds, 15 patent families directed to our platform technology, 74 patent families directed to bicyclic peptides and related conjugates, and ten patent families directed to methods of using certain bicyclic peptide conjugates for treating various indications. In total, as of December 31, 2020, we owned about 75 patents in the United States and in foreign jurisdictions, such as Australia, Canada, China, Europe, Hong Kong, Japan, New Zealand, Russia and Singapore, with terms expiring at various dates in February 2029 to February 2039 exclusive of potential patent term adjustment and/or patent term extension.

In addition, as of December 31, 2020, we had about 280 patent applications pending in the United States and in foreign jurisdictions, such as Argentina, Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, Korea, New Zealand, Russia, Singapore, Taiwan, and Venezuela, as well as pending international applications under the Patent Cooperation Treaty, or PCT, 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 December 2041, 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 Stemline Therapeutics 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-specific antibodies. 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, there are a variety of regulations in other jurisdictions governing, among other things, clinical trials, commercial sales and distribution of medicinal products. Even if FDA approval of a particular product is obtained, 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. Currently in the European Union, for example, a clinical trial application must be submitted to each country's national regulatory authority in which the clinical trial is to take place, together with an independent ethics committee, much like the FDA and IRB, respectively. It is expected, however, that the Clinical Trials Regulation 536/2014 shall start to apply during the course of 2021. This new Regulation takes direct effect in each European Union Member State and seeks to simplify and streamline the approval of clinical trials in the European Union, for example, by allowing the clinical trial sponsor to submit a single application for approval of a clinical trial across the European Union via a new E.U. Portal. The new Regulation also aims to streamline and simplify the rules on safety reporting and introduces enhanced transparency requirements, such as mandatory submission of a summary of the clinical trial results to a new E.U. Database.

Medicinal products can only be commercialized in the European Economic Area, or EEA, after a marketing authorization, or MA, has been obtained. There are two types of marketing authorizations:

- The centralized 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 entirety 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 an active substance not authorized in the EEA before May 20, 2004, for products that constitute a significant therapeutic, scientific or technical innovation or for which a centralized authorization would be in the interest of patients.

- 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.

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. Products receiving orphan designation, can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product's market exclusivity 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. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;

- the applicant consents to a second orphan medicinal product application; or

- the applicant cannot supply sufficient quantities of the orphan medicinal product.

The criteria for designating an “orphan medicinal product” in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and scientific assistance for study proposals. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

In the European Union, companies developing a new medicinal product must agree to a Paediatric Investigation Plan, or PIP, with the EMA and must conduct pediatric clinical trials in accordance with that PIP, unless a deferral or waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The MA application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted. For other countries outside of the European Union, such as certain 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.

Additionally, we may develop companion diagnostic tests for use with our product candidates. Companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical products, will apply to companion diagnostics.

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, health information 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, as defined by such law, 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 other transfers of value provided to, during the previous year, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse-midwives.

In addition, we may be subject to certain analogous state and foreign laws of each of the above federal healthcare laws. In some instances, such laws may be broader in scope than its federal counterpart, such as certain state anti-kickback and false claims laws, which may apply to claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers. In addition, certain states and local jurisdictions 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 and other healthcare professionals. Additionally, we may be subject to state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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, significant administrative, civil and criminal penalties, damages, fines, disgorgement, imprisonment, 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 now provide a 70% 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 the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, HHS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

There remain judicial and Congressional challenges to certain aspects of the ACA. President Trump signed several 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. 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, eliminating 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. On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court is currently reviewing this case, but it is unknown when a decision will be reached. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the ACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how the U.S. Supreme Court ruling, other such litigation, and the healthcare reform measures of the Biden administration will impact the ACA and our business.

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 2030 unless additional Congressional action is taken. However, pursuant to certain COVID-19 relief legislation, these Medicare sequester reductions have been suspended from May 1, 2020 through March 31, 2021. 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. At the federal level, the former Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, former President Trump signed several Executive Orders aimed at lowering drug pricing that seek to implement several of the administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development, or OECD, countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all U.S. states and territories for a seven-year period and was scheduled to begin on January 1, 2021 and end on December 31, 2027. On December 28, 2020, the U.S. District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. Additionally, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers the implementation of which have also been delayed pending review by the Biden administration until March 22, 2021. However, it is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives.

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. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic. 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.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit, and the United Kingdom officially withdrew from the European Union on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom was subject to a transition period until December 31, 2020, or the Transition Period, during which European Union rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, which outlines the future trading relationship between the United Kingdom and the European Union, was agreed upon in December 2020.

Great Britain is no longer covered by the European Union’s procedures for the grant of marketing authorizations , though Northern Ireland will be covered by the centralized authorization procedure and can be covered under the decentralized or mutual recognition procedures. A separate marketing authorization will be required to market drugs in Great Britain. However, for two years from January 1, 2021, the United Kingdom’s regulator, the Medicines & Healthcare products Regulatory Agency, or MHRA, may adopt decisions taken by the European Commission on the approval of new marketing authorizations through the centralized procedure, and the MHRA will have regard to marketing authorizations approved in a country in the EEA (although in both cases a marketing authorization will only be granted if any Great Britain-specific requirements are met). Various national procedures are now available to place a drug on the market in the United Kingdom, Great Britain or Northern Ireland, with the main national procedure having a maximum timeframe of 150 days (excluding time taken to provide any further information or data required). The data exclusivity periods in the United Kingdom are currently in line with those in the European Union, but the Trade and Cooperation Agreement provides that the periods for both data and market exclusivity are to be determined by domestic law, and so there could be divergence in the future. It is currently unclear whether the MHRA in the United Kingdom is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive.

Orphan designation in Great Britain following Brexit is essentially identical to the position in the European Union, but it is based on the prevalence of the condition in Great Britain. It is therefore possible that conditions that are currently designated as orphan conditions in Great Britain will no longer be and that conditions that are not currently designated as orphan conditions in the European Union will be designated as such in Great Britain.

The European Union's regulatory environment for clinical trials is being harmonized as part of the Clinical Trial Regulations, which are due to enter into full effect at the end of 2021, but it is currently unclear as to what extent the United Kingdom will seek to align its regulations with the European Union.

Employees and Human Capital

As of December 31, 2020, we had 87 full-time or part-time employees, including 41 with M.D. or Ph.D. degrees. Of these employees, 68 employees are engaged in research and development activities and 19 employees are engaged in general and administrative activities. Our employees are primarily based at the locations of our office and laboratory facilities: 52 are located in the U.K. and 35 are located in Massachusetts, U.S. 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.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees to support the continued growth of our company and progress the development of our product candidates. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of equity-based compensation awards.

Corporate Information

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 our IPO, was re-registered as a public limited company named Bicycle Therapeutics plc. Bicycle Therapeutics plc is 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, 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.

Available Information

Our website address is http://www.bicycletherapeutics.com. We make available on our website, free of charge, our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information regarding our filings at www.sec.gov. The information found on our website is not incorporated by reference into this Annual Report on Form 10-K or any other report we file with or furnish to the SEC.

Item 1A Risk Factors.

Risk Factors

Our operations and financial results are subject to various risks and uncertainties, including those described below. The following information about these risks and uncertainties, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our consolidated financial statements and related notes thereto, should be carefully considered before a decision to invest in our ADSs. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. Additional risks that are currently unknown to us or that we currently believe to be immaterial may also impair our business. In these circumstances, the market price of our ADSs could decline and holders of our ADSs may lose all or part of their investment. We cannot provide assurance that any of the events discussed below will not occur.

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. Since inception, we have incurred recurring losses, including losses of $51.0 million, $30.6 million and $21.8 million for the years ended December 31, 2020, 2019 and 2018, respectively. In addition, our accumulated deficit as of December 31, 2020 was $151.6 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' equity (deficit) 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 BTC and TICA™ programs and our other pipeline programs;
- 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 Genentech, AstraZeneca AB, or AstraZeneca, Sanofi (formerly Bioverativ Inc.), Oxurion NV (formerly ThromboGenics NV), or Oxurion, and Dementia Discovery Fund, or DDF. There can be no assurance that we will generate revenue from our 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 holders of our ADSs or ordinary shares 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, any current or prospective holder of our ADSs or ordinary shares 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, all of which delays and difficulties may be exacerbated as a result of the ongoing COVID-19 pandemic. Any predictions made 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 and reliance should not be made upon the results of any quarterly or annual periods as indications of future operating performance.

We may 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. 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, 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 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, 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 our existing cash of $136.0 million as of December 31, 2020, will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Annual Report on Form 10-K. 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, including the unanticipated impacts of the ongoing COVID-19 pandemic, 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.

The spread of COVID-19, which continues to cause a broad impact globally, may materially affect us economically. While the long-term economic impact of the pandemic is difficult to assess or predict, it has already significantly disrupted global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity.

Raising additional capital may cause dilution to our existing shareholders or holders of our ADSs, 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, the ownership interest of existing holders of our ADSs or ordinary shares will be diluted and the terms may include liquidation or other preferences that adversely affect existing holders' rights. 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.

Our failure to comply with the covenants or payment obligations under our existing term loan facility with Hercules could result in an event of default, which may result in increased interest charges, acceleration of our repayment obligations or other actions by Hercules, any of which could negatively impact our business, financial condition and results of operations.

We are party to a secured term loan facility with Hercules. As of December 31, 2020, our outstanding borrowings under this facility totaled $15.0 million. Subject to satisfaction of customary conditions, we may borrow an additional term loan of up to $15.0 million available through March 15, 2021, and subject to our achievement of certain performance milestones and satisfaction of customary conditions we may borrow an additional term loan of $10.0 million through March 15, 2022. In connection with the Loan Agreement with Hercules, or the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control (as defined by the Loan Agreement), financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a material adverse effect as set forth in the Loan Agreement, cross acceleration to third-party indebtedness and certain events relating to bankruptcy or insolvency. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal balance, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement, including proceeding against the collateral securing such indebtedness.

Such increased interest charges, accelerated repayment, proceedings against the collateral or other actions may have a negative impact on our business, financial condition and results of operations.

Our existing and any future indebtedness may limit our cash flow available to invest in the ongoing needs of our business.

As of December 31, 2020, we had $15.0 million of borrowings outstanding under the Loan Agreement with Hercules, and we may borrow up to an additional $25.0 million in the aggregate under the Loan Agreement, subject to certain conditions. We could also in the future incur additional indebtedness pursuant to additional loan agreements.

Our debt combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

- requiring us to dedicate cash flow from operations or cash on hand to the payment of interest on, and principal of, our debt, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- subjecting us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and our industry; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash and funds from external sources. Nonetheless, we may not have sufficient funds or may be unable to arrange for additional financing to pay the amounts due under our existing or any future debt facility. Funds from external sources may not be available on acceptable terms, if at all. In addition, a failure to comply with the covenants under the Loan Agreement or any future loan agreements we may enter into could result in an event of default and acceleration of amounts due. If an event of default occurs and the lenders accelerate the amounts due under such loan agreements, we may not be able to make accelerated payments, and such lenders could seek to enforce security interests in the collateral securing such indebtedness.

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 and tumor-targeted immune cell agonist programs 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 and tumor-targeted immune cell agonist programs.

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 Cancer Research UK Centre for Drug Development, or Cancer Research UK. 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 Cancer Research UK 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. In addition, we are evaluating BT5528, a second-generation BTC that targets Ephrin type-A receptor 2, or EphA2 and carries a monomethyl auristatin E, or MMAE cytotoxin payload, in an ongoing, company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics and preliminary clinical activity in patients with advanced malignancies associated with EphA2 expression as a monotherapy and in combination

with nivolumab, and BT8009, a second-generation BTC targeting Nectin-4, in a company sponsored Phase I/II clinical trial. We are also developing BT7480, which is a TICA targeting Nectin-4 and agonizing CD137, for oncology indications. These target proteins have an established role in cell invasion and metastasis and are overexpressed in many solid tumors. There can be no assurance our BTCs or TICAs will ever demonstrate evidence of safety or effectiveness for any use or receive regulatory approval in the United States, the European Union, or any other country in any indication. Even if clinical trials show positive results, there can be no assurance that the U.S. Food and Drug Administration, or FDA, in the United States, European Commission, whose decision is based on a recommendation from the European Medicines Agency, or 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, tumor-targeted immune cell agonists, and our other product candidates will depend on, among other things, our ability to:

- successfully complete preclinical studies and clinical trials, which may be delayed;
- receive regulatory approvals from the FDA, the European Commission based on a recommendation from 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 and maintain freedom to operate for such products with respect to the intellectual property rights of third parties.

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 provide assurance 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 have limited 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 European Commission based on a recommendation from the EMA, or other European regulatory authorities, in the European Union and the European Economic Area, or EEA, 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 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 European Commission based on a recommendation from 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. The ongoing COVID-19 pandemic, including many jurisdictions' shelter-in-place, stay-at-home and similar restrictions, may also impact our and our collaboration partners' abilities to activate trial sites or enroll patients in clinical trials or to otherwise advance those clinical trials. Although some jurisdictions have relaxed such restrictions and vaccination against COVID-19 has commenced, previously relaxed restrictions may be re-instituted, and vaccination is not yet widespread on a global basis. Ongoing, new or re-imposed COVID-19-related shelter-in-place, stay-at-home and similar restrictions, site closures, travel limitations and supply chain interruptions, or infection of site personnel or trial patients with COVID-19, may also reduce our or our collaboration partners' abilities to administer the investigational product to enrolled patients, present difficulties for enrolled patients to adhere to protocol-mandated visits and laboratory/diagnostic testing, increase the possibility of patient dropouts, or impact our and our suppliers' abilities to provide investigational product to trial sites, all of which could negatively impact the data we are able to obtain from our clinical trials and complicate regulatory review.

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, including as a result of the ongoing COVID-19 pandemic, 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.

In addition, our ability to conduct clinical trials has been and may continue to be affected by the ongoing COVID-19 pandemic. For example, all clinical sites for the Phase I/IIa trial of BT1718 being conducted by Cancer Research UK in the United Kingdom temporarily paused enrollment of new patients due to the ongoing COVID-19 pandemic during the first half of 2020. While the pause in enrollment was lifted during the second quarter of 2020 and patient enrollment in the Phase IIa portion of the clinical trial is underway, changes in circumstances related to the ongoing pandemic could result in future pauses in or other impacts on enrollment. Further clinical site initiation and patient enrollment may be delayed due to prioritization of hospital resources toward the COVID-19 pandemic, including with respect to vaccination efforts. Some key clinical trial activities, such as clinical trial site monitoring, may also be impacted due to limitations on travel, quarantines or social distancing protocols imposed or recommended by federal or state governments, employers and others in connection with the ongoing COVID-19 pandemic. Some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may adversely impact our future clinical trial operations.

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, BT5528 and BT8009 is currently taking place outside of the United States. 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 Cancer Research UK at up to seven sites in the United Kingdom, and our company-sponsored trials of BT5528 and BT8009 are also ongoing, and the interim results in all three of these trials, including specific patient responses we have observed and disclosed, may not be replicated in the completed data sets or in future trials at global clinical trial sites in a later stage clinical trial conducted by us or our collaborators. Additionally, notwithstanding the commencement of vaccination efforts, the ongoing COVID-19 pandemic may negatively impact our ability to enroll participants in future or later stage trials. 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, our ability to enroll trial participants, including as a result of the ongoing COVID-19 pandemic and notwithstanding the commencement of vaccination efforts, 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. As of January 25, 2021, the most recent date for which information has been provided by the Cancer Research UK, the most common treatment-related adverse events (>15%, n=45) in subjects exposed to BT1718 in the ongoing Phase I/IIa clinical trial were anemia, diarrhea, nausea, vomiting, fatigue, alanine aminotransferase increase, aspartate aminotransferase increase, gamma-glutamyltransferase increase, decreased appetite, lethargy, peripheral neuropathy, and weight decrease. BT5528 has been dosed up to 8.5 mg/m^2 weekly, which we believe, based on pre-clinical studies, is toward the top of the therapeutic range, with transient neutropenia observed at that dose. In addition, administered doses of BT8009, a second-generation BTC targeting Nectin-4, appear well-tolerated with manageable adverse events in the dose-escalation phase in the ongoing Phase I/II trial.

If unacceptable side effect profiles arise, or side effects beyond those identified to date develop or worsen, as we continue development of our current or future 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, cause delays in ongoing clinical trials, 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.

Three of our product candidates are currently undergoing safety testing in the form of Phase I/IIa or Phase I/II 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 rarer, 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, BT5528, BT8009 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 be delayed or 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 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 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.

The withdrawal of the United Kingdom from the European Union, commonly referred to as "Brexit," may adversely impact our ability to obtain regulatory approvals of our product candidates in the European Union, result in restrictions or imposition of taxes and duties for importing our product candidates into the European Union, and may require us to incur additional expenses in order to develop, manufacture and commercialize our product candidates in the European Union.

Following the result of a referendum in 2016, the United Kingdom left the European Union on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom was subject to a transition period until December 31, 2020, or the Transition Period, during which European Union rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, which outlines the future trading relationship between the United Kingdom and the European Union, was agreed upon in December 2020.

The potential impact on our results of operations and liquidity resulting from Brexit remains unclear. The actual effects of Brexit will depend upon many factors and significant uncertainty remains with respect to the terms of the ultimate resolution of the Brexit negotiations.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit has had, and may continue to have, a material impact on the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, Great Britain is no longer covered by the centralized procedures for obtaining European Union-wide marketing authorization

from the EMA, and a separate marketing authorization will be required to market our product candidates in Great Britain. It is currently unclear as to whether the Medicines & Healthcare products Regulatory Agency, or MHRA, is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. 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.

While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the United Kingdom and the European Union, there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the United Kingdom diverge from the European Union from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. We could, therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the European Union.

Brexit may influence the attractiveness of the United Kingdom as a place to conduct clinical trials. The European Union's regulatory environment for clinical trials is being harmonized as part of the Clinical Trial Regulations, which are due to enter into full effect at the end of 2021, but it is currently unclear as to what extent the United Kingdom will seek to align its regulations with the European Union. Failure of the United Kingdom to closely align its regulations with the European Union may have an effect on the cost of conducting clinical trials in the United Kingdom as opposed to other countries and/or make it harder to seek a marketing authorization for our product candidates on the basis of clinical trials conducted in the United Kingdom. In the short term, there will be few changes to clinical trials that only have sites in the United Kingdom. The MHRA has confirmed that the sponsor of a clinical trial can be based in the EEA for an initial period following Brexit. Further investigational medicinal products can be supplied directly from the European Union/EEA to a trial site in Great Britain without further oversight until January 1, 2022, and to Northern Ireland beyond such date. The United Kingdom is now a "third country" for the purpose of clinical trials that have sites in the EEA. For such trials the sponsor/legal representative must be based in the EEA, and the trial must be registered on the E.U. Clinical Trials Register (including data on sites outside of the EEA).

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. Due to the ongoing COVID-19 pandemic, it is possible that we could experience delays in the timing of our interactions with regulatory authorities due to absenteeism by governmental employees, inability to conduct planned physical inspections related to regulatory approval, or the diversion of regulatory authority efforts and attention to approval of other therapeutics or other activities related to COVID-19, which could delay anticipated approval decisions and otherwise delay or limit our ability to make planned regulatory submissions or obtain new product approvals. 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, if any, 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 trial. 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, third-line or later-line therapies, 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, BT5528, BT8009 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, 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, and prohibitions on the promotion of an approved product for uses not included in the product's approved labeling. 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 may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products.

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 are 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 Stemline Therapeutics 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-specific antibodies.

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, European 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 candidates 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 CMS, 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.

We or our collaborators will be required to obtain coverage and reimbursement for companion diagnostic tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved. There is significant uncertainty regarding our and our collaborators ability to obtain coverage and adequate reimbursement for any companion diagnostic test for the same reasons applicable to our product candidates.

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 clinical research, proposed sales, marketing and educational programs and other interactions with healthcare professionals. 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, including the FCA, and civil monetary penalty laws, 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 and their subcontractors that use disclose or otherwise process 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, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants 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 FCA, 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. Certain states and local jurisdictions also require the registration of pharmaceutical sales representatives. 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 significant 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 share 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, significant administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, imprisonment, 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 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 may have a negative impact on our business and results of operations.

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements, (ii) additions or modifications to product labeling, (iii) the recall or discontinuation of our products, (iv) restriction on coverage, reimbursement, and pricing for our products, (v) transparency reporting obligations regarding transfers of value to health care professionals or (vi) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect our business, financial condition and results of operations.

Among policy makers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, the Affordable Care Act, or ACA, was passed, which substantially changed the way healthcare is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, subjected biological products to potential competition by lower-cost biosimilars, created 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, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since January 2017, former President Trump signed 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. One Executive Order directed federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Another Executive Order terminated the cost- sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. On April 27, 2020, the U.S. Supreme Court reversed the Federal Circuit decision that previously upheld Congress'

denial of $12 billion in “risk corridor.” The full effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

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, several bills affecting implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or the Tax Act, includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act 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.” In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated “Cadillac” tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the Affordable Care Act are invalid as well. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court is currently reviewing this case, but it is unknown when a decision will be reached. Although the U.S. Supreme Court has yet ruled on the constitutionality of the ACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how the Supreme Court ruling, other such litigation, and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013, and due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030 unless additional Congressional action is taken. However, pursuant to certain COVID-19 relief legislation these Medicare sequester reductions have been suspended from May 1, 2020 through March 31, 2021. The American Taxpayer Relief Act of 2012, 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.

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. At the federal level, the former Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, former President Trump signed several Executive Orders aimed at lowering drug pricing that seek to implement several of the administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all U.S. states and territories for a seven-year period and was scheduled to begin on January 1, 2021 and end on December 31, 2027. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. Additionally, on November

20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers the implementation of which have also been delayed pending review by the Biden administration until March 22, 2021. However, it is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation, administrative or executive action. We expect that these and other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug, which could have an adverse effect on customers for our product candidates. It is possible that additional governmental action is taken to address the ongoing COVID-19 pandemic. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

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. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Such reforms could have an adverse effect on anticipated revenue 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.

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, our employees and our 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 the 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 Business and Our International Operations

COVID-19 could impact our business.

Our business could be adversely affected by the effects of the ongoing COVID-19 pandemic in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or

other business operations. The COVID-19 pandemic could materially affect our operations as well as causing significant disruption in the operations and business of third-party manufacturers, CROs, other services providers, and collaborators with whom we conduct business.

In response to the COVID-19 pandemic, many state, local and foreign governments, including the UK and U.S. put in place quarantines, executive orders, shelter-in-place or stay-at-home orders and similar government orders and restrictions in order to control the spread of the disease. While some restrictions have recently been relaxed, others have been re-imposed following prior relaxation as a result of continually evolving incidence and rates of infection. Such orders or restrictions, or the perception that such orders or restrictions could occur or continue for a protracted period of time, have resulted in business closures, work stoppages, slowdowns and delays, work-from-home policies, travel restrictions and cancellation of events, among other effects that could negatively impact productivity and disrupt our business and those of third-party manufacturers, CROs, other services providers, and collaborators with whom we conduct business. While the rollout of vaccines has begun, the timing of vaccinations, lifting of movement restrictions, and reinstitution of in-person events is unknown.

As a result of the COVID-19 pandemic, certain of our employees continue to work remotely. We have prepared plans to reopen our offices to allow non-laboratory based employees to return to the office, which will be based on a phased approach. However, in light of continually changing circumstances regarding infection rates and local government recommendations, we may be required to suspend or reverse any planned return to the office in the future. Additionally, we may experience disruptions if our employees become ill, despite the availability of vaccines, and are unable to perform their duties. The effects of any of our work-from-home policies may negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course.

In addition, our ability to conduct clinical trials has been and may continue to be affected by the COVID-19 pandemic. For example, all clinical sites for the Phase I/IIa trial of BT1718 being conducted by Cancer Research UK in the United Kingdom temporarily paused enrollment of new patients due to the COVID-19 pandemic during the first half of 2020. While the pause in enrollment has been lifted during the second quarter of 2020 and patient enrollment in the Phase IIa portion of the clinical trial is again underway, further clinical site initiation and patient enrollment may be suspended again or delayed due to prioritization of hospital resources toward the COVID-19 pandemic, including vaccination efforts, or new or renewed shelter-in-place or stay-at-home orders. Some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may adversely impact our future clinical trial operations.

The pandemic and related government and private sector responsive actions have affected the broader economies and financial markets, triggering an economic downturn, which has at points adversely affected, and could again adversely affect, our ability to access capital, which could negatively affect our liquidity. In addition, a recession or resulting adverse impacts on the capital markets resulting from the ongoing spread of COVID-19 could materially affect our business.

It is impossible to predict all effects and the ultimate impact of the COVID-19 pandemic, as the situation continues to evolve. The full extent of COVID-19's impact on our clinical development and other operations and financial performance depends on future developments that are uncertain and unpredictable, including the timing of vaccine rollouts and herd immunity, virus mutations and variants, and any new information that may emerge concerning the virus, vaccines, and containment, all of which may vary across regions. Any of these factors could have a material adverse impact on our business, financial condition, operating results, and ability to execute and capitalize on our strategies.

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, natural disasters, including earthquakes, typhoons, floods and fires, or public health crises, including outbreaks of COVID-19 or H1N1 flu.

Any or all of these factors could have a material adverse impact on our business, financial condition and results of operations.

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 data (including health-related personal data) in the EEA, is governed by the provisions of the E.U. General Data Protection Regulation 2016/679, or GDPR, which became effective and enforceable across all then-current member states of the EEA on May 25, 2018. The GDPR also provides that EEA member states may make their own national laws and regulations to introduce specific requirements related to the processing of "special categories of personal data," including personal data related to health, biometric data used for unique identification purposes and genetic information, as well as personal data related to criminal offenses or convictions.

The GDPR sets out a number of requirements that must be complied with when handling personal data (i.e., data relating to an identified or identifiable living individual) including: the obligation to appoint a data protection officer in certain circumstances; increased accountability and record-keeping obligations; increased transparency obligations for data controllers; onerous obligations on service providers who process personal data simply on behalf of others; the obligation to carry out so-called data protection impact assessments in certain circumstances; obligations to comply with data subjects' exercise of an increased set of rights in certain circumstances (such as rights for individuals to be "forgotten," rights to data portability, rights to object, etc., together with express rights to seek legal remedies in the event the individual believes his or her rights have been violated); a heightened and more-codified standard of data subject consent; and the obligation to notify certain significant personal data breaches to the relevant supervisory authority(ies) and affected individuals. In addition, the GDPR materially expanded the definition of what is expressly provided to constitute personal data (including, for example, by expressly clarifying that the GDPR applies to "pseudonymized" (i.e., key-coded) data, which is often processed by sponsors in the context of clinical trials where identification of underlying subjects is not required).

The GDPR has "extra-territorial" reach in that it applies to any controller or process of personal data that processes personal data in the context of an establishment in the EEA, or to a controller or processor with no establishment in the EEA where their processing concerns the offering of goods or services to individuals in the EEA and/or the monitoring of their behavior.

In addition, European data protection laws, such as the GDPR, generally prohibit the transfer of personal data from the EEA, and Switzerland to the United States, and most other countries, unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. One of the primary safeguards used for transfers of personal data to the United States was the E.U.-U.S. Privacy Shield framework administered by the U.S. Department of Commerce. On July 16, 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU-U.S. Privacy Shield, under which personal data could be transferred from the EEA and the United Kingdom to U.S. entities that had self-certified under the Privacy Shield. To align with the CJEU's decision in respect of the E.U.-U.S. Privacy Shield, on September 8, 2020, the Swiss Federal Data Protection and Information Commissioner announced that the Swiss-U.S. Privacy Shield regime was also inadequate for the purposes of personal data transfers from Switzerland to the U.S. entities who had self-certified under the Swiss Privacy Shield.

The CJEU decision referenced above also cast doubt on the ability to use one of the primary alternatives to the E.U.-U.S. Privacy Shield and Swiss-U.S. Privacy Shield, namely, the European Commission's Standard Contractual Clauses, to lawfully transfer personal data to the United States and most other countries. Use of the Standard Contractual Clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals, and additional measures and/or contractual provisions may need to be put in place; however, the nature of these additional measures is currently uncertain. At present, there are few if any viable alternatives to the Privacy Shield and the Standard Contractual Clauses. As such, our transfers of personal data to the United States may not comply with European data protection law and may increase our exposure to the GDPR's heightened sanctions for violations of its cross-border data transfer restrictions, including fines of up to 4% of annual global revenue or €20 million, whichever is higher, and injunctions against transfers. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the Standard Contractual Clauses can and cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data

between and among countries and regions in which we operate and/or engage providers and/or otherwise transfer personal data, it could affect the manner in which we receive and/or provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results and generally increase compliance risk. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of operating our business.

Further, Brexit has created uncertainty regarding data protection regulation in the United Kingdom. Following the United Kingdom's withdrawal from the European Union on January 31, 2020, pursuant to the transitional arrangements agreed to between the United Kingdom and European Union, the GDPR continued to have effect in law in the United Kingdom, and continued to do so until December 31, 2020 as if the United Kingdom remained a Member State of the European Union for such purposes. Following December 31, 2020, and the expiry of those transitional arrangements, the data protection obligations of the GDPR continue to apply to United Kingdom-related processing of personal data in substantially unvaried form under the so-called "UK GDPR" (i.e., the GDPR as it continues to form part of law in the United Kingdom by virtue of section 3 of the European Union (Withdrawal) Act 2018, as amended (including by the various Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) Regulations)). However, going forward, there will be increasing scope for divergence in application, interpretation and enforcement of the data protection law as between the United Kingdom and EEA. Furthermore, the relationship between the United Kingdom and the EEA in relation to certain aspects of data protection law remains somewhat uncertain. For example, it is unclear whether transfers of personal data from the EEA to the United Kingdom will be permitted to take place on the basis of a future adequacy decision of the European Commission, or whether a "transfer mechanism," such as the Standard Contractual Clauses, will be required. For the meantime, under the Trade and Cooperation Agreement, it has been agreed that transfers of personal data to the United Kingdom from European Union Member States will not be treated as "restricted transfers" to a non-EEA country for a period of up to four months from January 1, 2021, plus a potential further two months extension, or the extended adequacy assessment period. This will also apply to transfers to the United Kingdom from EEA Member States, assuming those Member States accede to the relevant provision of the Trade and Cooperation Agreement. Although the current maximum duration of the extended adequacy assessment period is six months it may end sooner, for example, in the event that the European Commission adopts an adequacy decision in respect of the United Kingdom, or the United Kingdom amends the U.K. GDPR and/or makes certain changes regarding data transfers under the U.K. GDPR/ Data Protection Act 2018 without the consent of the European Union (unless those amendments or decisions are made simply to keep relevant United Kingdom laws aligned with the European Union's data protection regime). If the European Commission does not adopt an 'adequacy decision' in respect of the United Kingdom prior to the expiry of the extended adequacy assessment period, from that point onwards the United Kingdom will be an "inadequate third country" under the GDPR and transfers of data from the EEA to the United Kingdom will require a "transfer mechanism," such as the Standard Contractual Clauses.

Additionally, as noted above, the United Kingdom has transposed the GDPR into United Kingdom domestic law by way of the U.K. GDPR with effect from January 2021, which could expose us to two parallel regimes, each of which potentially authorizes similar fines and other potentially divergent enforcement actions for certain violations (each regime separately having the ability to fine up to the higher of €20,000,000/£17,000,000 or 4% of an undertaking's total global annual turnover). Also, following the expiry of the post-Brexit transitional arrangements, the U.K. Information Commissioner's Office is not able to be our "lead supervisory authority" in respect of any "cross border processing" for the purposes of the GDPR. For so long as we are unable to, and/or do not, designate a lead supervisory authority in an EEA member state, with effect from January 1, 2021, we are not able to benefit from the GDPR's "one stop shop" mechanism. Amongst other things, this would mean that, in the event of a violation of the GDPR affecting data subjects across the United Kingdom and the EEA, we could be investigated by, and ultimately fined by the United Kingdom Information Commissioner's Office and the supervisory authority in each and every EEA member state where data subjects have been affected by such violation. Other countries have also passed or are considering passing laws requiring local data residency and/or restricting the international transfer of data.

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 and Asia that are billed in U.S. dollars. 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. Any fluctuation in the exchange rate of these foreign currencies may negatively impact our business, financial condition and operating results. Global economic events, such as the ongoing COVID-19 pandemic, have and may continue to significantly impact local economies and the foreign exchange markets, which may increase the risks associated with sales denominated in foreign currencies.

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 Genentech, AstraZeneca, Oxurion, and DDF, 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 Cancer Research UK, Cancer Research UK 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, and will sponsor and fund development of BT7401 from current preclinical studies through the completion of a Phase IIa trial 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 provide assurance 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;

- that the ongoing COVID-19 pandemic

- could materially affect our operations as well as causing significant disruption in the operations and business of our collaborators and the third-party manufacturers, CROs and other service providers that we and/or our collaborators conduct business with; 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 were previously involved in litigation with Pepscan Systems B.V., and its affiliates, or Pepscan, related to a non-exclusive patent license agreement that our subsidiary, BicycleRD Limited, or BicycleRD, entered into with Pepscan in 2009.

On November 20, 2020, we announced that we entered into a settlement and license agreement with Pepscan Systems B.V. regarding Bicycle's use of Pepscan's CLIPS peptide technology. The companies have agreed to settle all intellectual property disputes worldwide. Under the terms of the settlement, Bicycle has been granted a license to use CLIPS peptide technology in the development of its product candidates BT1718 and THR-149. We paid €3 million in November 2020, will pay €1 million on the first anniversary of the date of settlement, and will make potential additional payments to Pepscan based on achievement of specified clinical, regulatory and commercial milestones.

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. 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.

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, Cancer Research UK 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 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 are being or may be conducted, we do 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 the ability to obtain a license to obtain access to use and reference the data, including for our own regulatory submissions, resulting from the investigator-sponsored trials. However, we do not have control over the timing and reporting of the data from investigator-sponsored trials, nor do 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. Additionally, our manufacturers may experience delays as a result of shelter-in-place, stay-at-home or

similar orders or other impacts due to the ongoing COVID-19 pandemic. If our 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 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, BT5528 and BT8009, 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, including as a result of the impacts of the ongoing COVID-19 pandemic on the global workforce and manufacturing operations, 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 31, 2020, our intellectual property portfolio included four patent families directed to novel scaffolds, 15 patent families directed to our platform technology, 74 patent families directed to bicyclic peptides and related conjugates, and ten patent families directed to methods of using certain bicyclic peptide conjugates for treating various 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 may materially harm our intellectual property estate, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections.

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 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 provide assurance 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.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we were previously party to protracted litigation with Pepscan, which we settled in 2020. We may become party to, or be 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 on 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 have been in the past and may be subject in the future 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. 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 invalid, 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 objections. Although we would be given an opportunity to respond to those objections, we may be unable to overcome such objections. In addition, in the USPTO and in comparable Intellectual Property Offices 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 have been and may in the future 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.

Our UK trademark application for TICA has been opposed by a German company called Immatics Biotechnologies GmbH. The opposition is based on Immatics Biotechnologies' earlier registered rights for the trademarks TCER and TiCR which cover similar goods and services. Submissions have been filed by both parties and we are currently awaiting a decision from the UK IPO.

Risks Related to Employee Matters and Managing Growth

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

As of December 31, 2020, we had 87 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 provide assurance 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. In addition, due to the ongoing COVID-19 pandemic, we have enabled our non-laboratory-based employees to work remotely, which may make us more vulnerable to cyberattacks. We have been the target of cyber-attacks in the past. For example, in 2019 we were targeted in a phishing incident, which included email accounts being accessed by unauthorized third parties. Promptly after discovery, we performed third-party investigations and as there was no evidence of access or acquisition of any personal information as a result of the incident, we believe that no further action was required under U.K, E.U. (GDPR) or U.S. federal or state law. There was no material impact to our business or financial condition. While we believe we responded appropriately, including implementing remedial measures to stop the cyber-attacks 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. We are aware that some public companies have recently received Civil Investigative Demands from the Federal Trade Commission, or FTC, requesting information and documents following disclosures of privacy or security incidents in SEC filings. The FTC has taken the position that inadequately disclosing privacy and security incidents in SEC filings may be a deceptive business practice, and the FTC has relied on SEC filings as a launching pad for incident investigations even where the filings were not inadequate. We cannot be certain that the FTC will consider our disclosure adequate or that the FTC will not rely on our disclosure to initiate an incident investigation.

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 CROs 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. Further, because of the work-from-home policies we implemented due to COVID-19, information that is normally protected, including company confidential information, may be less secure. In May 2019, we adopted 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 significant 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, imprisonment, 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 office and laboratory space in Cambridge, U.K. and 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 Ownership of Our Securities

The market price of our ADSs is highly volatile, and holders of our ADSs may not be able to resell their ADSs at or above the price at which they purchased their ADSs.

The market price of our ADSs is highly volatile. Since our initial public offering, or IPO, in May 2019, through March 5, 2021, the trading price of our ADSs has ranged from $33.00 to $6.24. 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, holders of our ADSs may not be able to sell their ADSs at or above price at which they purchased their ADSs. 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;
- changes in the structure of healthcare payment systems;
- 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 partners 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, including very recently in connection with the ongoing COVID-19 pandemic, which has resulted in decreased stock prices for many companies notwithstanding the lack of a fundamental change in their underlying business models or prospects. Broad market and industry factors, including potentially worsening economic conditions and other adverse effects or developments relating to the ongoing COVID-19 pandemic, may negatively affect the market price of our ADSs, regardless of our actual operating performance.

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.

As of December 31, 2020, our executive officers, directors, greater than 5% shareholders and their affiliates beneficially own approximately 77.4% of our ordinary shares and ordinary shares in the form of ADSs. Depending on the level of attendance at our general meetings of shareholders, these shareholders either alone or voting together as a group could be in a position to determine 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, and the approval of certain significant corporate transactions. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that holders of our ADSs may believe are in their best interest as holders of our ordinary shares or ADSs. Some of these persons or entities may have interests different than current holders of our ordinary shares and ADSs. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the current trading price of our ADSs 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 our ADSs 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

current trading prices of the ADSs. 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, holders of an aggregate of approximately 1,497,905 ordinary shares 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. We have also registered our ordinary shares that we may issue under our equity compensation plans. These ordinary shares may be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

We have broad discretion in the use of our cash reserves and may not use them effectively.

Our management has broad discretion to use our cash reserves and could use our cash reserves in ways that do not improve our results of operations or enhance the value of our ordinary shares or ADSs. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our ADSs to decline, and delay the development of our product candidates. Pending their use, we may invest our cash reserves in a manner that does not produce income or that loses value.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be the sole source of gains for holders of our ADSs, and they may never receive a return on their 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. In addition, the terms of our indebtedness with Hercules prohibit us from paying dividends. 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 a holder's sole source of gains for the foreseeable future, and holders will suffer a loss on their investment if they are unable to sell their ADSs at or above the original purchase price.

We are an "emerging growth company" and a "smaller reporting company," and the reduced disclosure requirements applicable to emerging growth companies and smaller reporting 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 2024, (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;
- 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 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.

We are also a smaller reporting company as defined in the Securities Exchange Act of 1934, as amended, or the Exchange Act. We may continue to be a smaller reporting company even after we are no longer an emerging growth company. We will be a smaller reporting company and may take advantage of the scaled disclosures available to smaller reporting companies for so long as (i) the market value of our voting and non-voting ordinary shares held by non-affiliates is less than $250.0 million measured on the last business day of our second fiscal quarter or (ii) (a) our annual revenue is less than $100.0 million during the most recently completed fiscal year and (b) the market value of our voting and non-voting ordinary shares held by non-affiliates is less than $700.0 million measured on the last business day of our second fiscal quarter.

Risks Related to Our Incorporation Under the Laws of England and Wales

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.

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, indirectly or constructively through the application of attribution rules) 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 2020 taxable year and we do not expect to be a CFC in the 2021 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) 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. 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:

- an individual who is a citizen or individual resident of the United States;
- 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;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- 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.

If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. holders.

Under the Code, we will be a passive foreign investment company, or 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 not a PFIC in the 2020 taxable year. 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. As a result, there can be no assurance regarding if we will be PFIC or will not be a PFIC in the future. In addition, 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 and our corporate structure.

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 an entity incorporated and tax resident in the United Kingdom, 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. Subject to numerous utilization criteria and restrictions (including the Corporate Income Loss Restriction and the Corporate Capital Loss Restriction that, broadly, restrict the amount of carried forward losses that can be utilized to 50% of group profits or gains arising above £5.0 million per tax year, we expect losses to be eligible for carry forward and utilization against future operating profits. In addition, if we were to have a major change in the nature of the conduct or the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a group 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 Credit 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 carry them 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. The U.K. government has published draft legislation through which it intends to introduce a cap on payable credit claims in excess of £20,000 with effect from April 2021 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception. If such cap comes into force, and such exception does not apply, this could restrict the amount of payable credit that we claim.

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, and our ADSs and ordinary shares are, 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 Organization 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, or the stamp duty or stamp duty reserve tax treatment of our ADSs or ordinary shares. 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, while we believe that we operate in compliance with applicable transfer pricing laws and intend to continue to do so, our transfer pricing procedures are not binding on applicable tax authorities. 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.

Provisions in the U.K. City Code on Takeovers and Mergers that may have anti-takeover effects do not apply to us.

The U.K. City Code on Takeovers and Mergers, or the Takeover Code, applies to an offer for, among other things, a public company whose registered office is in the United Kingdom if the company is considered by the Panel on Takeovers and Mergers, or the Takeover Panel, to have its place of central management and control in the United Kingdom (or the Channel Islands or the Isle of Man). This is known as the "residency test." The test for central management and control under the Takeover Code is different from that used by the U.K. tax authorities. Under the Takeover Code, the Takeover Panel will determine whether we have our place of central management and control in the United Kingdom by looking at various factors, primarily where the directors are resident.

In September 2019, the Takeover Panel Executive confirmed that, based on our current circumstances, we are not subject to the Takeover Code. As a result, our shareholders are not entitled to the benefit of certain takeover offer protections provided under the Takeover Code. We believe that this position is unlikely to change at any time in the near future but, in accordance with good practice, we will review the situation on a regular basis and consult with the Takeover Panel if there is any change in our circumstances which may have a bearing on whether the Takeover Panel would determine our place of central management and control to be in the United Kingdom.

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 2006, 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. 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, the number of shares determines the number of votes a holder may cast only on a poll. 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, if we were 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, as well as the sanction of the U.K. court;

- 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 that 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.

General Risks

Requirements associated with being a public company have increased our costs significantly and have diverted significant company resources and management attention.

As a U.S. public company, we are incurring and will continue to 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 currently devote and will continue to devote a substantial amount of time to these compliance initiatives. In addition, after we are no longer an EGC, we will incur additional legal accounting and other expenses. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition, results of operations, stock price and prospects. The increased costs will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Pursuant to Section 404, we are 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, and under certain circumstances even after we are no longer 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, we engaged in a process to document and evaluate our internal control over financial reporting. We will need to continue to dedicate internal resources, and potentially engage outside consultants to continue 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 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.

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.

We are 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.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

An active trading market for our ADSs may not be sustained.

Prior to our IPO in May 2019, there had been no public market for our ADSs. Although our ADSs are listed on The Nasdaq Global Select Market, an active trading market for our shares may not be sustained. If an active market for our ADSs is not sustained, it may be difficult for holders of our ADSs to sell ADSs without depressing the market price for the shares, or at all.

An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling additional shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

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 depends 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. Although we have obtained research coverage from certain analysts, there can be no assurance that analysts will continue to cover us or provide favorable 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.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

Not applicable.

ITEM 2. PROPERTIES.

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.

ITEM 3. LEGAL PROCEEDINGS.

From time to time, we may become subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Other than as described below, we are not currently subject to any material legal proceedings.

License Litigation

In 2009, our subsidiary, BicycleRD Limited, or BicycleRD, entered into a non-exclusive patent license agreement with Pepscan Systems B.V. and its affiliates, or Pepscan, pursuant to which its licensed rights related to the scaffold used for *Bicycles* contained in our lead product candidate, BT1718, which is currently in clinical trial sponsored by Cancer Research UK, and in THR-149, which has been licensed to Oxurion. The agreement required BicycleRD to enter into a framework services agreement with Pepscan under which Pepscan would provide certain *Bicycles* not produced by BicycleRD. In 2010, BicycleRD entered into such a framework services agreement. In 2015, BicycleRD terminated the framework services agreement in accordance with its terms. In 2016, Pepscan terminated the patent license agreement.

BicycleRD instituted proceedings in the District Court of The Hague, or the District Court, to contest the right of Pepscan to terminate the patent license agreement. BicycleRD included a conditional claim for a ruling that the licensed patent relevant to BicycleRD's activities is invalid. In response, Pepscan claimed, among other things, that the termination of the framework services agreement and alleged breaches by BicycleRD of confidentiality obligations constituted grounds for the termination of the patent license agreement.

Following several years of ongoing litigation and appeals, on February 18, 2020, the Court of Appeal of The Hague, or the Court of Appeal, ruled that Pepscan was entitled to terminate the license agreement and granted a worldwide injunction against BicycleRD exploiting the licensed Pepscan patents and any related know-how, subject to a civil daily fine of EUR 25,000 in the event of non-compliance. BicycleRD subsequently appealed the decision of the Court of Appeal to the Dutch Supreme Court.

In September, 2020, BicycleRD filed two petitions requesting inter partes review (IPR) with the Patent Trial and Appeal Board of the United States Patent and Trademark Office (USPTO) of two of Pepscan's U.S. patents forming part of the WO 2004 077062 patent family, and a revocation action against the German patent forming part of Pepscan's WO 2004 077062 patent family in the German Federal Patent Court.

On November 20, 2020, we announced that we entered into a settlement and license agreement with Pepscan regarding our use of Pepscan's CLIPS peptide technology. We and Pepscan have agreed to settle all intellectual property disputes worldwide, including those described in the preceding paragraphs. Under the terms of the settlement, Pepscan granted us a license to use CLIPS peptide technology in the development of our product candidates BT1718 and THR-149. We paid €3 million in November 2020, will pay €1 million on the first anniversary of the date of settlement, and will make potential additional payments to Pepscan based on achievement of specified clinical, regulatory and commercial milestones. We also entered into a separate settlement agreement with Pepscan concerning European patent opposition proceedings, which is described below.

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. Pursuant to a separate settlement agreement entered into with Pepscan in November 2020, Pepscan has withdrawn its appeal, and the decision of the Opposition Division maintaining the patent as granted, for the purposes of the opposition proceedings, has become final.

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 an amended form, in which the patent was limited to the use of TBMB scaffolds. Pepscan subsequently filed a notice of appeal to revoke the patent in its entirety, along with supporting materials. Concurrently, Bicycle also filed a notice of appeal, requesting that the limitation to the use of TBMB be removed. Pursuant to the aforementioned separate settlement agreement entered into with Pepscan on November 20, 2020, Pepscan has withdrawn its appeal, leaving Bicycle as the sole appellant. A hearing date has been scheduled for October 5, 2021, at which we plan to argue for reversal of the amendments made by the Opposition Division. The withdrawal of Pepscan's appeal means that, for the purposes of the opposition proceedings, the scope of the patent cannot now be restricted further than the version in which it was maintained by the Opposition Division.

In May 2017, the company and Oxurion filed a notice of opposition in respect of Dyax Corp's European patent 1 854 477, which contained the following claim 1 (among other claims): "A composition comprising at least one peptide that inhibits plasma kallikrein for the use in the treatment of ophthalmic disorders in a patient in need thereof." Dyax Corp subsequently filed a Main Request to replace the granted claims with a claim scope which was limited to a specific consensus sequence. Oral Proceedings were held on October 15, 2019, and the European Patent Office issued a decision to restrict the claims of European patent 1 854 477 to specific peptides and to two specific ophthalmic disorders (namely macular oedema and retinal vein occlusion). Oxurion filed an appeal against this decision at the EPO Technical Board of Appeal to challenge any action from Dyax Corp to broaden the current claims.

In January and February 2019, the company, Oxurion and a further anonymous party filed a notice of opposition in respect of Dyax Corp's European patent 2 374 472, which is a divisional filing of European patent 1 854 477. Claim 1 of this divisional patent reads as follows: "A composition comprising at least one plasma kallikrein inhibitor for the use in the treatment of an ophthalmic disorder." Oral Proceedings before the European Patent Office are scheduled for 11 March 2021.

Trademark Opposition Proceedings

Our UK trademark application for TICA has been opposed by a German company called Immatics Biotechnologies GmbH. The opposition is based on Immatics Biotechnologies' earlier registered rights for the trademarks TCER and TiCR which cover similar goods and services. Submissions have been filed by both parties and we are currently awaiting a decision from the UK IPO.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market Information

Our ordinary shares, par value £0.01 per share, are not publicly traded. Our American Depositary Shares, or ADSs, each represent one ordinary share of Bicycle Therapeutics plc and began trading on The Nasdaq Global Select Market on May 23, 2019 under the symbol "BCYC." Prior to that date, there was no public trading market for our ADSs or our ordinary shares.

Holders of Ordinary Shares

As of March 5, 2021, there were approximately 73 holders of record of our ordinary shares and one holder of record of our ADSs. The number of beneficial owners of the ADSs in the United States is likely to be much larger than the number of record holders of our ordinary shares in the United States.

Recent Sales of Unregistered Equity Securities

None.

Use of Proceeds from Registered Securities

On May 28, 2019, we completed our IPO of 4,333,333 ADSs at a public offering price of $14.00 per ADS for an aggregate offering price of approximately $60.7 million. In addition, in June 2019, we issued 304,333 ADSs at a public offering price of $14.00 per ADS for an aggregate offering price of approximately $4.3 million in connection with the underwriters' partial exercise of their option to purchase additional ADSs. Goldman Sachs & Co. LLC, Jefferies LLC, Piper Jaffray & Co. and Canaccord Genuity LLC served as the underwriters of the IPO. The offer and sale of all of the ADSs in the offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-231076), which was declared effective by the SEC on May 22, 2019.

We received aggregate net proceeds from the offering of approximately $56.4 million, after deducting underwriting discounts and commissions of $4.5 million and offering expenses of $4.0 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

There has been no material change in our planned use of the net proceeds from the offering as described in the final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act. As of December 31, 2020, we had consumed all of the net proceeds from the IPO, primarily to advance our BT1718, BT5528, BT8009, BT7480, and other discovery development programs, as well as for continued drug discovery efforts and translational research activities, and for working capital and other general corporate purposes.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. SELECTED FINANCIAL DATA.

You should read the following selected financial data together with the "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and the accompanying notes included elsewhere in this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the years ended December 31, 2020, 2019, 2018 and the consolidated balance sheet data as of December 31, 2020 and 2019 from our audited consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the year ended December 31, 2017 and the consolidated balance sheet data as of December 31, 2018 and 2017 from our audited consolidated financial statements not included in this report. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Year ended December 31,			
	2020	2019	2018	2017
	(in thousands, except share and per share data)			
Statement of Operations Data:				
Collaboration revenues	$ 10,390	$ 13,801	$ 7,136	$ 2,060
Operating expenses:				
Research and development	33,149	25,540	20,761	11,866
General and administrative	29,201	14,560	8,121	6,407
Total operating expenses	62,350	40,100	28,882	18,273
Loss from operations	(51,960)	(26,299)	(21,746)	(16,213)
Other income (expense):				
Interest income	683	814	169	50
Interest expense	(457)	—	—	
Other expense, net	—	(5,377)	(665)	(119)
Total other income (expense), net	226	(4,563)	(496)	(69)
Net loss before income tax provision	(51,734)	(30,862)	(22,242)	(16,282)
Benefit from income taxes	(724)	(254)	(396)	(23)
Net loss	$ (51,010)	$ (30,608)	$ (21,846)	$ (16,259)
Net loss attributable to ordinary shareholders	$ (51,010)	$ (30,608)	$ (21,846)	$ (16,259)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.66)	$ (2.77)	$ (49.78)	$ (48.81)
Weighted average ordinary shares outstanding, basic and diluted	19,145,938	11,045,370	438,862	333,125

See Note 2 within the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a description of the method used to calculated basic and diluted net loss per share applicable to ordinary shareholders.

	As of December 31,			
	2020	2019	2018	2017
	(in thousands)			
Balance Sheet Data:				
Cash	$ 135,990	$ 92,117	$ 63,380	$ 67,663
Working capital	132,594	95,325	67,840	62,061
Total assets	161,152	110,194	81,626	74,001
Total deferred revenue	35,156	5,657	14,635	14,467
Warrant liability	—	—	4,804	4,411
Convertible preferred shares	—	—	122,197	96,441
Total shareholders' equity (deficit)	$ 95,460	$ 93,198	$ (69,826)	$ (47,184)

ITEM 7. 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 Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, 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 Annual Report on Form 10-K, 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 "Forward-Looking Statements."

For the discussion of the financial condition and results of operations for the year ended December 31, 2019 compared to the year ended December 31, 2018, refer to "Management's Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations" and "—Liquidity and Capital Resources" included in the Company's Annual Report on Form 10-K for the year ended December 31, 2019, which was filed with the Securities and Exchange Commission, or the SEC, on March 10, 2020.

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 facilitates target binding with high affinity and selectivity, making *Bicycles* attractive candidates for drug development. *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. The relatively large surface area presented by *Bicycles* allow targets to be drugged that have historically been intractable to non-biological approaches. *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 candidates, BT1718, BT5528 and BT8009, are Bicycle Toxin Conjugates®, or BTCs. These *Bicycles* are chemically attached to a toxin that when administered is cleaved from the *Bicycle*® and kills the tumor cells. BT1718 is being developed to target tumors that express Membrane Type 1 matrix metalloproteinase, or MT1 MMP and is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Cancer Research UK Centre for Drug Development, or Cancer Research UK. We are also evaluating BT5528, a second-generation BTC targeting Ephrin type A receptor 2, or EphA2, in a company-sponsored Phase I/II clinical trial as a monotherapy and in combination with nivolumab, and BT8009, a second-generation BTC targeting Nectin-4, in a company-sponsored Phase I/II clinical trial. Our discovery pipeline in oncology includes *Bicycle*-based systemic immune cell agonists and Bicycle tumor-targeted immune cell agonists, or TICAs.

Beyond our wholly-owned oncology portfolio, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas in which 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 in immuno-oncology, anti-infective, cardiovascular, ophthalmology, dementia and respiratory indications.

Financial Overview

Since our inception, we have devoted substantially all of our resources to developing our *Bicycle* platform and our product candidates, BT1718, BT5528, BT8009, BT7480, BT7455, and BT7401, 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 our American Depositary Shares, or ADSs, ordinary shares, and convertible preferred shares, proceeds received from upfront payments, research and development payments, and development milestone payments from our collaboration agreements with Genentech Inc., or Genentech, Oxurion NV (formerly ThromboGenics NV), or Oxurion, AstraZeneca AB, or AstraZeneca, Sanofi and the Dementia Discovery Fund, or DDF; and borrowings pursuant to our debt facility with Hercules Capital, Inc., or Hercules. From our inception in 2009 through December 31, 2020, we have received gross proceeds of $243.4 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering and at-the-market, or ATM, offering program; and $63.1 million of cash payments under our collaboration revenue arrangements, including $31.0 million from Genentech, $10.3 million from AstraZeneca, $4.1 million from Oxurion, $15.0 million from Sanofi, $1.7 million from DDF; and $15.0 million of borrowings pursuant to our Loan and Security Agreement, or Loan Agreement with Hercules. In January 2021, we received $2.4 million from Oxurion due to a milestone achieved for the initiation of a Phase II trial of THR-149 and $3.0 million of proceeds under an evaluation and option agreement. 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 $51.0 million, $30.6 million and $21.8 million for the years ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $151.6 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. 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, BT5528 and BT8009;
- progress the preclinical and clinical development of BT7480, BT7455 and BT7401;
- 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 operations as a public company.

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. The COVID-19 pandemic has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, whether as a result of the ongoing COVID-19 pandemic or otherwise, we could experience an inability to access additional capital.

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, 2020, we had cash of $136.0 million. We believe that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Annual Report on Form 10-K. 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.”

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 primarily consists of collaboration revenue under our arrangements with our collaboration partners, including amounts that are recognized related to upfront payments, milestone payments and option exercise payments, and amounts due to us for research and development services. In the future, revenue may include additional milestone payments and 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, 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, 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 and government grant funding 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 Cancer Research Technology Limited, or CRTL and Cancer Research UK, pursuant to which the Cancer Research UK Centre for Drug Development is sponsoring and funding a Phase I/IIa clinical trial for our product candidate, BT1718, in patients with advanced solid tumors. Cancer Research UK 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, CRTL may elect to receive an assignment and 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 in the agreement). The Cancer Research UK 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 Cancer Research UK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, upon a change in control involving a tobacco related entity, and in certain other specified circumstances, and includes provisions that require the repayment of costs to Cancer Research UK upon certain termination events or change in control events. The costs incurred by Cancer Research UK are recorded as a liability in accordance with ASC 730, *Research and Developmen*t as the payments are not based solely on the results of the research and development having future economic benefit. The liability is recorded as incremental research and development expense in the consolidated statements of operations and comprehensive loss. 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 seek to obtain marketing approval for our product candidates, including BT1718, BT5528 and BT8009; (ii) initiate clinical trials for our product candidates, including BT7480, BT7455 and BT7401; 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:

- whether our business will be adversely affected by the ongoing COVID-19 pandemic, which could materially affect our operations, delay our research efforts and clinical trials and cause significant disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business; and
- completing research and preclinical development of our product candidates, including conducting future clinical trials of BT1718, BT5528 and BT8009;
- progressing the preclinical and clinical development of BT7480, BT7455 and BT7401;
- 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, including the impacts of the ongoing COVID-19 pandemic, in which case we would be required to expend significant additional financial resources and time on the completion of clinical development. For instance, all clinical sites for the Phase I/IIa trial of BT1718 being conducted by Cancer Research UK in the United Kingdom temporarily paused enrollment of new patients due to the ongoing COVID-19 pandemic during the first half of 2020. The pause in enrollment was lifted in the second quarter of 2020, and patient enrollment in the Phase IIa portion of the clinical trial is again underway. However, changes in circumstances related to the ongoing pandemic could result in future pauses in or other impacts on enrollment. 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, insurance, 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, intellectual property, regulatory and tax compliance services, director and officer insurance costs and investor and public relations costs.

Other Income (Expense)

Interest Income

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

Interest Expense

Interest expense consists primarily of interest expense for financing arrangements. On September 30, 2020, we entered into the Loan Agreement with Hercules and borrowed $15.0 million. Consequently, we expect interest expense to increase in future periods.

Other Expense, net

Prior to our IPO, other expense, net consisted primarily of changes in the fair value associated with the remeasurement of the warrant liability for warrants we issued to subscribe for Series A and Series B1 convertible preferred shares. We remeasured the warrant liability at fair value at each reporting period until completion of our IPO in May 2019. Upon the completion of the IPO, the respective warrants were exercised or converted to warrants to subscribe for ordinary shares, and as such, we will not incur additional expense related to the remeasurement of the warrant liability in future periods.

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 benefit from income taxes presented in our consolidated statements of operations and comprehensive loss represents the tax impact from our operating activities in the United States, which have generated taxable income based on intercompany service arrangements.

The research and development tax credit received in the United Kingdom 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 United Kingdom, 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 were eligible for the RDEC Program for the year ended December 31, 2020. 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.

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 United Kingdom of $72.0 million and $41.7 million as of December 31, 2020 and 2019, respectively.

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 and is included as a component of prepaid and other current assets in our consolidated balance sheets.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2020, 2019 and 2018:

	Year Ended December 31,		
	2020	2019	2018
	(in thousands)		
Collaboration revenues	$ 10,390	$ 13,801	$ 7,136
Operating expenses:			
Research and development	33,149	25,540	20,761
General and administrative	29,201	14,560	8,121
Total operating expenses	62,350	40,100	28,882
Loss from operations	(51,960)	(26,299)	(21,746)
Other income (expense):			
Interest income	683	814	169
Interest expense	(457)	—	—
Other expense, net	—	(5,377)	(665)
Total other income (expense), net	226	(4,563)	(496)
Net loss before income tax provision	(51,734)	(30,862)	(22,242)
Benefit from income taxes	(724)	(254)	(396)
Net loss	$ (51,010)	$ (30,608)	$ (21,846)

Comparison of the Years Ended December 31, 2020 and 2019

	Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
Collaboration revenues	$ 10,390	13,801	$ (3,411)
Operating expenses:			
Research and development	33,149	25,540	7,609
General and administrative	29,201	14,560	14,641
Total operating expenses	62,350	40,100	22,250
Loss from operations	(51,960)	(26,299)	(25,661)
Other income (expense):			
Interest income	683	814	(131)
Interest expense	(457)	—	(457)
Other expense, net	—	(5,377)	5,377
Total other income (expense), net	226	(4,563)	4,789
Net loss before income tax provision	(51,734)	(30,862)	(20,872)
Benefit from income taxes	(724)	(254)	(470)
Net loss	$ (51,010)	(30,608)	$ (20,402)

Collaboration Revenues

Collaboration revenues decreased by $3.4 million during the year ended December 31, 2020 compared to the year ended December 31, 2019, primarily due to a decrease of $10.7 million of revenue from our collaboration with Sanofi. In March 2019, Sanofi exercised its right to terminate the sickle cell program and in October 2019, Sanofi terminated the hemophilia program, resulting in the recognition of revenue of $5.3 million and $4.7 million, respectively, for amounts allocated to material rights when these options expired, as well as a decrease in revenue of $1.0 million related to a one-time payment pursuant to a Material Transfer Agreement in 2019. These amounts were offset by an increase of $4.9 million of revenue from our collaboration with Genentech entered into in 2020, an increase of $2.4 million of revenue from a collaboration arrangement with Oxurion due to a milestone achieved for the initiation of a Phase II trial of THR-149, and $1.0 million of revenue from our collaboration arrangement with AstraZeneca primarily as AstraZeneca exercised its right to terminate a collaboration program, which resulted in the recognition of revenue of $1.5 million for amounts allocated to a material right when an option expired.

Research and Development Expenses

The following table summarizes our research and development expenses for the years presented:

	Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
BT1718 (MT1)	$ 743	$ 1,211	$ (468)
BT5528 (EphA2)	5,893	3,878	2,015
BT8009 (Nectin-4)	5,037	3,260	1,777
Tumor-targeted immune cell agonists	4,208	1,082	3,126
Other discovery and platform related expense	10,480	11,128	(648)
Employee and contractor related expenses	11,927	9,122	2,805
Share-based compensation	2,603	1,286	1,317
Facility expenses	1,384	1,297	87
Research and development incentives	(9,126)	(6,724)	(2,402)
Total research and development expenses	$ 33,149	$ 25,540	$ 7,609

Research and development expense increased by $7.6 million in the year ended December 31, 2020 as compared to the year ended December 31, 2019, primarily due to increases of $5.8 million in direct program spend, primarily due to increased clinical and TICA program development expenses offset by a $0.6 million decrease in other unallocated discovery and platform expense due to the timing of development activities, as well as an increase of $2.8 million in employee and contractor related expenses attributable to increased headcount and $1.3 million of incremental share-based compensation expense, offset by a $2.4 million increase in the research and development tax credit reimbursement due to the corresponding increase in research and development spending in the United Kingdom.

We begin to separately track program expenses beginning at candidate nomination and accumulate all costs incurred to support each program to date. Through December 31, 2020, we have incurred approximately $13.5 million, $14.3 million, $11.1 million and $5.3 million of direct expenses for the development of the BT1718, BT5528, BT8009 and TICA programs, respectively.

General and Administrative Expenses

The following table summarizes our general and administrative expenses for the years presented:

	Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
Personnel related costs	$ 6,494	$ 4,594	$ 1,900
Professional and consulting fees	14,633	6,084	8,549
Other general and administration costs	4,738	2,983	1,755
Share-based compensation	3,911	1,797	2,114
Effect of foreign exchange rates	(575)	(898)	323
Total general and administrative expenses	$ 29,201	$ 14,560	$ 14,641

General and administrative expenses increased by $14.6 million for the year ended December 31, 2020 as compared to the year ended December 31, 2019, primarily due to increases of $8.5 million in professional and consulting fees, including $4.7 million of expense related to the settlement and license agreement with Pepscan entered into in November 2020 as well as increased legal, human resources, and consulting costs to support operations as a public company, $2.1 million in share-based compensation expense; $1.9 million in personnel related costs due to increases in headcount; $1.8 million in other general and administrative costs, including insurance expense to support operations as a public company; and $0.3 million unfavorable effect of foreign exchange rates during the year ended December 31, 2020 as compared to the year ended December 31, 2019.

Other Income (Expense), net

Other income (expense), net decreased by $4.8 million for the year ended December 31, 2020, compared to the year ended December 31, 2019. In the year ended December 31, 2020, we recognized $0.7 million of interest income and $0.5 million in interest expense related to our debt facility entered into on September 30, 2020, whereas in the year ended December 31, 2019, we recognized $5.4 million of other expense associated with changes in the fair value of the warrant liability and final re-measurement upon completion of the IPO, offset by $0.8 million of interest income.

Liquidity and Capital Resources

From our inception through December 31, 2020, we have not generated any revenue from product sales and have 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 ordinary shares (including in the form of ADSs) and 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 Genentech, AstraZeneca, Oxurion, Sanofi, DDF, and borrowings pursuant to our debt facility.

From our inception in 2009 through December 31, 2020, we have received gross proceeds of $243.4 million from the sale of ordinary shares (including in the form of ADSs) and convertible preferred shares, including the proceeds from our IPO; $63.1 million of cash payments under our collaboration revenue arrangements including $31.0 million from Genentech, $10.3 million from AstraZeneca, $4.1 million from Oxurion, $15.0 million from Sanofi, $1.7 million from DDF; $15.0 of borrowings pursuant to our Loan Agreement with Hercules. In January 2021, we received $2.4 million from Oxurion due to a milestone achieved for the initiation of a Phase II trial of THR-149 and $3.0 million of proceeds under an evaluation and option agreement.

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2020, 2019 and 2018:

	Year Ended December 31,		
	2020	2019	2018
		(in thousands)	
Net cash used in operating activities	$ (17,789)	$ (28,613)	$ (26,078)
Net cash used in investing activities	(1,200)	(1,555)	(1,186)
Net cash provided by financing activities	62,843	58,440	25,430
Effect of exchange rate changes on cash	19	465	(2,449)
Net increase (decrease) in cash	$ 43,873	$ 28,737	$ (4,283)

Operating Activities

Net cash used in operating activities for the year ended December 31, 2020 included our net loss of $51.0 million, net cash used in our operating assets and liabilities of $25.4 million and non-cash charges of $7.9 million, which included share-based compensation expense of $6.5 million, depreciation and amortization of $1.3 million, and non-cash interest related to the Loan Agreement of $0.1 million. Net changes in our operating assets and liabilities for the year ended December 31, 2020 consisted primarily of an increase in deferred revenue of $24.6 million primarily due to upfront payments received from collaboration arrangement with Genentech; an increase of $4.8 million in accrued expenses and other current liabilities, primarily due to accrued external research and development costs; and an increase of $0.5 million in other long-term liabilities. These were offset by an increase of $2.1 million in accounts receivable and an increase of $1.8 million in research and development incentives receivable.

Net cash used in operating activities for the year ended December 31, 2019 included our net loss of $30.6 million, net cash used in our operating assets and liabilities of $7.4 million and non-cash charges of $9.4 million, which included share-based compensation expense of $3.1 million, depreciation and amortization of $1.0 million, and changes in the fair value of the warrant liability of $5.4 million. Net changes in our operating assets and liabilities for the year ended December 31, 2019, consisted primarily of a decrease in accounts receivable of $4.9 million, primarily due to a payment received from AstraZeneca for its exercise of an option; a decrease in deferred revenue of $9.3 million, primarily due to the recognition of revenue related to the Sanofi collaboration arrangement; a decrease in accrued expenses and other current liabilities of $0.9 million; and an increase in prepaid expenses and other assets of $3.1 million, primarily due to prepaid clinical costs, offset by an increase in accounts payable of $0.2 million and an increase in other long-term liabilities of $1.1 million.

Investing Activities

During the years ended December 31, 2020 and 2019, we used $1.2 million and $1.6 million, respectively, of cash in investing activities for purchases of property and equipment consisting primarily of laboratory equipment.

Financing Activities

During the year ended December 31, 2020, net cash provided by financing activities was $62.8 million, primarily consisting of net proceeds from our ATM program of $48.1 million and borrowings of $15.0 million under our Loan Agreement with Hercules, offset by the payment of debt issuance costs of $0.6 million.

During the year ended December 31, 2019, net cash provided by financing activities was $58.4 million, primarily consisting of net proceeds of $57.0 million from our IPO, and net proceeds of $1.3 million from our Series B2 convertible preferred shares issued in January 2019.

Loan Agreement

On September 30, 2020, or the Closing Date, we entered into the Loan Agreement with Hercules as agent, which provided for aggregate maximum borrowings of up to $40.0 million, consisting of (i) a term loan of $15.0 million, which was funded on the Closing Date, (ii) subject to customary conditions, an additional term loan of up to $15.0 million available from the Closing Date through March 15, 2021, and (iii) subject to our achievement of certain performance milestones and satisfaction of customary conditions and available until March 15, 2022, an additional term loan of $10.0 million. Borrowings under the Loan Agreement, including the $15.0 million term loan issued as of September 30, 2020 bear interest at an annual rate equal to the greater of (i) 8.85% and (ii) the prime rate of interest plus 5.60%. The Loan Agreement provides for interest-only payments until November 1, 2022, which may be extended to May 1, 2023 upon our achievement of certain performance milestones, followed by equal monthly payments of principal and interest through October 1, 2024, or the Maturity Date. We may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to 2.0% of the principal amount outstanding if the prepayment occurs during the first year following the Closing Date, 1.5% of the principal amount outstanding if the prepayment occurs during the second year following the Closing Date and 1.0% thereafter but prior to the Maturity Date. The Loan Agreement also provides for an end of term charge, payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. In connection with the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. The Loan Agreement includes a right for the lenders to invest in an amount of up to $2.0 million in the closing of any our financings after the Closing Date that result in aggregate proceeds to us of at least $10.0 million. In addition, the Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control (as defined in the Loan Agreement), financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a “material adverse effect” as set forth in the Loan Agreement, cross acceleration to third-party indebtedness and certain events relating to bankruptcy or insolvency. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal balance, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement. There are no financial covenants. If we fail to make payments when due, or breach any operational covenant or have any event of default, this could have a material adverse effect on our business and financial condition.

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 for BT1718, BT5528, and BT8009;
- progress the preclinical and clinical development of BT7480, BT7455, and BT7401;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to seek 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 operations as a public company.

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.

As of December 31, 2020, we had cash of $136.0 million. We expect that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least twelve months from the date of filing of this Annual Report on Form 10-K. 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:

- our ability to raise capital in light of the impacts of the ongoing global COVID-19 pandemic on the global financial markets;
- 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, particularly in light of the ongoing global COVID-19 pandemic;
- 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 Genentech, AstraZeneca, Oxurion and DDF;
- 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, ownership interests of existing holders of our ADSs and ordinary shares will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of holders of our ADSs or ordinary shares. 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. Future debt financing, if available, may involve covenants restricting our operations or our ability to incur additional debt. Any debt or equity financing that we raise may contain terms that are not favorable to us or our shareholders. The ongoing COVID-19 pandemic continues to evolve and has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, whether as a result of the pandemic or otherwise, we could experience an inability to access additional capital, which could in the future negatively affect our operations. 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, 2020 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	3 to 5 years	More than 5 years
			(in thousands)		
Operating lease commitments (1)	$ 1,352	$ 908	$ 444	$ —	$ —
Debt obligations (2)	19,662	1,346	18,316	—	—
Total	$ 21,014	$ 2,254	$ 18,760	$ —	$ —

(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 an operating lease that expires in December 2022.

(2) Amounts in the table reflect the contractually required principal, interest and the final payment under the Loan Agreement with Hercules as of December 31, 2020

In the ordinary course of business, we enter into various agreements with contract research organizations to provide clinical trial services, 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 with advanced written notice, with a notice period of 90 days or less. From the time of notice until termination, we are contractually

obligated to make certain minimum payments to the vendors, based on the timing of the notification and the exact terms of the agreement.

Our arrangements with Cancer Research UK provide for additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $111.2 million, as well as royalty payments based on a single digit percentage on net sales of products developed. In addition, in November 2020, we entered into a settlement and license agreement with Pepscan Systems B.V. regarding our use of Pepscan's CLIPS peptide technology, which agreement provides for additional future milestone payments by us upon the achievement of development, regulatory and commercial milestones, with an aggregate total value of $92.4 million. We have not included future payments under this agreement in the table of contractual obligations above since these obligations are contingent upon future events. As of December 31, 2020, we were unable to estimate the timing or likelihood of achieving these milestones.

Legal Proceedings

For a discussion of legal matters as of December 31, 2020, see Note 13, "Commitments and Contingencies," within the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K

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 elsewhere in the Annual Report on Form 10-K, 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 recognize revenue in accordance with ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* or ASC 606, and all subsequent amendments. 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. As of December 31, 2020, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Share-Based Compensation

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 vests 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.

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. The assumptions used in

computing the fair value of stock option awards reflect our best estimates but involve uncertainties related to market and other conditions, many of which are outside of our control. Changes in any of these assumptions may materially affect the fair value of share-based awards granted and the amount of share-based compensation recognized in future periods.

Research and Development Incentives and Receivable

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 our subsidiaries in the United Kingdom are reimbursed up to 14.5% of the surrenderable 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 represents an amount due in connection with the above program.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, We will remain an EGC until the earlier of (1) the last day of the fiscal year following the fifth anniversary of the completion of our initial public offering (December 31, 2024), (2) the last day of the fiscal year in which we have total annual gross revenue 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" as defined in Rule 12b-2 under the Exchange Act of 1934, as amended, or the Exchange Act, which would occur if the market value of our ordinary shares held by non-affiliates exceeded $700.0 million as of the last business day of the second fiscal quarter of such fiscal year or (4) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period. The JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to "opt out" of this provision and, as a result, we will comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies.

In addition, we intend to rely on the other exemptions and reduced reporting requirements available to EGCs provided by the JOBS Act. Subject to certain conditions set forth in the JOBS Act, 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 until the earlier to occur of (i) the end of the year in which the fifth anniversary of our IPO occurs, or December 31, 2024, or (b) we no longer meet the requirements of being an emerging growth company.

We are also a smaller reporting company as defined in the Exchange Act. We may continue to be a smaller reporting company even after we are no longer an emerging growth company. We may, and intend to, take advantage of certain of the scaled disclosures available to smaller reporting companies for so long as we are a smaller reporting company. We may be a smaller reporting company in any year in which (i) the market value of our voting and non-

voting ordinary shares held by non-affiliates is less than $250.0 million measured on the last business day of our second fiscal quarter or (ii) (a) our annual revenue is less than $100.0 million during the most recently completed fiscal year and (b) the market value of our voting and non-voting ordinary shares held by non-affiliates is less than $700.0 million measured on the last business day of our second fiscal quarter.

Off-balance Sheet Arrangements

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

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Interest Rate Sensitivity

As of December 31, 2020, we had cash of $136.0 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.

We are subject to interest rate risk in connection with our borrowings under our credit facility with Hercules, which were $15.0 million as of December 31, 2020. Our outstanding indebtedness with Hercules bears interest at the greater of 8.85%, or 5.60% plus the Wall Street Journal prime rate. As of December 31, 2020, our outstanding indebtedness with Hercules bears interest at 8.85%. If the prime rate increases to over 3.25%, the interest on our loan with Hercules will increase. We currently do not engage in any interest rate hedging activity, and we have no intention to do so in the foreseeable future. Based on the current interest rate of the term loan and the scheduled payments thereunder, we do not believe a 1.0% increase in interest rates would have a material impact on our financial condition or results of operations.

Foreign Currency Exchange Risk

The functional currency is the currency of the primary economic environment in which an entity’s operations are conducted. The functional currency of Bicycle Therapeutics plc and Bicycle Therapeutics Inc. is the United States dollar. The functional currency of 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 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 foreign exchange gains of $0.6 million, $0.9 million and $0.3 million for the years ended December 31, 2020, 2019 and 2018, respectively.

For financial reporting purposes, our consolidated financial statements have been translated into U.S. dollars. We translate the assets and liabilities of 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’ equity (deficit) amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net loss but are included in our foreign exchange

adjustment included in the consolidated statements of convertible preferred shares and shareholders' equity (deficit) 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.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

The financial statements required by this item are set forth beginning on page F-1 of this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures.

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. Based on the evaluation of our disclosure controls and procedures as of December 31, 2020, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective.

Management's Report on Internal Control Over Financial Reporting.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate. Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

Our management conducted an assessment of our internal control over financial reporting based on the framework established in 2013 by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013). Based on the assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2020.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm due to an exemption for "emerging growth companies."

Changes in Internal Control over Financial Reporting.

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

First Amendment to Loan and Security Agreement

On March 10, 2021, or the Amendment Closing Date, we and our subsidiaries entered into the First Amendment to the Loan and Security Agreement, or the First Amendment to LSA, with Hercules, in its capacity as administrative agent and collateral agent, and the Lenders named in the First Amendment to LSA. The First Amendment to LSA amended certain terms of our debt facility with Hercules.

Pursuant to the First Amendment to LSA, payments on our borrowings under our debt facility with Hercules will be interest-only until the first payment is due on August 1, 2023, which date was extended from November 1, 2022. If we achieve certain performance milestones, the interest-only period will be extended, with the first principal payment due on February 1, 2024, which date was extended from May 1, 2023.

On the Amendment Closing Date and pursuant to the terms of the First Amendment to LSA, we borrowed the additional term loan of $15.0 million that had been available from September 30, 2020 to March 15, 2021.

The foregoing summary description of the First Amendment to LSA does not purport to be complete and is qualified in its entirety by reference to the full text of the First Amendment to LSA, which is attached as Exhibit 10.28 to this Annual Report and is incorporated herein by reference.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

The information required by this Item 10 will be included in the sections titled “Board of Directors and Corporate Governance” and “Executive Officers of the Company” in our Proxy Statement and is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION.

The information required by this Item 11 will be included in the sections titled “Director Remuneration” and “Executive Compensation” in our Proxy Statement and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

The information required by this Item 12 will be included in the sections titled “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” in our Proxy Statement and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE.

The information required by this Item 13 will be included in the sections titled “Board of Directors and Corporate Governance” and “Transactions with Related Persons” in our Proxy Statement and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES.

The information required by this Item 14 will be included in Proposal 5 in the section titled “Independent Registered Public Account Firm Fees” in our Proxy Statement and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

The financial statements schedules and exhibits filed as part of this Annual Report on Form 10-K are as follows:

(a)(1) Financial Statements

Reference is made to the financial statements included in Item 8 of Part II hereof.

(a)(2) Financial Statement Schedules

All other schedules are omitted because they are not required or the required information is included in the financial statements or notes thereto.

(a)(3) Exhibits

The exhibits listed below are filed as part of this Form 10-K other than Exhibit 32.1, which shall be deemed furnished:

Number	Description
3.1	Articles of Association (incorporated by reference to Exhibit 3.2 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.1	Form of Deposit Agreement (incorporated by reference to Exhibit 4.1 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.2	Form of American Depositary Receipt (included in Exhibit 4.1) (incorporated by reference to Exhibit 4.2 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.3	Letter Agreement, dated July 1, 2020, between Bicycle Therapeutics plc and Citibank, N.A. (incorporated by reference to Exhibit 4.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on November 5, 2020).
4.4	Amendment to Letter Agreement, dated October 27, 2020, between Bicycle Therapeutics plc and Citibank, N.A.
4.5	Registration Rights Agreement by and among Bicycle Therapeutics Limited and the Investors listed therein, dated December 21, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
4.6	Description of Securities (incorporated by reference to Exhibit 4.4 to the Registrant's Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.1+	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in England (incorporated by reference to Exhibit 10.2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).

Number	Description
10.2+	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in the United States (incorporated by reference to Exhibit 10.3 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.3+	Rules of the Bicycle Therapeutics Share Option Plan, as amended on September 12, 2019 (incorporated by reference to Exhibit 10.3 to the Quarterly Report on Form 10-Q (File No. 001-38916) filed with the Securities and Exchange Commission on November 7, 2019).
10.4+	Forms of award agreements under the Bicycle Therapeutics Share Option Plan, as amended (incorporated by reference to Exhibit 10.4 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.5+	2019 Employee Share Purchase Plan (incorporated by reference to Exhibit 10.5 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
10.6+	Bicycle Therapeutics plc 2020 Equity Incentive Plan and forms of award thereunder (incorporated by reference to Exhibit 10.2 to the Quarterly Report on Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on August 5, 2020).
10.7+	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.4 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
10.8+	Service Agreement, dated September 26, 2019, by and between BicycleTx Ltd. and Kevin Lee (Incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on September 30, 2019).
10.9+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between Bicycle Therapeutics Inc. and Lee Kalowski (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on September 30, 2019).
10.10+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between BicycleTx Ltd. and Michael Skynner, Ph.D. (incorporated by reference to Exhibit 10.9 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.11+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between Bicycle Therapeutics Inc. and Nicholas Keen, Ph.D. (incorporated by reference to Exhibit 10.10 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.12+	Service Agreement, dated September 26, 2019, by and between BicycleTx Ltd and Nigel Crockett , Ph.D. (incorporated by reference to Exhibit 10.11 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.13+	Form of letter agreement to amend Service Agreement by and between the BicycleTx Ltd. and its executive officers in the United Kingdom, effective January 1, 2020 (incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on May 7, 2020).
10.14+	Service Agreement, dated July 9, 2020, by and between BicycleTx Ltd. and Dominic Smethurst, MA, MBChB, MRCP, MFPM.

Number	Description
10.15+	Form of Deed of Indemnity between the Company and each of its directors (incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on November 12, 2019).
10.16+	Form of Deed of Indemnity between the registrant and each of its executive officers (incorporated by reference to Exhibit 10.2 to Current Report on Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on November 12, 2019).
10.17+	Non-employee Director Compensation Policy, amended as of December 17, 2019 (incorporated by reference to Exhibit 10.14 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.18+	Non-employee Director Compensation Policy, amended as of December 16, 2020.
10.19	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 (incorporated by reference to Exhibit 10.13 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
10.20	Lease Agreement, by and between Bicycle Therapeutics Inc. and King 4 Hartwell Place, LLC, dated September 26, 2017 (incorporated by reference to Exhibit 10.14 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.21	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 (incorporated by reference to Exhibit 10.15 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.22††	Discovery Collaboration and License Agreement between BicycleTx Limited and Genentech, Inc., dated February 21, 2020 (incorporated by reference to Exhibit 10.18 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.23††	Settlement and Licence Agreement, dated November 20, 2020, by and among Bicycle Therapeutics plc, Bicycle Therapeutics Inc., BicycleRD Limited, BicycleTx Limited and Pepscan Systems BV, Pepscan Presto BV, Pepscan Therapeutics BV, Pepscan Holding NV, Pepmab BV.
10.24††	Settlement Agreement, dated November 20, 2020, by and among Bicycle Therapeutics plc, Bicycle Therapeutics Inc., BicycleRD Limited, BicycleTx Limited and Pepscan Systems BV, Pepscan Presto BV, Pepscan Therapeutics BV, Pepscan Holding NV, Pepmab BV.

Number	Description
10.25	Controlled Equity Offering℠ Sales Agreement, dated June 5, 2020, among Cantor Fitzgerald & Co., Oppenheimer & Co. Inc. and Bicycle Therapeutics plc (incorporated by reference to Exhibit 1.2 to the Registration Statement on Form S-3 (File No. 333-238996), filed with the Securities and Exchange Commission on June 5, 2020).
10.26	Loan and Security Agreement, dated September 30, 2020, by and among Bicycle Therapeutics plc, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics, Inc., the lenders party thereto, and Hercules Capital, Inc., as administrative and collateral agent (incorporated by reference to Exhibit 10.1 to Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on October 1, 2020).
10.27+	Form of letter agreement to amend Service Agreement by and between the BicycleTx Ltd. and its executive officers in the United Kingdom, effective January 1, 2021.
10.28	First Amendment to Loan and Security Agreement, dated March 10, 2021, by and among Bicycle Therapeutics plc, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics, Inc., the lenders party thereto, and Hercules Capital, Inc., as administrative and collateral agent.
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Company's Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney (included on the signature page of this report).
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document.
101.SCH	XBRL Taxonomy Extension Schema Document.
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.

* Furnished herewith and not deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and shall not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

+ Indicates a management contract or compensatory plan.

† Confidential treatment has been granted for certain portions of this exhibit. These portions have been omitted and filed separately with the SEC.

†† Portions of this Exhibit (indicated with [***]) have been omitted as the registrant has determined that (i) the omitted information is not material and (ii) the omitted information would likely cause competitive harm to the registrant if publicly disclosed.

ITEM 16. FORM 10-K SUMMARY

None.

Index to Consolidated Financial Statements of
Bicycle Therapeutics, plc

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Bicycle Therapeutics plc

Opinion on the Financial Statements

We have audited the accompanying Consolidated Balance Sheets of Bicycle Therapeutics plc and its subsidiaries (the "Company") as of December 31, 2020 and 2019, and the related Consolidated Statements of Operations and Comprehensive Loss, of Convertible Preferred Shares and Shareholders' Equity (Deficit) and of Cash Flows for each of the three years in the period ended December 31, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020 in conformity with accounting principles generally accepted in the United States of America.

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. 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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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 11, 2021

We have served as the Company's or its predecessor's auditor since 2010, which includes periods before the Company become subject to SEC reporting requirements.

Bicycle Therapeutics plc

Consolidated Balance Sheets

(amounts in thousands, except share and per share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash	$ 135,990	$ 92,117
Accounts receivable	5,456	201
Prepaid expenses and other current assets	5,100	4,884
Research and development incentives receivable	9,177	6,944
Total current assets	155,723	104,146
Property and equipment, net	2,317	2,292
Operating lease right-of-use assets	1,290	2,056
Other assets	1,822	1,700
Total assets	$ 161,152	$ 110,194
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 1,365	$ 1,949
Accrued expenses and other current liabilities	11,629	6,144
Deferred revenue, current portion	10,135	728
Total current liabilities	23,129	8,821
Long-term debt	14,505	—
Operating lease liabilities	426	1,251
Deferred revenue, net of current portion	25,021	4,929
Other long-term liabilities	2,611	1,995
Total liabilities	65,692	16,996
Commitments and contingencies (Note 13)		
Shareholders' equity:		
Ordinary shares, £0.01 nominal value; 31,995,653 shares authorized at December 31, 2020 and December 31, 2019; 21,094,557 and 17,993,701 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	266	227
Additional paid-in capital	249,947	195,056
Accumulated other comprehensive loss	(3,193)	(1,535)
Accumulated deficit	(151,560)	(100,550)
Total shareholders' equity	95,460	93,198
Total liabilities and shareholders' equity	$ 161,152	$ 110,194

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics plc

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2020	2019	2018
Collaboration revenues	$ 10,390	$ 13,801	$ 7,136
Operating expenses:			
Research and development	33,149	25,540	20,761
General and administrative	29,201	14,560	8,121
Total operating expenses	62,350	40,100	28,882
Loss from operations	(51,960)	(26,299)	(21,746)
Other income (expense):			
Interest income	683	814	169
Interest expense	(457)	—	—
Other expense, net	—	(5,377)	(665)
Total other income (expense), net	226	(4,563)	(496)
Net loss before income tax provision	(51,734)	(30,862)	(22,242)
Benefit from income taxes	(724)	(254)	(396)
Net loss	$ (51,010)	$ (30,608)	$ (21,846)
Net loss attributable to ordinary shareholders	$ (51,010)	$ (30,608)	$ (21,846)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.66)	$ (2.77)	$ (49.78)
Weighted average ordinary shares outstanding, basic and diluted	19,145,938	11,045,370	438,862
Comprehensives Loss:			
Net loss	$ (51,010)	$ (30,608)	$ (21,846)
Other comprehensive income (loss):			
Foreign currency translation adjustment	(1,658)	216	(1,820)
Total comprehensive loss	$ (52,668)	$ (30,392)	$ (23,666)

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics plc

Consolidated Statements of Convertible Preferred Shares and Shareholders' Equity (Deficit)

(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' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2017	2,800,001	$ 41,820	3,947,198	$ 54,621	—	$ —	368,995	$ 5	$ 838	$ 69	$ (48,096)	$ (47,184)
Issuance of convertible preferred shares, net of issuance costs of $327	—	—	—	—	1,323,248	25,756	—	—	—	—	—	—
Issuance of restricted share awards	—	—	—	—	—	—	95,644	1	223	—	—	224
Issuance of ordinary shares in exchange for surrender of vested share options	—	—	—	—	—	—	340,728	4	(4)	—	—	—
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	9,361	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	—	—	800	—	—	800
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(1,820)	—	(1,820)
Net loss	—	—	—	—	—	—	—	—	—	—	(21,846)	(21,846)
Balance at December 31, 2018	2,800,001	41,820	3,947,198	54,621	1,323,248	25,756	814,728	10	1,857	(1,751)	(69,942)	(69,826)
Issuance of convertible preferred shares	—	—	—	—	80,385	1,583	—	—	—	—	—	—
Conversion of convertible preferred shares to ordinary shares	(2,800,001)	(41,820)	(3,947,198)	(54,621)	(1,403,633)	(27,339)	11,647,529	146	123,634	—	—	123,780
Reclassification of warrant liability to additional paid-in capital and exercise of warrants	—	—	—	—	—	—	723,992	9	10,018	—	—	10,027
Issuance of ADSs in initial public offering, net of underwriting discounts, commissions and offering expenses of $8.5 million	—	—	—	—	—	—	4,637,666	59	56,322	—	—	56,381
Issuance of restricted share awards	—	—	—	—	—	—	83,947	2	395	—	—	397
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	85,839	1	142	—	—	143
Share-based compensation expense	—	—	—	—	—	—	—	—	2,688	—	—	2,688
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	216	—	216
Net loss	—	—	—	—	—	—	—	—	—	—	(30,608)	(30,608)
Balance at December 31, 2019	—	—	—	—	—	—	17,993,701	227	195,056	(1,535)	(100,550)	93,198
Issuance of ordinary shares upon exercise of warrants	—	—	—	—	—	—	92,885	1	—	—	—	1
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	79,158	1	270	—	—	271
Issuance of ADSs, net of commissions and offering expenses of $1.9 million	—	—	—	—	—	—	2,928,813	37	48,107	—	—	48,144
Share-based compensation expense	—	—	—	—	—	—	—	—	6,514	—	—	6,514
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(1,658)	—	(1,658)
Net loss	—	—	—	—	—	—	—	—	—	—	(51,010)	(51,010)
Balance at December 31, 2020	—	$ —	—	$ —	—	$ —	21,094,557	$ 266	$ 249,947	$ (3,193)	$ (151,560)	$ 95,460

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics plc
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2020	2019	2018
Cash flows from operating activities:			
Net loss	$ (51,010)	$ (30,608)	$ (21,846)
Adjustments to reconcile net loss to net cash used in operating activities:			
Share-based compensation expense	6,514	3,083	1,023
Depreciation and amortization	1,277	960	712
Non-cash interest	78	—	—
Change in fair value of warrant liability	—	5,381	665
Changes in operating assets and liabilities:			
Accounts receivable	(2,149)	4,909	(400)
Research and development incentives receivable	(1,786)	(383)	(3,586)
Prepaid expenses and other current assets	(49)	(2,723)	(1,329)
Operating lease right-of-use assets	771	712	—
Other assets	(122)	(397)	(301)
Accounts payable	(663)	220	(169)
Accrued expenses and other current liabilities	4,832	(852)	2,557
Operating lease liabilities	(621)	(709)	—
Deferred revenue	24,622	(9,295)	(3,947)
Other long-term liabilities	517	1,089	543
Net cash used in operating activities	(17,789)	(28,613)	(26,078)
Cash used in investing activities:			
Purchases of property and equipment	(1,200)	(1,555)	(1,186)
Net cash used in investing activities	(1,200)	(1,555)	(1,186)
Cash flows from financing activities:			
Proceeds from issuance of series B2 convertible preferred shares, net of issuance costs	—	1,334	26,005
Proceeds from the issuance of ADSs, net of issuance costs	48,144	56,957	(576)
Proceeds from the exercise of share options and sale of ordinary shares	271	143	1
Proceeds from the exercise of warrants	1	6	—
Proceeds from issuance of debt	15,000	—	—
Payments of debt issuance costs	(573)	—	—
Net cash provided by financing activities	62,843	58,440	25,430
Effect of exchange rate changes on cash	19	465	(2,449)
Net increase (decrease) in cash	43,873	28,737	(4,283)
Cash at beginning of period	92,117	63,380	67,663
Cash at end of period	$ 135,990	$ 92,117	$ 63,380
Supplemental disclosure of cash flow information			
Cash paid for interest	$ 378	$ —	$ —
Cash paid for income taxes	$ 124	$ 117	$ 73
Cash paid for amounts included in the measurement of operating lease liabilities	$ 961	$ 891	$ —
Purchases of property and equipment included in accounts payable and accrued expenses	$ 109	$ 76	$ —
Advance billings on deferred revenue included in accounts receivable	$ 3,000	$ —	$ 5,045
Series B2 convertible preferred financing costs accrued but not paid	$ —	$ —	$ 249
Debt issuance costs accrued but not paid	$ —	$ —	$ 1,076
Conversion of convertible preferred shares to ordinary shares upon closing of the initial public offering	$ —	$ 123,780	$ —
Reclassification of warrant liability to additional paid-in capital	$ —	$ 10,021	$ —

The accompanying notes are an integral part of the consolidated financial statements

Bicycle Therapeutics plc

Notes to Consolidated Financial Statements

1. Nature of the business and basis of presentation

Bicycle Therapeutics plc (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 metalloproteinase. 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 evaluating BT5528, a second-generation BTC targeting Ephrin type-A receptor 2 ("EphA2"), in a Company-sponsored Phase I/II clinical trial as a monotherapy and in combination with nivolumab, and BT8009, a second-generation BTC targeting Nectin-4, in a Company-sponsored Phase I/II clinical trial. The Company's discovery pipeline in oncology includes *Bicycle*-based systemic immune cell agonists and Bicycle tumor-targeted immune cell agonists (TICAs). Beyond the Company's wholly-owned oncology portfolio, the Company is collaborating with biopharmaceutical companies and organizations in immuno-oncology, anti-infective, cardiovascular, ophthalmology, dementia and respiratory indications.

The accompanying consolidated financial statements include the accounts of Bicycle Therapeutics plc 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").

Liquidity

On May 28, 2019, the Company completed its initial public offering (the "IPO"), pursuant to which it issued and sold 4,333,333 American Depositary Shares ("ADSs"), representing the same number of ordinary shares at a public offering price of $14.00 per ADS. In addition, in June 2019, the Company issued and sold an additional 304,333 ADSs, pursuant to the partial exercise of the underwriters' option to purchase additional ADSs. The aggregate net proceeds received by the Company from the IPO were $56.4 million, after deducting underwriting discounts and commissions of $4.5 million and offering expenses of $4.0 million.

On June 5, 2020, the Company entered into a Sales Agreement (the "Sales Agreement") with Cantor Fitzgerald & Co. and Oppenheimer & Co. Inc. (the "Sales Agents") with respect to an at-the-market offering program ("ATM") pursuant to which the Company may offer and sell through the Sales Agents, from time to time at the Company's sole discretion, ADSs, each ADS representing one ordinary share. As of December 31, 2020, the Company had issued and sold 2,928,813 ADSs, representing the same number of ordinary shares for gross proceeds of $50.0 million, resulting in net proceeds of $48.1 million after deducting sales commissions and offering expenses of $1.9 million.

On September 30, 2020, Bicycle Therapeutics plc and certain of its subsidiaries (together with Bicycle Therapeutics plc, the "Borrowers") entered into a loan and security agreement (the "Loan Agreement") with Hercules Capital, Inc. ("Hercules") as agent, which provided for maximum borrowings of up to $40.0 million in aggregate principal amount, consisting of (i) a term loan of $15.0 million, which was funded on September 30, 2020, (ii) subject to satisfaction of customary conditions, an additional term loan of up to $15.0 million available from September 30, 2020 through March 15, 2021, and (iii) subject to the achievement of certain performance milestones and satisfaction of customary conditions, an additional term loan of $10.0 million available until March 15, 2022.

The Company is subject to risks common to companies in the biotechnology industry and in light of the ongoing COVID-19 pandemic, including but not limited to, risks of delays in initiating or continuing research programs and clinical trials, 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.

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. Since inception, the Company has devoted substantially all of its efforts to business planning, research and development, recruiting management and technical staff, and raising capital. The Company has funded its operations with proceeds from the sale of its ordinary shares and ADSs, including in its IPO completed in May 2019 and pursuant to its ATM program, convertible preferred shares (Note 7), and proceeds received from its collaboration arrangements (Note 11), and proceeds from the Loan Agreement with Hercules (Note 6). The Company has incurred recurring losses since inception, including net losses of $51.0 million for the year ended December 31, 2020, $30.6 million for the year ended December 31, 2019 and $21.8 million for the year ended December 31, 2018. As of December 31, 2020, the Company had an accumulated deficit of $151.6 million. The Company expects to continue to generate operating losses in the foreseeable future. As of the issuance date of the annual consolidated financial statements for the year ended December 31, 2020, the Company expects that its cash will be sufficient to fund its operating expenses and capital expenditure requirements through at least twelve months from the issuance date of the annual consolidated financial statements.

The Company expects its expenses to increase substantially in connection with ongoing activities, particularly as the Company advances its preclinical activities and clinical trials for its product candidates in development. Accordingly, the Company will need to obtain additional funding in connection with continuing operations. If the Company is unable to raise capital when needed, or on attractive terms, it could be forced to delay, reduce or eliminate its research or drug development programs or any future commercialization efforts. Although management continues to pursue these plans, there is 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.

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 the valuation of the warrant liability prior to the Company's IPO, share-based compensation expense, 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.

Foreign currency and currency translation

The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. On June 1, 2019, Bicycle Therapeutics plc adopted the U.S. dollar as its functional currency. Bicycle Therapeutics plc is a holding company that has no operating activities and its primary functions are to serve as a

financing vehicle to fund the operations of the Company's operating entities, to serve as the listing company needed to access U.S. capital markets, and to hold investments. Therefore, its financing source is the primary indicator of its cash flows and its functional currency. The change in functional currency from the British Pound Sterling is due to a change in the source of Bicycle Therapeutics plc's financing and cash flows, which following the completion of the IPO is now primarily the U.S. Dollar ("USD"). Historically its financing had been in British Pound Sterling.

The functional currency of Bicycle Therapeutics plc's wholly owned non-U.S. subsidiaries, BicycleTx Limited and BicycleRD Limited, is the British Pound Sterling and the functional currency of its U.S. subsidiary, Bicycle Therapeutics Inc. is the USD. 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. The Company recorded foreign exchange gains of $0.6 million, $0.9 million and $0.3 million for the years ended December 31, 2020, 2019 and 2018, respectively.

The Company translates the assets and liabilities of 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' equity (deficit) as a component of accumulated other comprehensive 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"), between BicycleRD Limited and Oxurion NV (formerly ThromboGenics NV) ("Oxurion"), and pursuant to an evaluation and option agreement with another third party (the "Evaluation and Option Agreement") (Note 11), for which the Company does not obtain collateral. As of December 31, 2020, the Company's revenue to date has primarily been generated from the collaboration agreements with Genentech, Inc. ("Genentech"), AstraZeneca, Sanofi (formerly Bioverativ), the Dementia Discovery Fund ("DDF") 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, 2020 and 2019.

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, 2020 and 2019.

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' equity (deficit) 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.

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, 2020 and 2019, 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 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.

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.

Prior to the IPO, the Company's warrant liability was 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. At December 31, 2020, the carrying value of the long-term debt approximates its fair value, which was determined using unobservable Level 3 inputs, including quoted interest rates from a lender for borrowings with similar terms.

Warrant liability

Prior to the IPO, the Company classified warrants to subscribe for Series A convertible preferred shares ("Series A Preferred Shares") and Series B1 convertible preferred shares ("Series B1 Preferred Shares") (Note 7) as a liability on its consolidated balance sheets as these warrants to subscribe for Series A Preferred Shares and Series B1 Preferred Shares were free-standing financial instruments that might have required the Company to transfer assets upon exercise. The warrant liability was initially recorded at fair value upon the date of the warrants' issuance and was subsequently remeasured to fair value at each reporting date. Changes in the fair value of the warrant liability were recognized as a component of other expense, net in the consolidated statements of operations and comprehensive loss. Upon the closing of the IPO, warrants to subscribe for Series A Preferred Shares and Series B1 Preferred Shares that were not exercised or expired in conjunction with the IPO automatically became warrants to subscribe for ordinary shares, and meet the criteria to be classified as shareholders' equity (deficit). As such, following the final remeasurement on May 28, 2019, the Company reclassified the carrying value of the warrant liability to additional paid-in-capital in the consolidated balance sheet.

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.

Leases

The Company adopted ASC Topic 842, *Leases* (ASC 842), using a modified retrospective approach, as of January 1, 2019, with no restatement of prior periods or cumulative adjustment to retained earnings. The Company determines if an arrangement is a lease at inception. Operating leases are included in operating lease right-of-use ("ROU") assets, other current liabilities, and operating lease liabilities in the Company's consolidated balance sheet. The Company has not entered into any financing leases.

ROU assets represent the Company's right to use and control an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. ROU assets and liabilities are recognized at commencement date based on the present value of lease payments over the lease term. As the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at commencement date in determining the present value of lease payments. The ROU asset also includes lease payments made before the lease commencement date and excludes any lease incentives. The Company's

lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option.

The components of a lease shall be split into three categories, if applicable: lease components (e.g., land, building, etc.), non-lease components (e.g., common area maintenance, maintenance, consumables, etc.), and non-components (e.g., property taxes, insurance, etc.). The fixed and in-substance fixed contract consideration (including any related to non-components) must then be allocated based on fair values to the lease components and non-lease components. The Company's facilities operating leases may have lease and non-lease components to which the Company has elected to apply a practical expedient to account for each lease component and related non-lease component as one single component. The lease component results in a right-of-use asset being recorded on the balance sheet. Lease expense for lease payments is recognized on a straight-line basis over the lease term.

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 recognizes revenue in accordance with ASU 2014-09, *Revenue from Contracts with Customers* (Topic 606) ("ASC 606") and all subsequent amendments. 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.

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.

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 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 11, "Significant Agreements"

Government grants

From time to time, the Company may enter into arrangements with governmental entities for the purposes of obtaining funding for research and development activities. The Company recognizes government grant funding in the consolidated statements of operations and comprehensive loss as the related expenses being funded are incurred. The Company classifies government grants received under these arrangements as a reduction to the related research and development expense incurred. The Company analyzes each arrangement on a case-by-case basis. For the years ended December 31, 2020 and 2019, the Company recognized $0.7 million and $0.6 million, respectively, as a reduction of research and development expense related to government grant arrangements. There were no grant proceeds recognized for the year ended December 31, 2018.

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.

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 surrenderable 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 $9.1 million, $6.7 million and $5.9 million during the years ended December 31, 2020, 2019 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, the measurement date for non-employee awards is the date of grant. The compensation expense is then recognized over the requisite service period, which is the vesting period of the respective award, without subsequent changes in the fair value of the award.

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.

Prior to the IPO, the Company utilized significant estimates and assumptions in determining the fair value of its common stock. 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' equity (deficit) that result from transactions and economic events other than those with shareholders. The Company records unrealized gains and losses related to foreign currency translation as a component of other comprehensive loss in the consolidated statements of operations and comprehensive loss.

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 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.

Prior to the Company's IPO, convertible preferred shares contractually entitled 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 reported a net loss, such losses were not allocated to such preferred securities. In periods in which the Company reported 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 Issued Accounting Pronouncements

In June 2016, the FASB issued ASU No. 2016-13, *Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). ASU 2016-13 will change how companies account for credit losses for most financial assets and certain other instruments. For trade receivables, loans and held-to-maturity debt securities, companies will be required to recognize an allowance for credit losses rather than reducing the carrying value of the asset. In November 2019, the FASB issued ASU No. 2019-10, *Financial Instruments — Credit Losses (Topic 326), Derivatives and Hedging (Topic 815), and Leases (Topic 842): Effective Dates* to amend the effective date of ASU 2016-13, for entities eligible to be "smaller reporting companies," as defined by the SEC, to be effective for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. Early adoption is permitted. The Company has not elected to early adopt ASU No. 2016-13. The Company is currently evaluating the potential impact that the adoption of ASU 2016-13 will have on the Company's financial position and results of operations.

In 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"). ASU 2019-12 simplifies the accounting for income taxes and will be effective beginning after December 15, 2020. The Company is currently evaluating the impact of ASU 2019-12 in the consolidated financial statements.

3. Fair value of financial assets and liabilities

As of December 31, 2020 and December 31, 2019, there were no assets or liabilities measured at fair value on a recurring basis.

4. Property and equipment, net

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2020	2019
Laboratory equipment	$ 5,583	$ 4,326
Leasehold improvements	383	300
Computer equipment and software	188	229
Furniture and office equipment	195	120
	6,349	4,975
Less: Accumulated depreciation and amortization	(4,032)	(2,683)
	$ 2,317	$ 2,292

Depreciation expense was $1.3 million, $1.0 million and $0.7 million for the years ended December 31, 2020, 2019 and 2018, respectively.

5. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31,	
	2020	2019
Accrued employee compensation and benefits	$ 4,390	$ 2,515
Accrued external research and development expenses	4,428	2,055
Accrued professional fees	1,759	867
Current portion of operating lease liabilities	844	640
Other	208	67
	$ 11,629	$ 6,144

6. Long-term debt

On September 30, 2020 (the “Closing Date”), Bicycle Therapeutics plc and its subsidiaries (the “Borrowers”) entered into the Loan Agreement with Hercules, which provided for aggregate maximum borrowings of up to $40.0 million, consisting of (i) a term loan of $15.0 million, which was funded on the Closing Date, (ii) subject to customary conditions, an additional term loan of up to $15.0 million available from the Closing Date through March 15, 2021, and (iii) subject to the Borrowers achieving certain performance milestones and satisfying customary conditions and available until March 15, 2022, an additional term loan of $10.0 million.

Borrowings under the Loan Agreement bear interest at an annual rate equal to the greater of (i) 8.85% or (ii) 5.60% plus the Wall Street Journal prime rate. Payments under the Loan Agreement are interest-only until the first principal payment is due on November 1, 2022 (or if the Borrowers achieve the certain performance milestones, the interest only period is extended with the first principal payment due on May 1, 2023), followed by equal monthly payments of principal and interest through the scheduled maturity date on October 1, 2024 (the “Maturity Date”). At the Borrowers’ option, the Borrowers may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to (i) 2.0% of the principal amount outstanding if the prepayment occurs during the first year following the Closing Date, (ii) 1.5% of the principal amount outstanding if the prepayment occurs during the second year following the Closing Date, and (iii) 1.0% of the principal amount outstanding if the prepayment occurs thereafter but prior to the Maturity Date. The Loan Agreement also provides for an end of term charge (the “End of Term Charge”), payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid.

Borrowings under the Loan Agreement are collateralized by substantially all of the Borrower’s personal property and other assets, other than their intellectual property. Hercules has a perfected first-priority security interest in certain cash accounts. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control, as defined in the agreement. There are no financial covenants. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, cross acceleration to third-party indebtedness, certain events relating to bankruptcy or insolvency, and the occurrence of certain events that could reasonably be expected to have a material adverse effect. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal and interest payments due, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement. The Company has determined that the risk of subjective acceleration under the material adverse events clause is not probable and therefore has classified the outstanding principal in long-term liabilities based on scheduled principal payments.

The Company incurred fees and transaction costs totaling $0.6 million associated with the initial term loan, which are recorded as a reduction to the carrying value of the long-term debt in the consolidated balance sheets. The fees, transaction costs, and the End of Term Charge are amortized to interest expense through the Maturity Date using the effective interest method. The effective interest rate was 12.2% at December 31, 2020. The Company assessed all terms and features of the Loan Agreement in order to identify any potential embedded features that would require bifurcation. As part of this analysis, the Company assessed the economic characteristics and risks of the debt. The

Company determined that all features of the Loan Agreement are clearly and closely associated with a debt host and, as such, do not require separate accounting as a derivative liability. Interest expense for the year ended December 31, 2020 related to the Loan Agreement with Hercules was $0.4 million.

Long-term debt consisted of the following (in thousands):

	December 31, 2020
Term loan payable	$ 15,000
End of term charge	58
Unamortized debt issuance costs	(553)
Carrying value of term loan	$ 14,505

Future principal payments, including the End of Term Charge, are as follows (in thousands):

Year Ending December 31,	
2021	$ —
2022	1,148
2023	7,262
2024	7,340
Total	$ 15,750

In addition, the Company granted Hercules the right to purchase up to an aggregate of $2.0 million of the Company's equity securities sold to investors in certain subsequent financing upon the same terms and conditions afforded to such other investors. On October 1, 2020, Hercules purchased 98,100 ADSs, representing the same number of ordinary shares, at a public offering price of $19.05 per ADS ordinary share pursuant to the Sales Agreement, resulting in net proceeds of $1.8 million.

7. Convertible preferred shares

Prior to the IPO, the Company issued Series A Preferred Shares, Series B1 Preferred Shares, and Series B2 convertible preferred shares ("Series B2 Preferred Shares") (collectively the "Preferred Shares").

On December 20, 2018, the Company completed the issuance 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"). On January 3, 2019, the Company completed the issuance of 80,385 Series B2 Preferred Shares at a price per share of £15.55, for gross cash proceeds of $1.6 million.

In May 2019, the Company's board of directors and shareholders approved the reorganization of the Company's share capital by issuing ordinary shares as bonus shares to each holder of ordinary shares on the basis of 1.429 bonus shares for each ordinary share in issue (having the effect of a one for 1.429 share split (without having an impact on the nominal value of the ordinary shares)), which was effected on May 13, 2019 (the "Share Capital Reorganization"). All issued and outstanding share and per share amounts of ordinary shares and share options included in the accompanying consolidated financial statements have been adjusted to reflect this share split for all periods presented. Upon the closing of the IPO in May 2019, all of the Company's outstanding convertible preferred shares automatically converted into 11,647,529 ordinary shares on a 1:1.429 basis.

8. Warrant liability

In 2017, the Company issued 200,000 warrants to subscribe for Series A Preferred Shares, at £0.01 each. In conjunction with the completion of the IPO, 120,000 warrants to subscribe for Series A Preferred Shares were exercised for 171,480 ordinary shares. The remaining 80,000 warrants, which were exercisable into 114,320 ordinary shares following the completion of the IPO, as adjusted for the impact of the Share Capital Reorganization (Note 7), were exercised in 2019 and 2020.

In addition, in 2017, the Company issued a total of 743,287 warrants to subscribe for Series B1 Preferred Shares, with an exercise price of £0.01, in conjunction with the issuance of 3,947,198 Series B1 Preferred Shares.

On March 7, 2019, the holders of the warrants to subscribe for Series B1 Preferred Shares agreed that 50% of the warrants would be exercised in conjunction with the IPO and 50% of the warrants would expire. The modification resulted in an incremental change in fair value of $0.1 million, which is included in other expense for the year ended December 31, 2019. On May 28, 2019, in conjunction with the completion of the IPO, all Series B1 Preferred share warrants were exercised for 531,077 ordinary shares, as adjusted for the impact of the Share Capital Reorganization (Note 7).

Prior to the completion of the IPO, the warrants to subscribe for Series A and Series B1 Preferred Shares were recorded as a liability and remeasured to fair value at each reporting date. Changes in the fair value of the warrant liability were recognized as other expense, net in the consolidated statements of operations and comprehensive loss. Upon the closing of the IPO on May 28, 2019, warrants that were not exercised in conjunction with the IPO automatically became warrants to subscribe for ordinary shares, and meet the criteria to be classified as shareholders' equity (deficit). As such, following the final remeasurement on May 28, 2019, the Company reclassified the carrying value of the warrant liability to additional paid-in-capital in the consolidated balance sheet.

9. 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. Holders of ADSs are not treated as holders of the Company's 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 the Company's ordinary shares, other than the rights that they have pursuant to the deposit agreement with the depositary. As of December 31, 2020 and 2019, the Company has not declared any dividends.

As of December 31, 2020 and 2019, the Company's authorized capital share consisted of 31,995,653 ordinary shares, with a nominal value of £0.01 per share.

10. Share-based compensation

Employee incentive pool

2020 Share Option Plan

In June 2020, the Company's shareholders approved the Bicycle Therapeutics plc 2020 Equity Incentive Plan (the "2020 Plan"), under which the Company may grant market value options, market value stock appreciation rights or restricted shares, restricted share units, performance restricted share units and other share-based awards to the Company's employees. The Company's non-employee directors and consultants are eligible to receive awards under the 2020 Non-Employee Sub-Plan to the 2020 Plan. All awards under the 2020 Plan, including the 2020 Non-Employee Sub-Plan, will be set forth in award agreements, which will detail the terms and conditions of awards, including any applicable vesting and payment terms, change of control provisions and post-termination exercise limitations. In the event of a change of control of the Company, as defined in the 2020 Plan, any outstanding awards under the 2020 Plan will vest in full immediately prior to such change of control. Share options issued under the 2020 Share Option Plan have a 10 year contractual life, and generally vest over either a three year service period for non-employee directors, or 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 installments for employees and consultants. Certain options granted to the Company's non-employee directors vest immediately upon grant.

The Company initially reserved up to 4,773,557 ordinary shares for future issuance under the 2020 Plan, representing 574,679 new shares, 544,866 shares that remained available for future issuance under the Company's 2019 Share Option Plan (the "2019 Plan") immediately prior to the effectiveness of the 2020 Plan and up to 3,654,012 shares

subject to options that were granted under the 2019 Plan and that were granted pursuant to option contracts granted prior to the Company's IPO, in each case that expire, terminate, are forfeited or otherwise not issued from time to time, if any. Additionally, the number of ordinary shares reserved for issuance pursuant to the 2020 Plan will automatically increase on the first day of January of each year, commencing on January 1, 2021, in an amount equal to 5% of the total number of the Company's ordinary shares outstanding on the last day of the preceding year, or a lesser number of shares determined by the Company's board of directors. As of December 31, 2020, there were 4,699,470 shares available for issuance and options to purchase 196,550 shares outstanding under the 2020 Plan. The number of shares reserved for issuance under the 2020 Plan was increased by 1,054,727 shares effective January 1, 2021.

2019 Share Option Plan

In May 2019, the Company adopted the 2019 Plan, which became effective in conjunction with the IPO. As of December 31, 2020, there were 2,594,277 options to purchase ordinary shares outstanding under the 2019 Plan. In conjunction with the adoption of the 2020 Plan, all shares available for future issuance under the 2019 Plan as of June 29, 2020 became available for issuance under the 2020 Plan and the Company ceased making awards under the 2019 Plan. The 2020 Plan is the successor of the 2019 Plan.

Share options previously issued under the 2019 Share Option Plan have a 10 year contractual life, and generally either vest monthly over a three year service period, or 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 installments. Certain awards granted to the Company's non-employee directors were fully vested on the date of grant. The exercise price of share options issued under the 2019 Share Option Plan is not less than the fair value of ordinary shares as of the date of grant.

Pre-IPO Share Options and restricted shares

Prior to the IPO, the Company issued share options and ordinary shares, as administered by the board of directors, using standardized share option and share subscription agreements. To the extent such incentives were 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. Upon completion of the IPO, shares reserved for future issuance outside of the 2019 Share Option Plan were cancelled.

Options granted, as well as restricted shares granted as employee incentives prior to the IPO, 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 installments and expire no later than 10 years from the date of grant.

Certain equity awards were issued in 2017 and 2018 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 issued to U.K. employees prior to the IPO generally had an exercise price of £0.01 per share. The exercise price for share options granted to U.S. employees, had an exercise price that was not less than the fair value of ordinary shares as determined by the board of directors as of the date of grant. Prior to the IPO, the Company's board of directors valued 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.

Employee Share Purchase Plan ("ESPP")

In May 2019, the Company adopted the 2019 Employee Stock Purchase Plan (the "ESPP"), which became effective in conjunction with the IPO. The Company initially reserved 215,000 ordinary shares for future issuance under this plan. 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)

1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 430,000 ordinary shares or (iii) such lesser number of shares as determined by the Compensation Committee. 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. As of December 31, 2020, the total number of shares available for issuance under the ESPP was 394,937 ordinary shares. The number of shares reserved for issuance under the ESPP was increased by 210,945 shares effective January 1, 2021.

Once the Company commences offerings under the ESPP, each offering to the employees to purchase shares under the ESPP will begin on each June 1 and December 1 and will end on the following November 30 and May 31, respectively. On each purchase date, which will fall on the last date of each offering period, ESPP participants will purchase ordinary shares at a price per share equal to 85% of the lesser of (1) the fair market value of the shares on the offering date or (2) the fair market value of the shares on the purchase date. The occurrence and duration of offering periods under the ESPP are subject to the determinations of the Company's compensation committee. As of December 31, 2020, there have been no offering periods to employees under ESPP.

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,		
	2020	2019	2018
Research and development expenses	$ 2,603	$ 1,286	$ 513
General and administrative expenses	3,911	1,797	510
	$ 6,514	$ 3,083	$ 1,023

Share options

The following table summarizes the Company's option activity since December 31, 2019:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2019	2,634,346	$ 9.57	9.04	$ 6,107
Granted	1,370,984	12.00	—	—
Exercised	(79,158)	3.42	—	—
Forfeited	(189,509)	11.10	—	—
Outstanding as of December 31, 2020	3,736,663	$ 10.51	8.54	$ 27,553
Vested and expected to vest as of December 31, 2020	3,736,663	$ 10.51	8.54	$ 27,553
Options exercisable as of December 31, 2020	1,518,721	$ 8.81	7.90	$ 13,729

The weighted average grant-date fair value of share options granted during the years ended December 31, 2020, 2019 and 2018 was $7.87 per share, $6.07 per share and $3.73 per share, respectively.

For the years ended December 31, 2020, 2019 and 2018, the Company recorded share-based compensation expense for share options granted of $6.5 million, $2.7 million and $0.8 million, respectively. Expense for non-employee consultants for the years ended December 31, 2020, 2019 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, 2020, 2019 and 2018 was $1.3 million, $0.6 million and $23,000 respectively.

During the year ended December 31, 2018, the Company granted share options to purchase 70,875 ordinary shares with performance based vesting, 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. 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 $0.1 million, $0.1 million and $0.7 million, during the years ended December 31, 2020, 2019 and 2018, respectively, related to awards with performance based vesting, which includes the acceleration of vesting expense.

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,		
	2020	2019	2018
Risk-free interest rate	1.3 %	2.1 %	2.7 %
Expected volatility	74.8 %	77.9 %	78.6 %
Expected dividend yield	—	—	—
Expected term (in years)	5.98	5.86	6.07

As of December 31, 2020, total unrecognized compensation expense related to the unvested employee and director share-based awards was $13.7 million, which is expected to be recognized over a weighted average period of 2.5 years.

Restricted shares

Prior to the IPO, the Company granted restricted shares with service-based vesting conditions. In conjunction with the IPO in May 2019, the board of directors modified the vesting terms to accelerate vesting for all then unvested restricted shares. As a result, the Company recorded $0.2 million of expense upon the modification of the restricted shares during the year ended December 31, 2019.

For the years ended December 31, 2020, 2019 and 2018, the Company recorded share-based compensation of zero, $0.4 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, 2020, 2019 and 2018, based on estimated fair values of the ordinary shares underlying the restricted share awards on the day of vesting, was zero, $0.7 million and $0.2 million, respectively. As of December 31, 2020, there was no unrecognized compensation cost related to the unvested employee and director restricted share awards.

11. Significant Agreements

For the years ended December 31, 2020, 2019 and 2018, the Company had collaboration agreements with Genentech, AstraZeneca, Sanofi, Oxurion and DDF. 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,		
	2020	2019	2018
Collaboration revenues			
AstraZeneca	$ 2,696	$ 1,683	$ 1,386
Sanofi	—	10,724	4,007
Oxurion	2,362	—	1,743
Dementia Discovery Fund	436	394	—
Material transfer agreement	—	1,000	—
Genentech	4,896	—	—
Total collaboration revenues	$ 10,390	$ 13,801	$ 7,136

Genentech Collaboration Agreement

On February 21, 2020, the Company entered into a Discovery Collaboration and License Agreement (the "Genentech Collaboration Agreement") with Genentech. The collaboration is focused on the discovery and development of *Bicycle* peptides directed to biological targets selected by Genentech and aimed at developing up to four potential development candidates against multiple immuno-oncology targets suitable for Genentech to advance into further development and commercialization.

Under the terms of the Genentech Collaboration Agreement, Bicycle received a $30.0 million upfront, non-refundable payment. The initial discovery and optimization activities will focus on utilizing Bicycle's phage screening technology to identify product candidates aimed at two immuno-oncology targets ("Genentech Collaboration Programs"), which may also include additional discovery and optimization of *Bicycles* as a targeting elements for each Genentech Collaboration Program (each a "Targeting Arm"). Genentech has the option to nominate up to two additional immuno-oncology targets (each, an "Expansion Option"), which may also include an additional Targeting Arm for each Expansion Option, as additional Genentech Collaboration Programs during a specified period following completion of certain activities under an agreed research plan. If Genentech exercises one or more Expansion Options, Genentech will pay to the Company an expansion fee of $10.0 million per Expansion Option. Genentech also has rights, under certain limited circumstances, to select an alternative target to be the subject of a Genentech Collaboration Program, in some cases subject to payment of an additional target selection fee.

If Genentech elects for Bicycle to perform discovery and optimization services for certain Targeting Arms, the Company will be entitled to receive an additional advance payment for the additional research services. Genentech exercised its right to select a Targeting Arm for one of the initial Genentech Collaboration Programs at the inception of the arrangement, which entitled the Company to an additional $1.0 million payment. If a Targeting Arm achieves specified criteria in accordance with the research plan, Genentech will be required to pay a further specified amount in the low single digit millions for each such Targeting Arm as consideration for the additional services to be provided.

Bicycle granted to Genentech a non-exclusive research license under Bicycle's intellectual property solely to enable Genentech to perform any activities under the agreement. The activities under the Genentech Collaboration Agreement are governed by a joint research committee ("JRC") with representatives from each of the Company and Genentech. The JRC will oversee, review and recommend direction of each Genentech Collaboration Program, achievement of development criteria, and variations of or modifications to the research plans.

After the Company performs the initial discovery and optimization activities in accordance with an agreed research plan and achieves specified criteria, Genentech will have the option to have the Company perform initial pre-

clinical development and optimization activities in exchange for an additional specified milestone payment in the mid-single digit millions for each Genentech Collaboration Program (the "LSR Go Option"). Upon completion of such initial pre-clinical development and optimization activities for each Genentech Collaboration Program, Genentech will have the option to obtain an exclusive license to exploit any compound developed under such Genentech Collaboration Program in exchange for an additional specified payment in the mid to high single digit millions for each of the initial two Genentech Collaboration Programs and each of the two Expansion Option Genentech Collaboration Programs (the "Dev Go Option").

On a Genentech Collaboration Program by Genentech Collaboration Program basis, if Genentech elects to obtain exclusive development and commercialization rights and pays the applicable LSR Go Option and Dev Go Option fees, Genentech will be required to make milestone payments to the Company upon the achievement of specified development, regulatory, and initial commercialization milestones for products arising from each collaboration program, totaling up to $200.0 million. Specifically, the Company is eligible for additional development milestones totaling up to $65.0 million, as well as regulatory milestones of up to $135.0 million for each collaboration program. In addition, the Company is also eligible to receive up to $200.0 million in sales milestone payments on a Genentech Collaboration Program-by-Genentech Collaboration Program basis. In addition, to the extent any of the product candidates covered by the licenses conveyed to Genentech are commercialized, the Company would be entitled to receive tiered royalty payments on net sales at percentages ranging from the mid-single to low double-digits, subject to certain standard reductions and offsets. Royalties will be payable, on a product by product and country by country basis, until the later of the expiration of specified licensed patents covering such product in such country, or ten years from first commercial sale of such product in such country.

Accounting Analysis

Upon the execution of the Genentech Collaboration Agreement, the Company has identified the following performance obligations:

(i) Research license, and the related research and development and preclinical services through LSR Go for a first Genentech Collaboration Program (Genentech Collaboration Program #1);

(ii) Research license, and the related research and development and preclinical services through LSR Go for a second Genentech Collaboration Program with a specified Targeting Arm (Genentech Collaboration Program #2);

(iii) Material right associated with an option to a specified Targeting Arm for Genentech Collaboration Program #1;

(iv) Two material rights associated with the LSR Go Option for Genentech Collaboration Program #1 and Genentech Collaboration Program #2, which includes research services to be provided through the Dev Go Option and an option to receive an exclusive license;

(v) Material rights associated with certain limited substitution rights with respect to a limited number of collaboration targets;

(vi) Two material rights related to each Genentech Expansion Option, which upon exercise include the services for an additional immuno-oncology target through the LSR Go Option, an LSR Go Option which includes the services to be provided through the Dev Go Option and an option to receive an exclusive license, limited substitution rights, and an option to select a specified Targeting Arm.

The Company concluded that certain substitution rights that require the payment of additional consideration, which approximate the standalone selling price of the underlying services to be provided, do not provide the customer with a material right and therefore, are not considered as performance obligations and are accounted for as separate contracts upon exercise, if ever. 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 as Genentech 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. In addition, the Company concluded that the Dev Go Option is not distinct or separately exercisable from the LSR Go Option, as the customer cannot benefit from the Dev Go Option unless and until the LSR Go Option is exercised.

In assessing whether the various options under the Genentech Collaboration Agreement represent material rights, the Company considered the additional consideration the Company would be entitled to upon the option exercise, the standalone selling price of the underlying goods, services, and additional options. For the material rights identified above the Company concluded that each of the options provided Genentech with a discount that it otherwise would not have received.

The total transaction price was initially determined to be $31.0 million, consisting of the $30.0 million upfront fee and the additional $1.0 million for Genentech's selection of a new Targeting Arm at inception. 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 options by Genentech and subsequent milestones are excluded from the transaction price as they relate to option fees and milestones that can only be achieved subsequent to the exercise of an option. In addition, other variable consideration for development milestones not subject to option exercises was fully constrained, as a result of the uncertainty regarding whether any of the milestones will be achieved.

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 Genentech Collaboration Programs was 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 for 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 Genentech would pay to exercise the options, the estimated value of the underlying goods and services, and the probability that Genentech would exercise the option and any underlying options. 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
Genentech Collaboration Program #1 Performance Obligation	$ 3,775
Genentech Collaboration Program #2 Performance Obligation	7,550
Specified Targeting Arm Material Right Arm for Genentech Collaboration Program #1	330
Two material rights associated with the LSR Go Option for Collaboration Programs #1 and #2	11,650
Material rights associated with limited substitution rights	1,115
Two material rights for Expansion Options	6,580
	$ 31,000

The Company will recognize revenue related to amounts allocated to the Genentech Collaboration Program #1 and #2 Performance 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 efforts and external costs incurred to date as a percentage of total full-time equivalent time and external 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 respective option. The Company anticipates that the Genentech Collaboration Performance Program #1 and #2 obligations will be performed over a period of approximately two years, and the material rights will be exercised or expire within approximately four years from contract execution.

During the year ended December 31, 2020, the Company recognized revenue of $4.9 million, and as of December 31, 2020, the Company recorded $27.6 million of deferred revenue in connection with the Genentech Collaboration Agreement.

Dementia Discovery Fund Agreement

In May 2019, the Company entered into a collaboration with the Dementia Discovery Fund ("DDF") to use Bicycle technology for the discovery and development of novel therapeutics for dementia (the "DDF Collaboration Agreement"). In October 2019, the collaboration with DDF was expanded to include Oxford University's Oxford Drug Discovery Institute (ODDI). Under the terms of the DDF Collaboration Agreement, the Company and DDF will collaborate to identify *Bicycles* that bind to clinically validated dementia targets (the "DDF Research Plan"). The Company is obligated to use commercially reasonable efforts to perform research activities under the DDF Research Plan. DDF shall not be directly engaged in the conduct of any research activities under the arrangement. ODDI will then profile these *Bicycles* in a range of target-specific and disease-focused assays to determine their therapeutic potential. The activities under the DDF Collaboration Agreement will be governed by a project advisory panel, composed of two representatives from the Company and DDF. The Research Advisory Panel will oversee, review and recommend direction for the Research Plans and variations of or modifications of research plans.

The Company received an upfront payment of $1.1 million in May 2019. The Company may receive up to an additional $0.7 million, upon achievement of certain milestones such as the identification of lead *Bicycle* candidates with a certain affinity, which would be used to fund additional research and development services including lead optimization.

Intellectual property created by the collaboration shall be owned by the Company, and background intellectual property improvements shall be owned by the party from whose background intellectual property they exclusively relate. If promising lead compounds are identified, the Company, ODDI and DDF have the option (the "DDF Option") to establish a jointly owned new company ("NewCo") to advance the compounds through further development towards commercialization. NewCo will receive a royalty and milestone-bearing assignment and license of intellectual property from the Company for this purpose. The DDF Option is exercisable at any time until 90 days following the completion of the Research Plan and delivery of a final report. If DDF does not elect to exercise the DDF Option during the Option period, then DDF shall have no right in the collaboration intellectual property. NewCo will initially be owned 66% by the Company and 34% by DDF; however, the Company shall not be entitled to exercise more than 50% of the total voting rights related to its ownership interests. After completion of the DDF Option exercise, for a period of two years following the option exercise, NewCo shall have the right to initiate a new research program to develop up to three additional dementia targets, on a target by target basis, and the Company will be entitled to charge NewCo an agreed upon FTE rate for peptide screening and optimization for the active targets.

Either party may terminate the DDF Collaboration Agreement upon providing not less than 60 days written notice. A party may terminate the DDF Collaboration Agreement with immediate effect without notice if at any time the other party files for protection under bankruptcy or insolvency laws, makes an arrangement for the benefit of creditors, appoints a receiver, administrator, manager or trustee over its property, proposes a written agreement of composition or extension of its debts, is a party to any dissolution, winding-up or liquidation, or is in material breach that has not been remedied.

Accounting Analysis

The Company identified a single performance obligation associated with the performance of research and development services under the DDF Research Plan.

The Company concluded that the DDF Option is an immaterial obligation at the inception of the arrangement, as it represents a right to acquire shares of NewCo that have *de minimis* value. The DDF Option also does not contain a material right that otherwise would not have been received. The Company's participation in the Research Advisory Panel was assessed as immaterial in the context of the contract. In addition, the Company concluded that the option for NewCo to obtain additional peptide screening and optimization services is not an obligation at the inception of the

arrangement, as they are optional services and the amount that will be paid for the services 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 initially determined to be $1.1 million, consisting of the upfront payment for research and development funding. The Company may receive additional milestone payments during the DDF Research Plan, as well as for research and development services for additional targets following the exercise of DDF Option. These variable amounts are excluded from the transaction price as they relate to fees that can only be achieved subsequent to the exercise of an option, and therefore are treated as separate contracts.

The transaction price was allocated to the single performance obligation of research and development services. The Company will recognize revenue as the underlying services are performed using a proportional performance model, over the period of service using input-based measurements of total costs, including total full-time equivalent effort incurred to date as a percentage of total costs expected, which best reflects the progress towards satisfaction of the performance obligation.

For both of the years ended December 31, 2020 and 2019, the Company recognized $0.4 million of revenue. In December 2020, the Company received a payment of $0.5 million upon the achievement of specified scientific criteria. The Company concluded that the payment represents consideration for a single performance obligation to perform lead optimization activities, and will recognize revenue as the underlying services are performed using a proportional performance model, over the period of service using input based measurements of total costs, including total full time equivalent effort incurred to date as a percentage of total costs expected, which best reflects the progress towards satisfaction of the performance obligation. The Company recorded deferred revenue of $0.8 million and $0.7 million for the years ended December 31, 2020 and 2019, respectively, related to its collaboration with DDF.

Sanofi Collaboration Agreement (formerly Bioverativ)

Summary of Agreement

In August 2017, the Company entered into a Collaboration Agreement with Bioverativ Inc., which was acquired by Sanofi in March 2018 (“Sanofi”). Under the collaboration agreement with Sanofi (the “Sanofi Collaboration Agreement”), the Company provided research and development services focused on up to three collaboration programs; (i) Sickle cell disease, (ii) Hemophilia, and (iii) and had an option to a third program that expired unexercised. The Company used its bicyclic peptide screening platform to perform research and development services for the programs and Sanofi had 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.

Sanofi could terminate the Sanofi 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 identified four performance obligations associated with the Sanofi Collaboration Agreement, consisting of (i) Sickle Cell Research and Related Services, (ii) Hemophilia Research License and Related Services, (iii) a Sickle Cell License Option Material Right, and (iv) a Hemophilia License Option Material Right. The total transaction price consisted of a $10.0 million upfront payment and a non-refundable research and development funding of $4.2 million. The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The Company recognized revenue related to amounts allocated to the Sickle Cell and Hemophilia Research License and Related Services obligations as the underlying services were 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 reflected the progress towards satisfaction of the performance obligation. The amount allocated to the material rights was recorded as deferred revenue, and the Company commenced revenue recognition when the underlying option was exercised or upon expiry of the option.

On March 28, 2019, Sanofi notified the Company that it would not exercise the Sickle Cell License Option. In addition, the collaboration with Sanofi was terminated effective October 23, 2019. As a result, deferred revenue related to amounts allocated to the Sickle Cell License Option Material Right of $5.3 million and the Hemophilia License Option Material Right of $4.7 were recognized during the year ended December 31, 2019.

For the years ended December 31, 2020, 2019 and 2018, the Company recognized zero, $10.7 million, and $4.0 million, respectively, of collaboration revenue related to its collaboration with Sanofi. As of December 31, 2020 and 2019, the Company recorded zero deferred revenue related to its collaboration with Sanofi.

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 had an option to nominate up to four additional targets at any point up to the second anniversary of the agreement ("Additional Four Target Option").

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.

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.

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 at the inception of the arrangement:

(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 was not a material right, as the option did 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 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, and was raised to $2.0 million when both programs were extended, 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 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 recognized revenue related to amounts allocated to the Research License and Related Services as the underlying services were 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. In October 2020, AstraZeneca terminated the collaboration activities related to the second target. No revenue was recognized upon termination.

For the years ended December 31, 2020, 2019 and 2018 the Company recognized zero, $0.2 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, 2020 and 2019, the Company recorded zero deferred revenue in connection with the 2016 AstraZeneca Collaboration Agreement. In March 2021, AstraZeneca terminated the collaboration activities related to the first target.

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. 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 the Company as for the other products developed under the AstraZeneca Collaboration Agreement.

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 were not performance obligations at the inception of the arrangement, 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 initially 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 selling prices for each Research License and Related Services obligation was 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 was 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 recognizes 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 commences revenue

recognition upon exercise of or upon expiry of the option. The optional future research license and the related research and development services related to the fourth, fifth and sixth targets reflect their standalone selling prices and do not provide the customer with a material right and, therefore, are not considered performance obligations and are accounted for as separate contracts. In June 2019, AstraZeneca selected a replacement target for the third target, and as such a new Research Term was started related to the Target Three Research License and Related Services. The total transaction price under the arrangement increased to $6.3 million for the additional research and development funding to be received. During the year ended December 31, 2019, the Company commenced research and development services related to the fourth and fifth targets. During the year ended December 31, 2020, the Company commenced research and development services related to the sixth target. In October 2020, AstraZeneca terminated the collaboration activities related to the third target. As a result, deferred revenue related to the amount allocated to the Target 3 Material Right of $1.5 million was recognized during the year ended December 31, 2020.

For the year ended December 31, 2020, 2019 and 2018, the Company recognized $2.7 million, $1.5 million, and $0.4 million, respectively, of revenue related to the Target Three Research License and Related Service, and research and development services for the fourth, fifth and sixth targets related to the May 2018 AstraZeneca Option Exercise. As of December 31, 2020 and 2019, the Company recorded $3.8 million and $4.9 million, respectively, of deferred revenue in connection with the May 2018 AstraZeneca Option Exercise and related contracts.

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 was 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 granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Company is eligible to receive up to €8.3 million upon the achievement of specified research, development, regulatory and commercial events and research and development milestones, of which €1.8 million has been received as of December 31, 2020. 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 the European Union 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.

In November 2017, the parties executed the First Deed of Amendment to the Oxurion Collaboration Agreement ("First Amendment"), which confirmed that THR-149 was selected as a development compound. 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 performed work under Stage I of the research plan, which was funded at a specified FTE rate, plus any direct out of pocket expenses, and Oxurion is 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.

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.

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 were fully recognized prior to January 1, 2016. Under the First Amendment, the Company identified a single performance obligation associated with the performance of research services associated with Stage I of the research plan, which was 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. As of December 31, 2018, the research services under the First Amendment were complete. During the year ended December 31, 2018, the Company achieved a milestone related to the initiation of a Phase I clinical study and included $1.2 million in the transaction price, which was recognized in revenue during the year ended December 31, 2018, as there were no remaining performance obligations. During the year ended December 31, 2020, the Company achieved a milestone related to the initiation of a Phase II clinical trial and included $2.4 million in the transaction price, which was recognized in revenue during the year ended December 31, 2020, as there were no remaining performance obligations. No other unpaid development or regulatory milestones have been included in the transaction price, as all milestones are not considered probable at December 31, 2020 and December 31, 2019. For the years ended December 31, 2020, 2019 and 2018, the Company recognized $2.4 million, zero, and $1.7 million, respectively, of revenue related to its agreements with Oxurion.

Evaluation and Option Agreement

On December 31, 2020 (the "Effective Date"), the Company entered into the Evaluation and Option Agreement. Under the terms of the Evaluation and Option Agreement, the Company agreed to transfer *Bicycles* (the "Option Materials") to the recipient in order to evaluate a particular application of the Company's technology platform for a period of up to four months (the "Evaluation Period"). The recipient agreed to pay, a non-refundable, $3.0 million option fee within five business days after the Effective Date. The Evaluation Period may be extended by up to two months by written notice and the payment of an extension fee of $2.0 million.

At any point during the term of the agreement and continuing through 30 days after the expiration of the Evaluation Period, the recipient has the option to obtain an exclusive license to the Company's intellectual property for the purpose of continued research, development, manufacture and commercialization of products within a particular application of the Company's platform technology. The recipient may terminate the agreement for convenience upon 30 days written notice to the Company. The upfront payment of $3.0 million and extension payment of $2.0 million are fully creditable against any upfront payment to be paid upon the execution of a license agreement.

For the year ended December 31, 2020, the Company recognized zero revenue and $3.0 million of deferred revenue related to the Evaluation and Option Agreement. The Company concluded that the transaction price is $3.0 million, and all other amounts are excluded from the transaction price as they relate to fees that can only be achieved subsequent to the exercise of an option. The transaction price was allocated to the single performance obligation, an option to enter into a future license agreement which is a material right, as the Evaluation and Option Agreement payment is creditable against the upfront payments to paid for a license agreement. The Company will begin to recognize revenue when the option is exercised or when the option expires.

Material Transfer Agreement

In October 2018, the Company entered into a Materials Transfer Agreement. Under the terms of the agreement, the Company agreed to transfer bicyclic peptides (the "Materials") to the recipient for the purpose of testing the materials in order to evaluate the Company's technology platform. The recipient agreed to pay the Company $1.0 million within 30 business days after receipt of the materials and related data package, which was paid to the Company in May 2019. For the years ended December 31, 2020 and 2019, the Company recognized zero and $1.0 million, respectively, of revenue related to its Materials Transfer Agreement, as the Company concluded that the recipient has the ability to direct the use of and obtain substantially all of the remaining benefit from the Materials upon the delivery of the Materials and the data package.

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.

The following table presents changes in the balances of the Company's contract assets and liabilities (in thousands):

	Beginning Balance January 1, 2020	Additions	Deductions	Impact of Exchange Rates	Ending Balance December 31, 2020
Contract assets	$ —	$ —	$ —	$ —	$ —
Contract liabilities:					
Deferred revenue					
AstraZeneca collaboration deferred revenue	4,913	585	(2,696)	954	3,756
DDF collaboration deferred revenue	744	500	(436)	13	821
Genentech collaboration deferred revenue	—	31,000	(4,896)	1,475	27,579
Evaluation and Option Agreement deferred revenue	—	3,000	—	—	3,000
Total deferred revenue	$ 5,657	$ 35,085	$ (8,028)	$ 2,442	$ 35,156

	Beginning Balance January 1, 2019	Additions	Deductions	Impact of Exchange Rates	Ending Balance December 30, 2019
Contract assets	$ —	$ 149	$ (149)	$ —	$ —
Contract liabilities:					
Deferred revenue					
AstraZeneca collaboration deferred revenue	4,727	58	(35)	163	4,913
Sanofi collaboration deferred revenue	9,908	—	(9,984)	76	—
DDF collaboration deferred revenue	—	1,114	(394)	24	744
Total deferred revenue	$ 14,635	$ 1,172	$ (10,413)	$ 263	$ 5,657

The contract assets represent research and development services which have been performed but have not yet been billed, and are reduced when they are subsequently billed.

The AstraZeneca deferred revenue balance as of December 31, 2020 includes $3.5 million allocated to the 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.

The Genentech deferred revenue balance at December 31, 2020 includes $19.5 million allocated to material rights that will commence revenue recognition when the respective option is exercised or when the option expires.

During the years ended December 31, 2020, 2019 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,		
	2020	2019	2018
Revenue recognized in the period from:			
Revenue recognized based on proportional performance	$ (6,326)	$ (429)	$ (4,472)
Revenue recognized based on expiration of material rights	(1,702)	(9,984)	—
Total	$ (8,028)	$ (10,413)	$ (4,472)

Cancer Research UK

BT1718

On December 13, 2016, the Company entered into a Clinical Trial and License Agreement with Cancer Research Technology Limited ("CRTL"), a wholly owned subsidiary of Cancer Research UK that Cancer Research UK's commercial activities operate through, and Cancer Research UK (the "Cancer Research UK Agreement"). Pursuant to the Cancer Research UK Agreement, as amended in March 2017 and June 2018, Cancer Research UK'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.

Cancer Research UK is responsible for designing, preparing, carrying out and sponsoring the clinical trial at its cost. The Company is responsible for supplying agreed quantities of GMP materials for the trial, the supply of which has been completed. In the event that additional quantities are needed, the Company will provide Cancer Research UK with all reasonable assistance to complete the arrangements necessary for the generation and supply of such additional GMP materials, but Cancer Research UK will be responsible for supplying and paying for such additional quantities of GMP materials.

The Company granted Cancer Research UK a license to its 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 trial, 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 tiered royalties of 70% to 90% of the net revenue depending on the stage of development when the license is granted). The Cancer Research UK 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 single digit percentage on net sales of products developed.

The Cancer Research UK 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). Cancer Research UK 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 trial is terminated by Cancer Research UK prior to the completion of the Phase 1a dose escalation portion of the trial for such reasons or if Cancer Research UK 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, the Company will be obligated to refund fifty percent of the costs and expenses incurred or committed by Cancer Research UK to perform the clinical trial. If the trial is terminated by Cancer Research UK 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 Cancer Research UK 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 the Company is acquired by an

entity that generates its revenue from the sale of tobacco products or is an affiliate of such party, Cancer Research UK 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 CRTL an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company.

The Company concluded that the costs incurred by Cancer Research UK is a liability in accordance with ASC 730, *Research and Developmen*t, as certain payments are not based solely on the results of the research and development having future economic benefit. As such, for the year ended December 31, 2020 and 2019, the Company recorded a liability of $2.6 million and $2.0 million, 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 consolidated statements of operations and comprehensive loss.

BT7401

In December 2019, the Company entered into a clinical trial and license agreement with Cancer Research Technology Limited and Cancer Research UK. Pursuant to the agreement, Cancer Research UK's Centre for Drug Development will fund and sponsor development of BT7401, a multivalent *Bicycle* CD137 agonist, from current preclinical studies through the completion of a Phase IIa trial in patients with advanced solid tumors.

The Company granted to Cancer Research UK a license to the Company's intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial and all necessary preclinical activities to support the trial. The Company retains the right to continue the development of BT7401 during the clinical trial. Upon the completion of the Phase I/IIa clinical trial, 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 contain BT7401 or all the pharmaceutically active parts of BT7401, CRTL may elect to receive an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case the Company will receive tiered royalties of 55% to 80% of the net revenue depending on the stage of development when the license is granted) less certain costs, as defined by the agreement. The BT7401 Cancer Research UK agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash, with an aggregate total value of up to $60.3 million for each licensed product, as well as royalty payments based on a single digit percentage on net sales of products developed, and sublicense royalties to the Cancer Research UK in the low double digit percentage of sublicense income depending on the stage of development when the license is granted.

The BT7401 Cancer Research UK 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 upon written notice by either party prior to the last cycle of treatment has been completed under the clinical trial. If the trial is terminated by the Company prior to the filing of a clinical trial authorization, or by Cancer Research UK for an insolvency event or a material breach by the Company prior to the start of a clinical trial, the Company will reimburse Cancer Research UK for certain costs paid or committed prior to the start of the clinical trial. In such case where the Company is acquired by an entity that generates its revenue from the sale of tobacco products, Cancer Research UK will not be obliged to grant a license to us in respect of the results of the clinical trial and CRTL may elect to receive an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company. The Company concluded that the BT7401 Cancer Research UK arrangement does not represent a liability in accordance with ASC 730, *Research and Development*, as the payments are based solely on the results of the research and development having future economic benefit and risk of repayment is substantive and genuine, and as such there was no accounting impact as of and for the year ended December 31, 2020.

12. Income Taxes

The components of net loss before tax provision from income taxes are as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
United Kingdom	$ (52,521)	$ (31,906)	$ (22,229)
United States	787	1,044	(13)
Total	$ (51,734)	$ (30,862)	$ (22,242)

The components of the benefit for income taxes are as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Current income tax provision (benefit)			
Federal	$ (24)	$ 49	$ (25)
State	(27)	61	7
Total current income tax provision (benefit)	(51)	110	(18)
Deferred income tax (benefit) provision			
Federal	(435)	(295)	(167)
State	(238)	(69)	(211)
Total deferred income tax (benefit)	(673)	(364)	(378)
Total benefit from income taxes	$ (724)	$ (254)	$ (396)

A reconciliation of the benefit for income taxes computed at the statutory income tax rate to the benefit for income taxes as reflected in the financial statement is as follows:

	Year Ended December 31,		
	2020	2019	2018
Benefit for income taxes at statutory rate	19 %	19 %	19 %
(Decreases) increases resulting from:			
Federal tax credits	0.9 %	1.3 %	1.1 %
Change in valuation allowance	(15.4)%	(8.0)%	(7.2)%
Net losses surrendered for research credit	(6.2)%	(5.3)%	(3.7)%
Preferred share warrants	— %	(3.3)%	(0.6)%
Impact of statutory rate change	1.8 %	— %	— %
Other	1.3 %	(2.9)%	(6.8)%
Effective income tax rate	1.4 %	0.8 %	1.8 %

Significant components of the Company's current and deferred tax assets at December 31, 2020 and 2019, were as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Deferred tax assets:		
Operating loss carryforwards	$ 13,657	$ 7,082
Research credit carryforwards	1,233	434
Operating lease liability	285	439
Accrued expenses and other	3,050	1,779
Total deferred tax assets	18,225	9,734
Deferred tax liabilities:		
Operating lease right-of-use asset	(270)	(422)
Depreciation & amortization	(311)	(326)
Total deferred tax liabilities	(581)	(748)
Valuation allowance	(16,085)	(8,104)
Net deferred tax assets	$ 1,559	$ 882

During the years ended December 31, 2020, 2019 and 2018, the Company recorded an income tax benefit of $0.7 million, $0.3 million 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 therefore not paid United Kingdom corporation tax. The Company's income tax benefit is mainly the result of deferred tax assets benefited 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.

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 in the year ended December 31, 2020 by $8.0 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, 2020 and 2019.

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.

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, 2020, the Company had $72.0 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, 2020, the Company had $0.8 million and $0.4 million of federal and state research and development credit carryforwards, respectively, that expire at various dates through 2040.

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, 2020 and 2019. There are no amounts of interest or penalties recognized in the consolidated statements 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 2019 and 2018 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 2017 in the U.S. remain open to examination. The Company is currently not under examination by jurisdictions for any tax years.

13. Commitments and Contingencies

Leases

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. Bicycle Therapeutics Inc. has the option to extend for a successive period which is not included in the lease term as it is not reasonably certain that the option will be exercised. In conjunction with the lease agreement, Bicycle Therapeutics Inc. paid a security deposit of $0.2 million as well as prepaid rent of $0.1 million for the first month of the third, fourth, and fifth year of the lease. The deposit is recorded in other assets in the consolidated balance sheets. The Company has recorded a right-of-use asset (inclusive of the impact of prepaid rent) and corresponding lease liability, by calculating the present value of lease payments, discounted at 9%, the incremental borrowing rate, over the lease term.

In October 2017, the Company entered into a lease agreement for office and laboratory space in Building 900, Babraham Research Campus, Cambridge, U.K., 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 is not included in the lease term as it is not reasonably certain that the right will be exercised. Service charges are also payable based on floor area and are estimated to be approximately $0.1 million per year. In conjunction with the 2017 lease agreement, the Company paid a security deposit of $0.6 million, which is recorded in other assets in the consolidated balance sheets. The Company has recorded a right-of-use asset and corresponding lease liability, by calculating the present value of lease payments, discounted at 7.75%, the incremental borrowing rate, over the lease term.

The Company identified and assessed the following significant assumptions in recognizing the right-of-use assets and corresponding lease liabilities:

- *Expected lease term* — The expected lease term includes both contractual lease periods and, when applicable, cancelable option periods when it is reasonably certain that the Company would exercise such options. The Company has not included any option periods in the expected lease term as it is not reasonably certain that the Company will exercise such options.

- *Incremental borrowing rate* — The Company's lease agreements do not provide an implicit rate. As the Company does not have any external borrowings for comparable terms of its leases, the Company estimated the incremental borrowing rate by comparing interest rates available in the market for similar borrowings and third-party quotations.

- *Lease and non-lease components* — In certain cases, the Company is also responsible for certain additional charges for operating costs, including insurance, maintenance, taxes, and other costs incurred, which are billed based on both usage and as a percentage of the Company's share of total square footage. The amounts paid are considered non-lease components. The Company has elected the practical expedient which allows the non-lease components to be combined with the lease components. The payments for other operating costs are considered variable lease cost and are recognized in the period in which the costs are incurred.

The components of the Company's lease expense, which are recorded as a component of research and development expenses and general and administrative expenses in the consolidated statement of operations and comprehensive loss are as follows (in thousands):

	December 31, 2020	December 31, 2019
Operating lease cost	$ 896	$ 900
Variable lease cost	662	390
Total lease cost	$ 1,558	$ 1,290
Weighted-average remaining operating lease term (years)	1.6	2.6
Weighted-average discount rate	8.56 %	8.52 %

Also, as previously disclosed in the Company's 2019 Annual Report on Form 10-K and under the previous lease accounting standard, ASC 840, *Leases*, the Company recorded rent expense of $1.0 million during the year ended December 31, 2018.

Future minimum lease payments under non-cancelable operating leases under ASC 842 as of December 31, 2020 are as follows (in thousands):

Year Ending December 31,	
2021	908
2022	444
2023	—
Present value adjustment	(82)
Total lease liabilities	$ 1,270
Less: current lease liabilities	(844)
Long term lease liabilities	$ 426

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 operating lease payments 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's subsidiary, BicycleRD, filed a complaint in the District Court of the Hague against Pepscan Systems B.V. and its affiliates ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement entered into with Pepscan in 2009 ("PLA"). On November 20, 2020, the Company entered into a settlement and license agreement with Pepscan regarding Bicycle's use of Pepscan's CLIPS peptide technology. The

companies agreed to settle all intellectual property disputes worldwide. Under the terms of the settlement, Bicycle has been granted a license to use CLIPS peptide technology in the development of its product candidates BT1718 and THR-149. Bicycle paid €3 million in November 2020, will pay €1 million on the first anniversary of the date of settlement, and will make additional future milestone payments upon the achievement of development, regulatory and commercial milestones, with an aggregate total value of $92.4 million. The Company recorded $4.7 million of expense related to the settlement and license agreement with Pepscan during the year ended December 31, 2020, and a liability of $1.2 million related to the Pepscan litigation as of December 31, 2020, which is included in current liabilities in the consolidated balance sheet.

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, as amended, the Company will pay a royalty rate in the low single digit percentages on net product sales under the collaborations with Oxurion and AstraZeneca 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.

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 and officers 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, 2020 and 2019.

14. 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,		
	2020	2019	2018
Numerator:			
Net loss attributable to ordinary shareholders	$ (51,010)	$ (30,608)	$ (21,846)
Denominator:			
Weighted average ordinary shares outstanding, basic and diluted	19,145,938	11,045,370	438,862
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.66)	$ (2.77)	$ (49.78)

The Company's potentially dilutive securities, which include share options, warrants to subscribe for ordinary shares, and which prior to the completion of the IPO, included convertible preferred shares, 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,		
	2020	2019	2018
Convertible preferred shares (as converted to ordinary shares)	—	—	11,532,659
Warrants to subscribe for ordinary shares (as adjusted to reflect the impact of the share capital reorganization and issuance of bonus shares (Note 7))**(1)(2)**	—	92,885	1,347,953
Restricted ordinary shares	—	—	83,947
Options to purchase ordinary shares	3,736,663	2,634,346	863,712
	3,736,663	2,727,231	13,828,271

(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 would be exercised in conjunction with the IPO and 50% of the warrants would expire.

(2) At December 31, 2019, 65,000 warrants exercisable into 92,885 ordinary shares were outstanding (Note 8).

15. 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, 2020, 2019, and 2018 the Company made contributions totaling $0.2 million, $0.2 million 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 make contributions each year ("U.K Plan"). During the years ended December 31, 2020, 2019 and 2018 the Company made contributions totaling $0.5 million, $0.3 million and $0.2 million, respectively, to the U.K. Plan.

16. Related party transactions

The Company has entered into Founder Royalty Agreements with its founders and initial investors (Note 13). No royalties have been earned or paid under the Founder Royalty Agreements to date.

The Chairman of the Company's board of directors is associated with Stone Sunny Isles Inc., which provided consultancy services to the Company totaling $0.2 million and $0.1 million during each of the years ended December 31, 2020 and 2019, respectively. The former Chairman of the Company's board of directors is associated with 10X Capital Inc., which provided consultancy services to the Company totaling $50,000, and $0.2 million during the years ended December 31, 2019 and 2018, respectively.

17. 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,	
	2020	2019
United States	$ 1,708	$ 2,017
United Kingdom	1,899	2,331
	$ 3,607	$ 4,348

The Company's collaboration revenues are attributed to the operations of the Company in the United Kingdom.

18. Selected Quarterly Financial Data (Unaudited)

The following tables contain selected quarterly financial information for 2020 and 2019. The Company believes the following information includes all recurring adjustments necessary for a fair statement of such information (in thousands, except share and per share data):

	Three Months Ended			
	December 31, 2020	September 30, 2020	June 30, 2020	March 31, 2020
Statements of Operations Data:				
Collaboration revenues	$ 3,848	$ 3,842	$ 1,571	$ 1,129
Total operating expenses (1)	20,907	14,517	14,154	12,772
Total other income (expense), net	(429)	72	371	212
Net loss before income tax provision	(17,488)	(10,603)	(12,212)	(11,431)
Benefit from income taxes	(55)	(465)	(97)	(107)
Net loss	$ (17,433)	$ (10,138)	$ (12,115)	$ (11,324)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (0.83)	$ (0.52)	$ (0.67)	$ (0.63)
Weighted average ordinary shares outstanding, basic and diluted	21,057,855	19,426,833	18,077,770	17,997,929

	Three Months Ended			
	December 31, 2019	September 30, 2019	June 30, 2019	March 31, 2019
Statements of Operations Data:				
Collaboration revenues (2),(3)	$ 5,281	$ 614	$ 1,522	$ 6,384
Total operating expenses	10,045	10,867	9,510	9,678
Total other income (expense), net	220	440	(2,094)	(3,129)
Net loss before income tax provision	(4,544)	(9,813)	(10,082)	(6,423)
(Benefit from) provision for income taxes	(138)	(331)	135	80
Net loss	$ (4,406)	$ (9,482)	$ (10,217)	$ (6,503)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (0.25)	$ (0.53)	$ (1.40)	$ (7.80)
Weighted average ordinary shares outstanding, basic and diluted	17,926,165	17,900,978	7,298,139	834,043

(1) Operating expenses in the fourth quarter of 2020 include $4.7 million of expense related to the settlement and license agreement with Pepscan (Note 13).

(2) Collaboration revenues in the fourth quarter of 2019 include $4.7 million recognized upon notification that the collaboration with Sanofi was terminated for amounts allocated to a material right when an option expired (Note 11).

(3) Collaboration revenues in the first quarter of 2019 include $5.3 million recognized upon notification that Sanofi would not exercise the Sickle Cell License Option for amounts allocated to a material right when the option expired (Note 11).

19. Subsequent events

In January and February 2021, the Company issued and sold 1,958,485 ADSs, representing the same number of ordinary shares, pursuant to its ATM program for gross proceeds of $50.2 million, resulting in net proceeds of $48.7 million after deducting sales commissions and offering expenses of $1.5 million.

In March 2021, the Company achieved specified criteria in accordance with the research plan under the Genentech Collaboration agreement, for which Genentech owes the Company a $2.0 million payment.

On March 10, 2021 or the Amendment Closing Date, the Borrowers entered into the First Amendment to the Loan and Security Agreement (the “First Amendment to LSA”), with Hercules, in its capacity as administrative agent

and collateral agent, and the lenders named in the First Amendment to LSA. The First Amendment to LSA amended certain terms of the Company's debt facility with Hercules. Pursuant to the First Amendment to LSA, payments on borrowings under the Company's debt facility with Hercules will be interest-only until the first payment is due on August 1, 2023, which date was extended from November 1, 2022. If the Company achieves certain performance milestones, the interest-only period will be extended, with the first principal payment due on February 1, 2024, which date was extended from May 1, 2023. On the Amendment Closing Date and pursuant to the terms of the First Amendment to LSA, the Company borrowed the additional term loan of $15.0 million that had been available from September 30, 2020 to March 15, 2021.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Company has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Bicycle Therapeutics plc

Dated: March 11, 2021

/s/ Kevin Lee
Kevin Lee, Ph.D., MBA
Chief Executive Officer (Principal Executive Officer)

/s/Lee Kalowski
Lee Kalowski, MBA
Chief Financial Officer and President (Principal Financial and Accounting Officer)

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Kevin Lee and Lee Kalowski, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report on Form 10-K has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Kevin Lee Kevin Lee, Ph.D., MBA	Chief Executive Officer and Director (Principal Executive Officer)	March 11, 2021
/s/ Lee Kalowski Lee Kalowski, MBA	Chief Financial Officer and President (Principal Financial and Accounting Officer)	March 11, 2021
/s/ Pierre Legault Pierre Legault, MBA, CPA	Chairman of the Board and Director	March 11, 2021
/s/ Catherine Bingham Catherine Bingham, MBA	Director	March 11, 2021
/s/ Janice Bourque Janice Bourque, MBA	Director	March 11, 2021
/s/ Veronica Jordan Veronica Jordan, Ph.D.	Director	March 11, 2021
/s/ Richard Kender Richard Kender, MBA	Director	March 11, 2021
/s/ Sir Gregory Winter Sir Gregory Winter, FRS	Director	March 11, 2021

AMENDMENT TO LETTER AGREEMENT

This **Amendment to Letter Agreement** (this "***Amendment***") is effective as of October 27, 2020, by and between **Bicycle Therapeutics plc**, a public limited company incorporated under the laws of England and Wales (the "***Company***"), and **Citibank, N.A.**, a national banking association organized and existing under the laws of the United States of America ("***Citibank***" and, together with the Company, the "***Parties***" and each a "***Party***"). All capitalized terms used but not defined herein shall have the meanings assigned to such terms in the Letter Agreement (as defined below).

Recitals

A. The Parties previously entered in that certain Letter Agreement, dated as of July 1, 2020 (the "***Letter Agreement***"), pursuant to which the Parties agreed, inter alia, to certain terms and conditions with respect to the Deposit Agreement, the Sales Agreement, and Program Sales.

B. Section 6(e) of the Letter Agreement provides that the Letter Agreement may not be modified or amended except by a writing signed by each of the Company and Citibank.

C. Each of the Company and Citibank now desires to amend the Letter Agreement as set forth herein.

Agreement

In consideration of the foregoing and for other good and valuable consideration, the receipt and adequacy of which is hereby acknowledged by each Party, the Parties agree as follows:

1. Amendment of the Letter Agreement.

(a) The first sentence of the second full paragraph of the Letter Agreement is hereby amended and replaced in its entirety with the following:

> "The Company has, upon the terms set forth in the Sales Agreement, dated as of June 5, 2020 (the "Sales Agreement"), by and among the Company, Cantor Fitzgerald & Co. ("Cantor") and Oppenheimer & Co. Inc. ("Oppenheimer" and together with Cantor, the "Agents"), agreed to issue and sell through the Agents, each acting as agent and/or principal, ADSs (the "Program ADSs"), each Program ADS representing one (1) fully paid Share, with such Program ADSs having an aggregate offering price of up to U.S. $125,000,000 (the "Program Offer")."

(b) The words "and on October 27, 2020" shall be added to clause (i) of Section 4 of the Letter Agreement, such that the relevant portion of clause (i) of Section 4 of the Letter Agreement shall read as follows:

> "(i) at the time of execution of this Letter Agreement and on October 27, 2020"

(c) The first sentence of the first full paragraph of Exhibit A to the Letter Agreement is hereby amended and replaced in its entirety with the following:

> "Reference is made to (i) the Deposit Agreement, dated as of May 28, 2019, as amended and supplemented from time to time (the "Deposit Agreement"), by and among

Bicycle Therapeutics plc, a public limited company incorporated under the laws of England and Wales and its successors (the "Company"), Citibank, N.A., a national banking association ("Citibank") organized and existing under the laws of the United States of America, as Depositary (the "Depositary"), and all Holders and Beneficial Owners of American Depositary Shares (the "ADSs") issued thereunder, and (ii) the Letter Agreement, dated as of July 1, 2020, as amended on October 27, 2020, (the "Letter Agreement"), by and between the Company and the Depositary."

(d) The third full paragraph of Exhibit A to the Letter Agreement is hereby amended and replaced in its entirety with the following:

"The Company hereby (i) confirms that no United Kingdom stamp duty taxes (including any stamp duty reserve taxes) are applicable to, or payable in connection with, the initial issuance of the Shares or the initial deposit of the Shares by the Company with the Custodian against issuance of the Program ADSs, (ii) certifies that the Company is not, and after giving effect to the offering and sale of the Program ADSs in this Program Sale and the application of proceeds thereof, will not be required to be registered as an "investment company" under the Investment Company Act of 1940, as amended, and (iii) certifies that the Registration Statement (as defined in the Letter Agreement) is effective under the Securities Act and no stop order suspending the effectiveness of the Registration Statement has been issued and no proceeding for that purpose has been initiated or to the Company's knowledge threatened."

2. MISCELLANEOUS.

(a) This Amendment may be executed in counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature complying with the U.S. federal ESIGN Act of 2000, Uniform Electronic Transactions Act or other applicable law) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes.

(b) Except as expressly modified by this Amendment, the Letter Agreement shall remain unmodified and in full force and effect.

(c) Section 9 (*Miscellaneous*) of the Letter Agreement shall apply to this Amendment mutatis mutandis.

(d) This Amendment, together with the Letter Agreement (to the extent not amended hereby) and all exhibits thereto, constitutes the entire agreement of the Parties relating to the matters contemplated herein and shall supersede any and all previous oral or written contracts, arrangements or understandings between the Parties with respect to the subject matter herein.

(e) This Amendment may not be altered, amended or modified in any way except by written consent of each of the Company and Citibank. Waiver of any term or provision of this Amendment or forbearance to enforce any term or provision by any party shall not constitute a waiver as to any subsequent breach or failure of the same term or provision or a waiver of any other term or provision of this Amendment.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

In Witness Whereof, the parties hereto have executed this **Amendment to Letter Agreement** as of the date set forth in the first paragraph above.

COMPANY:

Bicycle Therapeutics plc

By: /s/ Kevin Lee

Name: Kevin Lee
Title: Director and Chief Executive Officer

In Witness Whereof, the parties hereto have executed this **Amendment to Letter Agreement** as of the date set forth in the first paragraph above.

DEPOSITARY

CITIBANK, N.A.

By: /s/Leslie DeLuca
Name: Leslie DeLuca
Title: Attorney-in-Fact

Exhibit 10.14

DATED 9th July 2020

BicycleTX Ltd

and

Dominic Smethurst

SERVICE AGREEMENT

221783187 v1

THIS AGREEMENT is made on 9th July 2020

BETWEEN:

(1) **BICYCLETX LIMITED** a company incorporated under the laws of England and Wales (Company Number 11036101) whose registered office is at Building 900 Babraham Research Campus, Babraham, Cambridgeshire, CB22 3AT, United Kingdom (the "**Company**"); and

(2) **DOMINC SMETHURST** of (the "**Employee**").

IT IS AGREED as follows:

1. COMMENCEMENT OF EMPLOYMENT

1.1 This Agreement shall take effect on 10 August 2020, or such other date as may be agreed between the parties (the "**Effective Date**").

1.2 Your employment shall commence on the Effective Date and shall continue unless and until either party gives notice to the other in accordance with paragraph 11 below. No employment with a previous employer is deemed to be continuous with your employment with the Company.

1.3 You warrant that by entering into this Agreement or any other arrangements with the Company you will not be in breach of or subject to any express or implied terms of any contract with, or other obligation to, any third party binding on you, including, without limitation, any notice period or the provisions of any restrictive covenants or confidentiality obligations arising out of any employment with any other employer or former employer.

1.4 You warrant that you have the right to work in the United Kingdom and you agree to provide to the Company copies of all relevant documents in this respect at the request of the Company. If at any time during the course of this Agreement you cease to have the right to work in the United Kingdom the Company may immediately terminate your employment without payment of compensation.

2. JOB TITLE

2.1 You shall serve as Chief Medical Officer ("**CMO**") reporting to the CEO. The nature of the Company's business may result in changes occurring to the content of your role from time to time. You may also be required to carry out such additional or alternative tasks as may from time to time be reasonably required of you consistent with your executive level and job title, provided that these do not fundamentally change or undermine your position.

2.2 You shall faithfully and diligently perform such duties as you are required to undertake from time to time and exclusively devote the whole of your working time, skills, ability and attention to the business of the Company and use your best endeavours to promote the interests and reputation of the Company and (where applicable) any Group Company.

2.3 The Company may require you to carry out work for, or become a director or officer of, any Group Company at any time.

3. PLACE OF WORK

The Company's offices at Building 900, Babraham Research Campus, Babraham, Cambridge, UK or such other location as the Company may reasonably determine. The CMO position may require extensive international travel on business.

4. REMUNERATION

4.1 Your salary will be USD420,000 per annum paid monthly in arrears on or about the last working day of each month (less statutory and voluntary deductions) ("**Salary**"). Your Salary will be converted to GBP and paid in GBP based on the trailing twelve-month average of the USD/GBP Bank of England daily spot exchange rate applicable on the Effective Date, with the exchange rate being revised according to the trailing twelve-month average of the USD/GBP Bank of England daily spot exchange rate as of 1 January of each year. Your Salary will be reviewed annually in accordance with the Company's practices from time to time (which is expected to be by the end of the first quarter of each year). You will be notified in writing of any changes to your Salary or benefits.

4.2 You agree that the Company may deduct from the Salary or any other sum due to you (including any pay in lieu of notice) any amounts due to the Company including, without limitation, any overpayment of salary, loan or advance.

4.3 For the purposes of this Agreement your earned salary shall mean the proportion of your Salary earned by and due to you in each calendar year of employment with the Company ("**Earned Salary**").

4.4 **Annual Performance Bonuses:**

You will be eligible to participate in the Company's discretionary annual performance related bonus scheme to a maximum value of 40% of your Earned Salary in relation to your performance against agreed annual corporate and personal performance objectives as set out below (the "**Annual Performance Bonus**"). That is, if the compensation committee (the "**Compensation Committee**") of the board of directors (the "**Board**") of the Company's parent company, Bicycle Therapeutics plc ("**BTL**") determines that you have completed all such corporate and personal objectives to its satisfaction in a given year, your bonus would be 40% of your Earned Salary in that year, excluding any other bonuses in this offer. Such bonus may be payable in cash or, in whole or in part, in share options in BTL, as agreed by you and the Compensation Committee following notification by you of your preference at least 90 days prior to the normal payment date (and in the case of share options with the appropriate HMRC valuation process (if required by the Compensation Committee) and Board approval so as to be compliant with BTL's share option plan rules), with due consideration for the operational requirements of the Company at that time in your role as CMO.

Any Annual Performance Bonus paid will not be pensionable and are subject to statutory applicable tax and National Insurance deductions. Performance will be assessed by the Compensation Committee at the end of each calendar year, against annual corporate and personal performance objectives agreed between you and the Board at the start of each calendar year, with any such bonus being payable in the first quarter of the following year. Qualification for your Annual Performance Bonus will require that you are employed by the Company (and have not served notice of termination of your employment to the Company) on

31 December of the year to which your bonus entitlement applies.

4.5 **Equity Incentives**

BTL has established the Bicycle Therapeutics Plc 2020 Equity Incentive Plan (the "**EIP**").

On or as soon as practicable following the Effective Date, it is intended that you will be granted an option under the EIP to acquire 120,000 ordinary shares in the capital of BTL ("**Shares**").

Any options granted under this paragraph 4.5 shall be subject to (i) the approval of the Compensation Committee; (ii) the rules of the EIP (as amended from time to time); and (iii) the terms of the option grant documentation which will be provided to you following such grant.

5 BENEFITS

5.1 The Company operates a group personal pension scheme. You will be automatically enrolled into the pension scheme upon joining the company, subject to satisfying certain eligibility criteria and the rules of the scheme as amended from time to time. The Company will contribute an amount equal to 12% of your basic annual salary to the Scheme each year, payable monthly and subject to the rules of the Scheme and the tax reliefs and exemptions available from HM Revenue & Customs, as amended from time to time. You may choose to make additional personal contributions into the pension scheme. You may opt out of the Pension Scheme by requesting this in writing. A contracting-out certificate is not in force in respect of your employment.

5.2 The Company currently operates a private healthcare scheme and subject to acceptance by the insurer on reasonable terms, you will be entitled to join.

5.3 The Company operates a death in service scheme to the level of four times your annual salary, which you automatically join upon commencement of employment.

5.4 Further details regarding benefits will be provided upon commencement of your employment. The Company reserves the right to replace or supplement any or all of the scheme(s) referred to in this paragraph 5, or to amend them at any time without compensation, provided that equivalent scheme(s) providing a similar level of benefit are put in place.

6 EXPENSES

The Company shall reimburse all reasonable out of pocket expenses properly incurred by you in the performance of the duties under this Agreement including travelling, subsistence and entertainment expenses provided you follow the Company's guidelines/allowances in force at the relevant time and provided that you shall, where reasonably practicable, provide the Company with vouchers, invoices or such other evidence of such expenses as the Company may reasonably require.

7 HOURS OF WORK

7.1 Your normal working hours are Monday to Friday from 9.00 am to 5.30 pm on each working day with one hour for lunch. You will be required to work such other hours as shall be reasonably necessary for you to perform your duties for which no further remuneration is

payable.

7.2 By entering into this Agreement you confirm, that in your capacity as CMO you may choose or determine the duration of your working time and the working time limits set out in part II of the Working Time Regulations 1998 do not apply to you.

8 HOLIDAYS

8.1 In addition to the usual public holidays you will be entitled to 25 working days paid holiday in each calendar year. The holiday will accrue on a pro rata basis throughout each calendar year.

8.2 Holidays may only be taken at such time or times as are approved beforehand by the CEO, such approval not to be unreasonably withheld or delayed. You must give reasonable notice of proposed holiday dates and use the HR system for approval.

8.3 The holiday year runs from January to December. With the agreement of the CEO, you may carry forward up to 5 days of untaken holiday into the next holiday year. Any carried over holiday must be taken by the end of March of the following calendar year or will be forfeited and no payment will be made in respect of any days so forfeited. You will not generally be permitted to take more than 10 days holiday at any one time.

8.4 Upon termination of your employment you will receive pay in lieu of accrued but untaken holiday. The Company may deduct an appropriate sum in respect of days taken in excess of your pro rata entitlement from your final remuneration on the basis that one day's holiday will be calculated as 1/260ths of your basic annual salary.

8.5 In the event that notice of termination of this Agreement is served by either party, the Company may require you to take any outstanding holiday during this notice period.

9 SICKNESS AND OTHER ABSENCE

9.1 If you are unable to attend at work by reason of sickness or injury or any unauthorised reason you must inform the Company as soon as possible on the first day of absence (and in any event not later than 11.00 am on the first day of absence) and, in the case of absence of uncertain duration, you must keep the Company regularly informed of your continued absence and your likely date of return. You are expected to observe this rule very strictly since failure to do so will entitle the Company to stop payment in respect of each day you fail to notify the Company.

9.2 If your absence, due to sickness or injury, is for less than seven (7) days, on your return to work you are required to immediately self-certificate on the HR system. If your absence continues for more than seven (7) consecutive days (whether or not working days) you must provide the Company with a doctor's certificate from the seventh consecutive day of sickness or injury. This doctor's certificate must be provided to the Company promptly following the seventh consecutive day of absence. If illness continues after the expiry of the first certificate, further certificates must be provided promptly to cover the whole period of absence.

9.3 Subject to your compliance with the Company's sickness absence procedures (as amended from time to time), the Company may in its sole and absolute discretion pay full salary and contractual benefits during any period of absence due to sickness or injury for up to an aggregate of 3 months in any fifty-two (52) week period (whether such absence is continuous

or intermittent in any calendar year). Such payment shall be inclusive of any statutory sick pay due in accordance with applicable legislation in force at the time of absence. The Company may, in its sole and absolute discretion, extend the period of allowance in an individual case if the circumstances so justify. Thereafter, the Company shall pay statutory sick pay or equivalent benefit to which you may be entitled subject to your compliance with the appropriate rules.

9.4 Whether absent from work or not, you may be, but only on reasonable grounds, required to undergo a medical examination by a Company doctor and your consent will be sought for a report to be sent to the Company.

9.5 The payment of sick pay in accordance with this paragraph 9 is without prejudice to the Company's right to terminate this Agreement prior to the expiry of your right to payments.

9.6 In the event you are incapable of performing your duties by reason of injuries sustained wholly or partly as a result of a third party's actions all payments made to you by the Company as salary or sick pay shall to the extent that compensation is recoverable from that third party constitute loans to you and shall be due and owing when and to the extent that you recover compensation for loss of earnings from the third party.

10 GARDEN LEAVE

10.1 After notice of termination has been given by you or the Company, the Company may at its discretion require you, for all or part of your notice period, to comply with any or all of the following instructions:

(a) not to carry out any further work for the Company or for any Group Company;

(b) to remain away from the Company's business premises and those of any Group Company (unless given written permission to do otherwise);

(c) not to contact any of the Company's clients, suppliers or employees or those of any Group Company without the Company's prior written permission;

(d) to carry out only part of your duties, or to carry out alternative duties or special projects for the Company within your skill set;

(e) to co-operate in the handover of your duties and responsibilities;

(f) to resign from any offices (including as a director) you hold within the Company or any Group Company or by virtue of your employment with us;

(g) to answer, in an honest and helpful way, such questions as the Company may reasonably ask of you;

(h) to keep the Company informed of your whereabouts and contact details and to remain reasonably contactable and available for work.

10.2 During any such period as described in paragraph 10.1 ("**Garden Leave**") the Company may appoint another person to carry out some or all of your duties. You will continue to owe all other duties and obligations (whether express or implied including fidelity and good faith) during Garden Leave and you shall continue to receive full pay and benefits (except that you will not

accrue any further entitlement to any cash or equity incentive awards or bonus payments in respect of the Garden Leave period).

10.3 By placing you on Garden Leave, the Company will not be in breach of this Agreement or any implied duty of any kind whatsoever nor will you have any claim against the Company in respect of any such action.

10.4 During any period of Garden Leave you will remain readily contactable and available for work save when on paid holiday taken in accordance with paragraph 8. In the event that you are not available for work having been requested by the Company to do so, you will, notwithstanding any other provision of this Agreement, forfeit any right to salary and contractual benefits.

10.5 During any period of Garden Leave the Company may require you to deliver up any Confidential Information or property of the Company or any Group Company and upon instruction, delete any emails, spreadsheets or other Confidential Information and you will confirm your compliance with this paragraph 10.5 in writing if requested to do so by the Company.

10.6 During any period of Garden Leave the Company may require you to take any outstanding holiday entitlement.

11 NOTICE

11.1 Without prejudice to the Company's right to summarily terminate your employment in accordance with paragraph 11.3 below and your right to summarily terminate your employment for Good Reason in accordance with paragraph 11.4 below, either you or the Company may terminate your employment by giving to the other not less than:

(a) during the first three months following the Effective Date (the "**Probationary Period**"), one month's notice in writing; and

(b) following successful completion of the Probationary Period, six months' notice in writing.

11.2 The Company reserves the right in its sole and absolute discretion to give written notice to terminate your employment forthwith and to make a payment to you in lieu of salary and the benefits set out in paragraph 5 of this Agreement for all or any unexpired part of the applicable notice period. For the avoidance of doubt, any payment in lieu made pursuant to this paragraph 11.2 will not include any element in relation to any payment in respect of (i) any Annual Performance Bonus or (ii) any holiday entitlement that would have otherwise accrued during the period for which the payment in lieu is made. For the further avoidance of doubt, if the Company elects to make a Payment in Lieu after notice of termination has been given by you, this will not constitute a termination by the Company without Cause for the purposes of paragraphs 11.7 and 11.8 below.

11.3 The Company may summarily terminate your employment hereunder (without notice) for Cause. For purposes of this Agreement, "**Cause**" shall mean where you:

(a) commit gross misconduct which includes, but is not limited to, dishonesty, fraud, theft, being under the influence of alcohol or drugs at work, causing actual or threatening physical harm and causing damage to Company property;

(b) commit a material breach or non-observance of your duties or any of the provisions of this Agreement, or materially fail to observe the lawful directions of the Company, or breach any material Company policy or code of conduct, including but not limited to the Company's policy from time to time on matters relating to harassment;

(c) are convicted of a criminal offence (other than an offence under the road traffic legislation in the United Kingdom or elsewhere for which a non-custodial sentence is imposed);

(d) act in a manner which in the reasonable opinion of the Company, brings the Company into disrepute or otherwise prejudices or is in the reasonable opinion of the Company considered likely to prejudice the reputation of the Company;

(e) in the reasonable opinion of the Company, are guilty of any serious negligence in connection with or affecting the business or affairs of the Company;

(f) are unfit to carry out the duties hereunder because of sickness, injury or otherwise for an aggregate period of 26 weeks in any fifty-two (52) week period even if, as a result of such termination, you would or might forfeit any entitlement to benefit from sick pay under paragraph 9.3 above.

Any delay or forbearance by the Company in exercising any right of termination in accordance with this paragraph 11.3 will not constitute a waiver of such right.

11.4 You may summarily terminate your employment hereunder at any time (without notice) for Good Reason after complying with the Good Reason Process. For purposes of this Agreement, "**Good Reason**" shall mean that you have complied with the "Good Reason Process" (hereinafter defined) following the occurrence of any of the following events: (i) a material diminution in your responsibilities, authority or duties; (ii) a material diminution in your Salary; (iii) a material change in the geographic location at which you provides services to the Company; or (iv) the material breach of this Agreement by the Company. "**Good Reason Process**" shall mean that (i) you reasonably determine in good faith that a "Good Reason" condition has occurred; (ii) you notify the Company in writing of the first occurrence of the Good Reason condition within 60 days of the first occurrence of such condition; (iii) you cooperate in good faith with the Company's efforts, for a period not less than 30 days following such notice (the "**Cure Period**"), to remedy the condition; (iv) notwithstanding such efforts, the Good Reason condition continues to exist; and (v) you terminate your employment (without notice) within 60 days after the end of the Cure Period. If the Company cures the Good Reason condition during the Cure Period, Good Reason shall be deemed not to have occurred.

11.5 Your employment hereunder shall also terminate immediately upon your death.

11.6 If your employment with the Company is terminated for any reason, the Company shall pay or provide to you (or to your authorised representative or estate) (i) any Salary earned through the Termination Date (as defined below); (ii) unpaid expense reimbursements (subject to, and in accordance with, paragraph 6 of this Agreement); and (iii) any vested benefits you may have under any employee benefit plan of the Company through the Termination Date, which vested benefits shall be paid and/or provided in accordance with the terms of such employee benefit plans (collectively, the "**Accrued Benefits**").

Severance Pay and Benefits Upon Termination by the Company without Cause or by the Executive for Good Reason outside the Change in Control Period (Following Successful Completion of the Probationary Period).

11.7 If your employment is terminated on account of your death or by the Company without Cause (being for any reason not covered by paragraph 11.3), or you terminate your employment for Good Reason (as provided in paragraph 11.4), in either case outside of the Change in Control Period and provided you have successfully completed the Probationary Period, then the Company shall pay you the Accrued Benefits. In addition, subject to (i) your (or your authorised representative or estate signing, if the termination is due to your death) signing a settlement agreement and a separation agreement and release (together the "**Settlement Agreements**") in a form and manner satisfactory to the Company, which shall include, without limitation, a general release of claims against the Company and all related persons and entities, a reaffirmation of all of your continuing obligations to the Company, including those set forth in paragraphs 13 – 15, and (in the case of the separation agreement and release) and a seven (7) business day revocation period; and (ii) the separation agreement and release becoming irrevocable, all within 60 days after the Termination Date (or such shorter period as set forth in the Settlement Agreements), the Company shall: (A) pay you (or your authorised representative or estate if the termination is due to your death) an amount equal to nine (9) months of your salary as of the Termination Date (which payment shall not be reduced by either the value of any salary paid to you during your notice period or by any payment in lieu of notice made pursuant to paragraph 11.2); and (B) pay you (or your authorised representative or estate if the termination is due to your death) an amount equal to the cost to the Company of providing you with the contractual benefits under paragraph 5 for nine (9) months or, at the Company's option, continue to provide you with such benefits for nine (9) months.

Severance Pay and Benefits Upon Termination by the Company without Cause or by the Executive for Good Reason Within the Change in Control Period Following Successful Completion of the Probationary Period).

11.8 The provisions of this paragraph 11.8 shall apply in lieu of, and expressly supersede, the provisions of paragraph 11.7 regarding severance pay and benefits upon a termination by the Company without Cause or by you for Good Reason if such termination of employment occurs within 12 months after the occurrence of the first event constituting a Change in Control (such period, the "**Change in Control Period**") and provided you have successfully completed the Probationary Period. These provisions shall terminate and be of no further force or effect after the Change in Control Period.

(a) Change in Control Period. If during the Change in Control Period your employment is terminated on account of your death or by the Company without Cause (being for any reason not covered by paragraph 11.3) or you terminate your employment for Good Reason (as provided in paragraph 11.4), then, subject to (i) your signing (or your authorised representative or estate signing, if the termination is due to your death) a settlement agreement and a separation agreement and release (together the Settlement Agreements) in a form and manner satisfactory to the Company, which shall include, without limitation, a general release of claims against the Company and all related persons and entities, a reaffirmation of all of your continuing obligations to the Company, including those set forth in paragraphs 13 – 15, and (in the case of the separation agreement and release) and a seven (7) business day revocation period;

and (ii) the separation agreement and release becoming irrevocable, all within 60 days after the Termination Date (or such shorter period as set forth in the Settlement Agreements):

(i) the Company shall pay you (or your authorised representative or estate if the termination is due to your death) an amount equal to the sum of (A) your annual salary as of the Termination Date (or your annual salary in effect immediately prior to the Change in Control, if higher) plus (B) your target annual performance bonus amount under the Annual Bonus Plan for the then-current year (the "Change in Control Payment"), which payment shall not be reduced by either the value of any salary paid to you during your notice period or by the value of any payment made to you in lieu of notice pursuant paragraph 11.2;

(ii) the Company shall: pay you (or your authorised representative or estate if the termination is due to your death) an amount equal to the cost to the Company of providing you with the contractual benefits under paragraph 5 for twelve (12) months or, at the Company's option, continue to provide you with such benefits for twelve (12) months; and

(iii) notwithstanding anything to the contrary in any applicable option agreement or other stock-based award agreement, all Time-Based Equity Awards shall immediately accelerate and become fully exercisable (for a period determined in accordance with the rules of the applicable equity plan) or nonforfeitable as of the later of (A) the Termination Date or (B) the Accelerated Vesting Date; *provided* that any termination or forfeiture of the unvested portion of such Time-Based Equity Awards that would otherwise occur on the Termination Date in the absence of this Agreement will be delayed until the Effective Date of the Settlement Agreements and will only occur if the vesting pursuant to this subsection does not occur due to the absence of the Settlement Agreements becoming fully effective within the time period set forth therein. Notwithstanding the foregoing, no additional vesting of the Time-Based Equity Awards shall occur during the period between your Termination Date and the Accelerated Vesting Date.

11.9 Definitions. For purposes of this paragraph 11, the following terms shall have the following meanings:

"**Accelerated Vesting Date**" means the effective date of the Settlement Agreements signed by you (or your authorised representatives or estate if the termination is due to your death).

"**Termination Date**" means the date on which your employment hereunder terminates.

"**Time-Based Equity Awards**" means all time-based stock options and other stock-based awards subject to time based vesting held by you.

"**Change in Control**" has the meaning given to that term in the Schedule to this Agreement.

12 DISCIPLINARY, DISMISSAL AND GRIEVANCE PROCEDURES

12.1 A copy of the Company's disciplinary, dismissal and grievance procedures are set out in

separate HR policies, available in the HR system.

12.2 Any grievance concerning your employment should be taken up orally in the first instance with the CEO. If the grievance is not resolved to your satisfaction, you should then refer it to the Chairman.

12.3 The Company reserves the right to suspend you on full pay and benefits at any time for a reasonable period to investigate any potential disciplinary matter that it reasonably believes you may be or may have been involved in.

13 OUTSIDE EMPLOYMENT, CONFIDENTIAL INFORMATION, CONFLICTING INTERESTS AND RETURN OF COMPANY PROPERTY

13.1 For the purposes of this paragraph 13, paragraph 10 above and paragraph 14 below the expression "**Confidential Information**" shall include, but not be limited to, any and all knowledge, data or information (whether or not recorded in documentary form or on computer disk or tape), which may be imparted in confidence or which is of a confidential nature or which you may reasonably regard as being confidential or a trade secret by the Company, concerning the business, business performance or prospective business, financial information or arrangements, plans or internal affairs of the Company, any Group Company or any of their respective customers. By way of illustration but not limitation, "**Confidential Information**" includes (a) trade secrets, inventions, mask works, ideas, processes, formulas, software in source or object code, data, records, reports, interpretations, the contents of any databases, programs, other works of authorship, know-how, materials, improvements, discoveries, developments, technical information, designs and techniques and any other proprietary technology and all IPRs (as defined below) therein (collectively, "**Inventions**"); (b) information regarding research, development, new products, planned products, planned surveys, marketing surveys, research reports, market share and pricing statistics, marketing and selling, business plans, financial details, budgets and unpublished financial statements, licenses, prices and costs, fee levels, margins, discounts, credit terms, pricing and billing policies, quoting procedures, commissions, commission charges, other price sensitive information, methods of obtaining business and other business methods, forecasts, future plans and potential strategies, financial projections and business strategies and targets, operational plans, financing and capital-raising plans, activities and agreements, internal services and operational manuals, methods of conducting Company business, corporate and business accounts, suppliers and supplier information, and purchasing; (c) information regarding clients or customers and potential clients or customers of the Company, including customer lists, client lists, names, addresses (including email), telephone, facsimile or other contact numbers and contact names, representatives, their needs or desires with respect to the types of products or services offered by the Company, proposals, bids, contracts and their contents and parties, the type and quantity of products and services provided or sought to be provided to customers and potential customers of the Company and other non-public information relating to customers and potential customers; (d) information regarding any of the Company's business partners and their services, including names, representatives, proposals, bids, contracts and their contents and parties, the type and quantity of products and services received by the Company, and other non-public information relating to business partners; (e) information regarding personnel, computer passwords, employee lists, compensation and remuneration, and employee skills; and (f) any other non-public information which a competitor of the Company could use to the competitive disadvantage of the Company.

13.2 You shall not, without the prior written consent of the Company, either solely or jointly, directly or indirectly, carry on or be engaged, concerned or interested in any other trade or business, including, but not limited to, carrying on business with the Company's suppliers or dealers, save that nothing in this paragraph 13.2 shall prevent you from holding (with the prior written consent of the Company, which shall not be unreasonably delayed or withheld) up to three percent (3%) of the issued equity share capital of any company where those equity shares are listed on a recognised investment exchange (as defined in section 285 of the Financial Services and Markets Act 2000) or traded on the AIM market operated by the London Stock Exchange. Failure to secure advance permission in accordance with this paragraph 13.2 may result in summary dismissal.

13.3 You will not (except with the prior written consent of the Board) except in the proper course of your duties during the continuance of this Agreement (which for the avoidance of doubt shall include the use of laptops and remote working), or at any time thereafter:

(a) disclose or use for your own or for another's purpose or benefit any Confidential Information which you may learn while in the employment of the Company except as required by a court of law or any regulatory body or that which may be in or become part of the public domain other than through any act or default on your part;

(b) copy or reproduce in any form or by or on any media or device or allow others access to copy or reproduce any documents (including without limitation letters, facsimiles and memoranda), disks, memory devices, notebooks, tapes or other medium whether or not eye-readable and copies thereof on which Confidential Information may from time to time be recorded or referred to ("**Documents**"); or

(c) remove or transmit from the Company or any Group Company's premises any Documents on which Confidential information may from time to time be recorded.

13.4 Upon termination of your employment for any reason by either party, you must immediately return to the Company all Company property including but not limited to documents, papers, records, keys, credit cards, mobile telephones, computer and related equipment, PDA or similar device, security passes, accounts, specifications, drawings, lists, correspondence, catalogues or the like relating to the Company's business which is in your possession or under your control and you must not take copies of the same without the Company's express written authority.

14 RESTRICTIVE COVENANTS

14.1 For the purpose of this paragraph 14 the following expressions shall have the following meanings:

"**Prospective Customer**" shall mean any person, firm, company or other business who was to your knowledge at the Termination Date negotiating with the Company or with any Group Company with a view to dealing with the Company or any Group Company as a customer;

"**Restricted Business**" means any business which (i) carries on research in the field of constrained peptides, including, without limitation, all work in the field of lead constrained peptide identification and optimization and pre-clinical development of constrained peptide therapeutics or (ii) is developing a drug conjugate compound for treating cancer that targets the same target as a drug conjugate compound in development by any Group Company;

"**Restricted Customers**" shall mean any person, firm, company or other business who was to your knowledge at any time in the twelve (12) month period ending with the Termination Date a customer of the Company or any Group Company;

"**Restricted Period (A)**" shall mean the period of six (6) months from the Termination Date;

"**Restricted Period (B)**" shall mean the period of nine (9) months from the Termination Date;

"**Restricted Territory**" means anywhere in the United States or the United Kingdom or in any other country in which the Company or any Group Company conducts business or as of the date of termination of my employment relationship had plans to conduct business; and

"**Termination Date**" shall mean the date on which your employment under this Agreement terminates either due to you or the Company terminating it in accordance with the terms of the Agreement or in breach of the terms of this Agreement.

14.2 During the course of your employment hereunder you are likely to obtain Confidential Information relating to the business of the Company or any Group Company and personal knowledge and influence over clients, customers and employees of the Company or any Group Company. You hereby agree with the Company that to protect the Company's and any and all Group Company's business interests, customer connections and goodwill and the stability of its or their workforce, that you will not:

(a) during the Restricted Period (A), in the Restricted Territory, compete with the business of the Company or any Group Company by being directly or indirectly employed or engaged in any capacity by any person, firm or company which engages in or provides Restricted Business or commercial activities competitive with the Restricted Business to Restricted Customers or Prospective Customers;

(b) during the Restricted Period (A), in the Restricted Territory, compete with the business of the Company or any Group Company either on your own account or for any person, firm or company directly or indirectly by transacting business in competition with the Restricted Business with any Restricted Customer or Prospective Customer of the Company or Group Company and with whom you personally dealt in respect of Restricted Business in the pursuance of the employment hereunder in the twelve (12) months prior to the Termination Date;

(c) during the Restricted Period (**B**), in the Restricted Territory, compete with the business of the Company or any Group Company either on your own account or for any person, firm or company directly or indirectly in competition with the Restricted Business by soliciting or endeavouring to solicit or entice the business or custom of any Restricted Customer or Prospective Customer and with whom you personally dealt in respect of Restricted Business in the pursuance of the employment hereunder in the twelve (12) months prior to the Termination Date;

(d) during the Restricted Period (B), either on your own account or for any person, firm or company directly or indirectly solicit or entice away or endeavour to solicit or entice away any director or senior employee of the Company or any Group Company employed in a managerial, scientific or technical role with whom you have had material personal dealings in the twelve (12) months prior to the Termination Date;

(e) at any time from the Termination Date for the purpose of carrying on any trade, or business represent or allow you to be represented or held out as having any present association with the Company or any Group Company; and

(f) at any time from the Termination Date carry on any trade or business whose name incorporates the word Bicycle or any deviation or extension thereof which is likely or which may be confused with the name of the Company or any Group Company.

14.3 While the restrictions set out in paragraph 14.2 above are considered by the parties to be reasonable in all the circumstances, it is agreed that if any one or more of such restrictions shall either taken by itself or themselves together be adjudged to go beyond what is reasonable in all the circumstances for the protection of the legitimate interests of the Company but would be adjudged reasonable if any particular restriction or restrictions were deleted or if any part or parts of the wording thereof were deleted, restricted or limited in a particular manner, then the restrictions set out in paragraph 14.2 above shall apply with such deletions or restrictions or limitations as the case may be.

14.4 For the avoidance of doubt nothing in this paragraph 14 shall prevent you from having any dealings with any Prospective Customer or Restricted Customer in relation to any business which is not Restricted Businesses and which is not competitive with the Restricted Business, nor from continuing to deal with any Prospective Customer or Restricted Customer where you either have a social or business relationship unconnected to the Company and that relationship does not compete with the Restricted Business.

14.5 The restrictions contained in paragraph 14.2 above are held by the Company for itself and on trust for any other Group Company and shall be enforceable by the Company on their behalf or by any Group Company (at their request). You shall during the employment hereunder enter into direct agreements with any Group Company whereby you will accept restrictions in the same or substantially the same form as those contained in paragraph 14.2 above.

14.6 In the event that the Company exercises its rights and places you on Garden Leave under paragraph 10 above then each of the Restricted Period (A) and the Restricted Period (B) shall be reduced by any period/s spent by you on Garden Leave prior to the Termination Date.

14.7 For so long as the Restricted Period (A) and/or the Restricted Period (B) apply, you shall provide a copy of the applicable restrictions contained at paragraph 13 above and this paragraph 14 to any employer or prospective employer or any other party with whom you become or will become engaged or provide service or services to.

15 INTELLECTUAL PROPERTY

15.1 For the purpose of this paragraph 15 "**IPRs**" shall mean all trade secrets, Copyrights, trademarks and trade and business names (including goodwill associated with any trademark or trade or business names and the right to sue for passing off or unfair competition), service marks, mask work rights, patents, petty patents, rights in ideas, concepts, innovations, discoveries, developments and improvements, drug formulations, technology, rights in domain names, rights in inventions, utility models, rights in know-how (including all data, methods, processes, practices and other results of research), unregistered design rights, registered design rights, database rights, semiconductor topography rights and other intellectual property rights recognized by the laws of any jurisdiction or country including all applications and rights

to apply for and be granted, renewals or extensions of, and rights to claim priority from, such rights and all similar or equivalent rights or forms of protection which subsist or will subsist now or in the future in any part of the world; the term "**Copyright**" means the exclusive legal right to reproduce, perform, display, distribute and make derivative works of a work of authorship (as a literary, musical, or artistic work) recognized by the laws of any jurisdiction or country; and the term "**Moral Rights**" means all paternity, integrity, disclosure, withdrawal, special and any other similar rights recognized by the laws of any jurisdiction or country.

15.2 It is contemplated that you may in the course of your employment with the Company create, author or originate (either alone or jointly with others) Inventions (as defined in paragraph 13.1), and/or records, reports, papers, databases, data, information, know how, literature, drawings, graphics, typographical arrangements, designs, works, documents, publications and other materials (in printed, electronic, or any other media or form) (together with Inventions constituting "**Works**").

15.3 You will promptly disclose to the Company full details of any Inventions on their creation and provide further details, explanations and demonstrations as the Company from time to time requests.

15.4 All IPRs subsisting in any Works shall be the exclusive property of the Company.

15.5 To the extent that such IPRs do not vest automatically in the Company by operation of law, you hereby assign and agree to assign to the Company all of your right, title and interest in any existing and future IPRs which may subsist in any Works for their full term of protection (including any extensions, revivals and renewals) together with the right to sue and claim remedies for past infringement and all materials embodying these rights to the fullest extent permitted by law in any and all countries of the world. Insofar as such IPRs do not vest automatically by operation of law or under this Agreement, the Consultant holds legal title in these rights and inventions on trust for the Company.

15.6 To the extent permitted by law you hereby irrevocably and unconditionally waive in favour of the Company, its licensees and successors in title, all existing and future Moral Rights (or similar rights existing in any part of the world) you may have in respect of any Works under Chapter IV of the Copyright Designs and Patents Act 1988 in England or any similar provisions of law in any jurisdiction, including (but without limitation) the right to be identified, the right of integrity and the right against false attribution, and agrees not to institute, support, maintain or permit any action or claim to the effect that any treatment, exploitation or use of such Works, Inventions or other materials infringes the Consultant's Moral Rights.

15.7 Without prejudice to the generality of paragraph 15.9 below, during your employment with the Company and thereafter, without limit in time, you shall at the request and expense of the Company, promptly assist the Company:

(a) to file, prosecute, obtain and maintain registrations and applications for registration of any IPRs subsisting in, or protecting, any Works; and

(b) to commence and prosecute legal and other proceedings against any third party for infringement of any IPRs subsisting in, or protecting, any Works and to defend any proceedings or claims made by any third party that the use or exploitation of any Works

infringes the IPRs or rights of any third party.

15.8 You shall keep details of all Inventions confidential and shall not disclose the subject matter of any Inventions to any person outside the Company without the prior consent of the Company. You acknowledge that any unauthorised disclosure of such subject matter may prevent the Company from obtaining patent or registered intellectual property protection for such Invention.

15.9 Whenever requested to do so by the Company and in any event on the termination or expiry of this Agreement, you shall promptly deliver to the Company all correspondence, documents, papers and records on all media (and all copies or abstracts of them), recording or relating to any part of the Works and the process of their creation which are in your possession, custody or power.

15.10 Subject to paragraph 15.11 below, during your employment with the Company and thereafter without limit in time you shall at the request and expense of the Company promptly execute and do all acts, matters, documents and things necessary or desirable to give the Company the full benefit of the provision of this paragraph 15. You shall not register nor attempt to register any of the IPRs in the Works, nor any of the Inventions, unless requested to do so in writing by the Company.

15.11 Nothing in this paragraph 15 shall be construed, or have the effect of, restricting your rights under sections 39 to 43 (inclusive) of the Patents Act 1977 (as amended from time to time).

16 LITIGATION ASSISTANCE

During the term of your employment and at all times thereafter subject always to your obligations to third parties, you shall furnish such information and proper assistance to the Company or any Group Companies as it or they may reasonably require in connection with the Company's intellectual property (including without limitation applying for, defending, maintaining and protecting such intellectual property) and in connection with litigation in which it is or they are or may become a party. This obligation on you shall include, without limitation, meeting with the Company or any Group Companies' legal advisers, providing witness evidence, both in written and oral form, and providing such other assistance that the Company or any Group Companies' legal advisors in their reasonable opinion determine. The Company shall reimburse you for all reasonable out of pocket expenses incurred by you in furnishing such information and assistance and in the event you are no longer employed by the Company a reasonable daily rate (as agreed between you and the Company for such assistance). Such assistance shall not require you to provide assistance for more than 5 days in any calendar month. For the avoidance of doubt the obligations under this paragraph 16 shall continue notwithstanding the termination of your employment with the Company.

17 COLLECTIVE AGREEMENTS

There are no collective agreements which directly affect your terms and conditions of employment.

18 DATA PROTECTION

Processing of personal data and our policies

18.1 Information relating to an individual (or from which an individual may be identified) is called "personal data".

18.2 In processing personal data, we are required to comply with the law on data protection. To help us achieve this, we have produced a privacy notice ("**Privacy Notice**"). This may be found in the Employee Handbook. You must read this and comply with it in carrying out your work.

Data protection principles

18.3 In complying with the law on data protection, we are required to comply with what are known as data protection principles. These are summarised in our Privacy Notice. In performing your role and carrying out your responsibilities, you must do your best to ensure that we comply with these principles.

18.4 A key element of the data protection principles is the duty to ensure that data is processed securely and protected against unauthorised or unlawful processing or loss. Key elements include the following:

(a) You must ensure that laptops, memory sticks, phones and other mobile devices are password protected and encrypted. You must not take such devices outside the office without encryption. You must take care of them and keep them secure.

(b) You must use strong passwords, changing them when asked and not sharing them with unauthorised colleagues.

(c) You must not access other individuals' personal data unless in the course of your work.

Data breach – and urgent notification

18.5 If you discover a data breach, you **must** notify the CFO or CFO (copied to the CEO) immediately – and, if practicable, within one hour. Depending on context, you may then need to provide further information on the circumstances of the breach.

18.6 A data breach occurs where there is destruction, loss, alteration or unauthorised disclosure of or access to personal data which is being held, stored, transmitted or processed in any way. For example, there is a data breach if our servers are hacked or if you lose a laptop or USB stick or send an email to the wrong person by mistake.

18.7 Failure to notify a breach or to provide information as set out above will be treated seriously and disciplinary action may be taken.

Why we process personal data

18.8 For information on the nature of the data we process, why we process it, the legal basis for processing and related matters, please refer to our Privacy Notice. In summary:

(a) We process personal data relating to you for the purposes of our business including management, administrative, employment and legal purposes.

(b) We monitor our premises and the use of our communication facilities, including using CCTV cameras, monitoring compliance with our data and IT policies, and where non-

compliance is suspected, looking in a more targeted way.

18.9 The summary above is for information only. We do not, in general, rely on your consent as a legal basis for processing. Agreeing the terms of this Agreement will not constitute your giving consent to our processing of your data.

18.10 We reserve the right to amend the documents referred to above from time to time.

19 THIRD PARTY RIGHTS

Save in respect of any rights conferred by this Agreement on any Group Company (which such Group Company shall be entitled to enforce), a person who is not a party to this Agreement may not under the Contracts (Rights of Third Parties) Act 1999 enforce any of the terms contained within this Agreement.

20 DEFINITIONS

In this Agreement:

"**Group Company**" means a subsidiary or affiliate and any other company which is for the time being a holding company of the Company or another subsidiary or affiliate of any such holding company as defined by the Companies Act 2006 (as amended) and "**Group Companies**" will be interpreted accordingly.

21 ENTIRE AGREEMENT

These terms and conditions constitute the entire agreement between the parties and supersede any other agreement whether written or oral previously entered into.

22 JURISDICTION AND CHOICE OF LAW

This Agreement shall be governed by and interpreted in accordance with the laws of England and Wales and the parties to this Agreement submit to the exclusive jurisdiction of the Courts of England and Wales in relation to any claim, dispute or matter arising out of or relating to this Agreement.

23 NOTICES

Any notices with respect to this Agreement shall be in writing and shall be deemed given if delivered personally (upon receipt), sent by email or sent by first class post addressed, in the case of the Company, to the Company Secretary at its registered office and in your case, addressed to your address last known to the Company.

Schedule

Definitions

Change in Control: means and includes each of the following:

(a) a Sale; or

(b) a Takeover.

The Compensation Committee shall have full and final authority, which shall be exercised in its sole discretion, to determine conclusively whether a Change in Control has occurred pursuant to the above definition, the date of the occurrence of such Change in Control and any incidental matters relating thereto; provided that any such Change in Control also qualifies as a "change in control event" as defined in Section 409A of the United States Internal Revenue Code of 1986, as amended and the regulations and other guidance thereunder and any state law of similar effect, and any exercise of authority in conjunction with a determination of whether a Change in Control is a "change in control event" is consistent with such regulation.

Control: shall have the meaning given to that word by Section 719 of the UK Income Tax (Earnings and Pensions) Act 2003 and "**Controlled**" shall be construed accordingly.

Sale: the sale of all or substantially all of the assets of BTL.

Takeover: circumstances in which any person (or a group of persons acting in concert) (the "**Acquiring Person**"):

(a) obtains Control of BTL as the result of making a general offer to:-

i. acquire all of the issued ordinary share capital of BTL, which is made on a condition that, if it is satisfied, the Acquiring Person will have Control of BTL; or

ii. acquire all of the shares in BTL; or

(b) obtains Control of BTL as a result of a compromise or arrangement sanctioned by a court under Section 899 of the UK Companies Act 2006, or sanctioned under any other similar law of another jurisdiction; or

(c) becomes bound or entitled under Sections 979 to 985 of the UK Companies Act 2006 (or similar law of another jurisdiction) to acquire shares in BTL; or

(d) obtains Control of BTL in any other way, including but not limited to by way of a merger.

THIS AGREEMENT has been executed and delivered as a deed by or on behalf of the parties on the date written at the top of page 1.

Executed as a Deed by **BICYCLETX LIMITED** acting by a director:

/s/ Kevin Lee (Director)

in the presence of:

/s/ Paula Barnes

Witness Name: Paula Barnes

Witness Address:

Executed as a Deed by **DOMINIC SMETHURST**:

/s/ Dominic Smethurst (Dominic Smethurst)

in the presence of:

/s/ Charlotte Whittaker

Witness Name: Charlotte Whittaker

Witness Address:

BICYCLE THERAPEUTICS PLC
NON-EMPLOYEE DIRECTOR COMPENSATION POLICY
AS AMENDED THROUGH DECEMBER 16, 2020

This Non-Employee Director Compensation Policy (the "Policy") has been established in order to attract and retain non-employee directors who have the knowledge, skills and experience to serve as a member of the Board of Directors (the "Board") of Bicycle Therapeutics plc (the "Company"). Directors who are employees of the Company or any of its subsidiaries will receive no additional compensation for their service as directors.

All equity awards granted in accordance with this Policy shall be granted under the Company's then-current equity incentive plan (or director equity incentive plan, if any).

A. EQUITY AWARDS

At the next scheduled meeting of the Board or the Compensation Committee, as applicable, following a non-employee director's initial election to the Company's Board, the Board or the Compensation Committee of the Board shall grant such non-employee director an option to purchase 32,000 ordinary shares (the "Initial Grant"). Initial Grants will vest in equal tranches of 1/36th at the end of each calendar month following the date of grant, subject to continued service by the director as of such vesting date.

In addition, in January of each year, the Board or the Compensation Committee of the Board will grant to each non-employee director (other than the Chair) who has not announced an intention either to resign from the Board or not to stand for election at the next annual general meeting of shareholders an option to purchase 19,000 ordinary shares, and the Chair will be granted an option to purchase 38,000 ordinary shares (the "Annual Grant"). If a new non-employee director joins the Board following the date of grant of the Annual Grant in any calendar year, such non-employee director will be granted a pro-rata portion of the next Annual Grant, based on the time between his or her appointment and the date of such Annual Grant. Annual Grants shall be vested in full as of the date of grant.

B. CASH FEES

Each non-employee director will receive an annual cash fee for service on the Board and for service on each committee of which the director is a member. The chairs of the Board and of each committee will receive higher fees for such service. The amounts of the fees paid to each non-employee director for service on the Board and for service on each committee of the board of directors on which the director is a member are as follows:

	Member Annual Fee	Chair Annual Fee
Board of Directors	$ 40,000	£ 5,000
Audit Committee	$ 8,500	$ 20,000
Compensation Committee	$ 6,500	$ 14,000
Nominating and Corporate Governance Committee	$ 4,000	$ 8,000
Strategic Committee	$ 30,000	N/A

These fees are payable in arrears in twelve equal monthly installments, subject to deduction of applicable income tax or national insurance which the Company is required by law to deduct and any other statutory deductions, provided that (i) the amount of such payment shall be prorated for any portion of such month during which the director was not serving and (ii) no fee shall be payable in respect of any period prior to the date of the Company's initial public offering.

C. EXPENSES

The reasonable expenses incurred by non-employee directors in connection with attendance at Board or committee meetings or other Company-related activities will be reimbursed upon submission of appropriate documentation.

D. ADMINISTRATION

This Program shall be administered by the Compensation Committee, which shall have the power to interpret these provisions and approve changes from time to time as it deems appropriate.

[***] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED.

Exhibit 10.23

Date: 20 November 2020

(1)	**BICYCLERD LIMITED**
(2)	**BICYCLETX LIMITED**
(3)	**BICYCLE THERAPEUTICS PLC**
(4)	**BICYCLE THERAPEUTICS INC**
(5)	**PEPSCAN SYSTEMS BV**
(6)	**PEPSCAN PRESTO BV**
(7)	**PEPSCAN THERAPEUTICS BV**
(8)	**PEPSCAN HOLDING NV**
(9)	**PEPMAB BV**

SETTLEMENT AND LICENCE AGREEMENT

TABLE OF CONTENTS

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

SETTLEMENT AND LICENCE AGREEMENT

THIS AGREEMENT is made the 20th day of November 2020

BETWEEN

1. **BICYCLERD LIMITED**, formerly named Bicycle Therapeutics Limited, a company incorporated in England and Wales under registration number 06960780, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England;

2. **BICYCLETX LIMITED**, a company incorporated in England and Wales under registration number 11036101, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England;

3. **BICYCLE THERAPEUTICS PLC**, a company incorporated in England and Wales under registration number 11036004, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England; and

4. **BICYCLE THERAPEUTICS INC**, a company incorporated in Delaware, United States of America, whose principal place of business is at 4 Hartwell Place, Lexington, MA, United States of America,

(each, a "**Bicycle Party**" and collectively, "**Bicycle**")

AND

1. **PEPSCAN SYSTEMS BV**, a company incorporated in The Netherlands under registration number 39060590, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

2. **PEPSCAN PRESTO BV**, a company incorporated in The Netherlands under registration number 39097142, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

3. **PEPSCAN THERAPEUTICS BV**, a company incorporated in The Netherlands under registration number 39097144, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

4. **PEPSCAN HOLDING NV**, a company incorporated in The Netherlands under registration number 39096665, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad; and

5. **PEPMAB BV**, a company incorporated in The Netherlands under registration number 62174169, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad,

(each, a "**Pepscan Party**", and collectively, "**Pepscan**")

Unless stated otherwise, Bicycle and Pepscan shall each comprise a "**Party**" and together shall comprise the "**Parties**").

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

RECITALS

A. Whereas, Pepscan is the registered owner of European patent [***] and its counterparts, and further patents and patent applications of the patent family of PCT-application WO 2004 / 0077062.

B. Whereas, the Parties are in on-going litigation in the Netherlands before the District Court The Hague (case number C/09/518528 / HA ZA 16-1091), the Court of Appeal The Hague (case number 200.246.353/01) and the Dutch Supreme Court (case number 20/01602) (the "**Proceedings**").

C. Whereas, the Parties are in ongoing *inter partes* review proceedings before the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("**PTAB**") against patents US 8,742,070 and US 8,748,105 (case numbers IPR 2020-01569 and IPR 2020-01626) (the "**Inter Partes Reviews**").

D. Whereas, the Parties are in ongoing invalidity proceedings before the *Bundespatentgericht* against patent [***], the German part of [***] (filed on 7 September 2020, with case number 3 Ni 25/20 (EP)).

E. Whereas, Pepscan Presto BV and Pepscan Systems BV (collectively, the "**Licensor**") granted BicycleRD Limited a licence under the Pepscan Know-How and under the Pepscan Patents (as defined in clauses 1.1.12 and 1.1.13, respectively) in a licence agreement of 13 August 2009 (the "**PLA 2009**"), replaced by a licence agreement of 1 July 2010 (the "**PLA 2010**"). The PLA 2009 and the PLA 2010 included an obligation for the parties to negotiate in good faith to conclude a service agreement pursuant to which Pepscan Presto BV would serve as BicycleRD Limited's exclusive supplier for the synthesis of so-called CLIPS peptides (article 3.2 of PLA 2010), and an obligation for BicycleRD Limited to keep secret and confidential all know-how communicated to it by the Licensor (article 6 of PLA 2010).

F. Whereas, BicycleRD Limited and Pepscan Presto BV concluded a Framework Service Agreement of 15 March 2010, which was terminated by BicycleRD Limited by letter of 22 May 2015 with effect from 22 August 2015 (the "**FSA**").

G. Whereas, the Licensor terminated the PLA 2010 with immediate effect by letter of 17 March 2016, which termination was confirmed by the Court of Appeal The Hague, which termination is currently the subject of the Supreme Court appeal.

H. Whereas, the Parties are in dispute about the Licensor's right to terminate the PLA 2010 and about the continued exploitation of the Pepscan Know-How and Pepscan Patents (as defined in clauses 1.1.12 and 1.1.13, respectively). As an alternative defence against the consequences of the Licensor's termination of the PLA 2010, BicycleRD Limited filed a conditional nullity claim against the Dutch part of Pepscan's European patent [***], a nullity claim against the German part of Pepscan's European patent [***] and the Inter Partes Reviews (collectively, the "**Bicycle Nullity Actions**").

I. Whereas, in the Proceedings, the District Court held (decision of 18 April 2018) that Bicycle did not breach article 3.2 of the PLA 2010 by breaching or terminating the FSA, but that "it seems likely" that BicycleRD Limited shared confidential know-how of the Licensor with third parties in breach of article 6 of the PLA 2010. Bicycle categorically refute this assumption and were entitled to submit evidence to challenge it; this matter is still outstanding. The Court of Appeal subsequently found (decision of 18 February 2020) that BicycleRD Limited had breached article 3.2 of the PLA 2010 by ordering

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

CLIPS peptides from third party suppliers without the prior consent of the Licensor, and that the Licensor had the right to terminate the PLA 2010. BicycleRD Limited appealed the decision of the Court of Appeal to the Supreme Court. Other grounds for the Licensor's termination of the PLA 2010, the issue as to whether the Licensor supplied any know-how to Bicycle and whether Bicycle used any such know-how or shared such know-how with third parties, and the Bicycle Nullity Actions, are still pending before the District Court.

J. Whereas, the Parties have agreed to settle their differences and have agreed terms for the full and final settlement of the disputes upon and subject to the terms and conditions set forth below, on a fully and effectively binding basis, in this Settlement and Licence Agreement.

IT IS AGREED:

1. DEFINITIONS AND INTERPRETATION

1.1 In this Settlement and Licence Agreement, unless the context otherwise requires:

1.1.1 "**Affiliate(s)**" means any entity from time to time which, directly or indirectly through one or more intermediaries, controls, is controlled by or is under common control with a Party. For the purposes of this definition, the term "control" means the beneficial ownership of more than 50% (fifty percent) of the issued share capital of a company or the legal power to direct or cause the direction of the general management of the company.

1.1.2 "**Bicycle Released Claims**" means any claim in an infringement, revocation or entitlement action, opposition, *inter partes* review, or in any other action relating to the misuse, misappropriation, validity or infringement of intellectual property rights, trade secrets or confidential information, including any claim for liability, right, demand and set-off (including any claims for interest, costs and disbursements), whether or not presently known to the Parties, their assignees, transferees, representatives, principals, officers or directors, and whether in law or equity, that Bicycle, its assignees, transferees, representatives, principals, officers or directors, ever had, may have or hereafter can, shall or may have against Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners prior to the Effective Date or in the future with regard to the Pepscan Patents.

1.1.3 "**BT1718**" is the molecule as illustrated in **Annex 3** (*Licensed Products*).

1.1.4 "**Business Day**" means any day which is not a Saturday or Sunday or a bank holiday in any part of the United Kingdom.

1.1.5 "**Effective Date**" means the terms as defined in clause 2 (*Effective Date*).

1.1.6 "**FDA**" means the Food and Drug Administration of the United States of America.

1.1.7 "**Licensed Products**" means BT1718 and THR149.

1.1.8 "**Marketing Authorisation**" means the authorisation to place a medicinal or healthcare product on the market in the European Union or any part of it, whether centrally or nationally authorised, or any equivalent authorisation

granted by any regulatory authority in any country or region outside the European Union.

1.1.9 "**Marketing Authorisation Application**" means any application for a Marketing Authorisation.

1.1.10 "**Net Sales**" is defined in **Annex 1** (*Net Sales*).

1.1.11 "**New Drug Application**" or "**NDA**" means a formal document submitted by a sponsor company to the FDA seeking approval of a new pharmaceutical for sale and marketing in the United States of America.

1.1.12 "**Pepscan Know-How**" means any confidential information (in the sense that it is or was not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question, has or had commercial value because it is or was secret, and has or had been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret), of which Pepscan is or was the rightful holder, and in respect of which Bicycle has or may have become aware in the course of the Parties' communications and collaborations in relation to the PLA 2009, the PLA 2010 and/or the FSA, which is in existence as at the Effective Date.

1.1.13 "**Pepscan Patents**" means [***].

1.1.14 "**Pepscan Payment Party**" means the term as defined in clause 5.2.

1.1.15 "**Pepscan Released Claims**" means any claim in an infringement, revocation or entitlement action, opposition, *inter partes* review, or in any other action relating to the misuse, misappropriation, validity or infringement of intellectual property rights, trade secrets or confidential information, including any claim for liability, right, demand and set-off (including any claims for interest, costs and disbursements), whether or not presently known to the Parties, their assignees, transferees, representatives, principals, officers or directors, and whether in law or equity, that Pepscan, its assignees, transferees, representatives, principals, officers or directors, ever had, may have or hereafter can, shall or may have against Bicycle, its licensees, suppliers and/or collaboration, development and/or commercialisation partners prior to the Effective Date or in the future with regard to the Pepscan Know-How and the Pepscan Patents, provided that with respect to the Pepscan Patents after the Effective Date this is limited solely to the Licensed Products.

1.1.16 "**Released Contract Claims**" means any contractual claims related to the PLA 2009, the PLA 2010, the FSA, including the Proceedings, whether or not presently known to the Parties, their assignees, transferees, representatives, principals, officers or directors, and whether in law or equity, that a Party, its assignees, transferees, representatives, principals, officers or directors, ever had, may have or hereafter can, shall or may have against the other Party prior to the Effective Date or in the future.

1.1.17 "**Settlement and Licence Agreement**" means this settlement and licence agreement together with any annexes to it.

1.1.18 "**THR149**" is the molecule as illustrated in **Annex 3** (*Licensed Products*).

1.1.19 "**Year**" means any twelve (12) month period during the term of this Settlement and Licence Agreement commencing on 1st January.

1.2 In this Settlement and Licence Agreement, the terms "Bicycle" and "Pepscan" shall include each of the respective entities listed on the cover page, including each Affiliate thereof.

1.3 Where any consent is required from the Bicycle Parties or Pepscan Parties (as applicable) for purposes of this Settlement and Licence Agreement, such consent shall be given by BicycleRD Limited on behalf of the Bicycle Parties, and by Pepscan Systems BV on behalf of the Pepscan Parties.

1.4 The clause and Annex headings are for convenience only and shall not affect the interpretation of this Settlement and Licence Agreement.

1.5 References to "clauses" are to clauses in the main body of this Settlement and Licence Agreement, references to "Annexes" are to schedules of this Settlement and Licence Agreement and references to "paragraphs" are to paragraphs of the Annexes.

1.6 References to the singular include the plural and *vice versa*, and references to one gender include the other genders.

1.7 Any phrase introduced by the expressions "including", "include", "in particular" or any similar expression shall be construed as illustrative and shall not limit the sense of the words preceding those terms.

1.8 Any reference to a statute, statutory provision or subordinate legislation ("**legislation**") (except where the context otherwise requires): (i) shall be deemed to include any bye laws, licences, statutory instruments, rules, regulations, orders, notices, directions, consents or permissions made under that legislation; and (ii) shall be construed as referring to any legislation which replaces, re-enacts, amends or consolidates such legislation (with or without modification) at any time.

1.9 In the case of any inconsistency between any provision of the Annexes to this Settlement and Licence Agreement and any term of this Settlement and Licence Agreement, the latter shall prevail.

2. EFFECTIVE DATE

This Settlement and Licence Agreement shall take effect upon signature of it by the last of the Parties and such date shall comprise the Effective Date. The licences to be granted under clause 3 (*Grant of Licences*) shall, however, take effect as soon as the Pepscan Payment Party has received Bicycle's lump sum payment in accordance with the provisions of clause 4.2.1 below.

3. GRANT OF LICENCES

In consideration for the payments referred to in clause 4 (*Financial Settlement Terms*) below, Pepscan hereby grants to Bicycle with effect from the date on which Pepscan has received Bicycle's lump sum payment in accordance with the provisions of clause 4.2.1 below, irrevocable, perpetual, sub-licensable (through multiple tiers), non-exclusive worldwide licences under the Pepscan Patents to make, develop, use, manufacture, import, sell, dispose of, offer to sell, stock or otherwise supply the

Licensed Products and to apply for Marketing Authorisations and/or NDAs in respect of the Licensed Products and/or exploit the Pepscan Patents in any other way in respect of the Licensed Products and under the Pepscan Know-How to develop, use, manufacture, import, sell, dispose of, offer to sell, or otherwise supply the Licensed Products and apply for Marketing Authorisations and/or NDAs in respect of the Licensed Products and/or exploit the Pepscan Know-How in any other way.

4. FINANCIAL SETTLEMENT TERMS

4.1 In consideration for the grant of the licences referred to in clause 3 (*Grant of Licences*) above, and to recognise the use that Bicycle has or may (if at all) have made of the Pepscan Patents and Pepscan Know-How in the development of the Licensed Products, the Parties hereby agree to the financial terms contemplated in this clause 4 (*Financial Settlement Terms*). For the avoidance of doubt, the payments contemplated in this clause 4 (*Financial Settlement Terms*) shall be the sole payments due and payable by Bicycle to Pepscan and no additional payments shall be made by Bicycle pursuant to this Settlement and Licence Agreement and the matters giving rise to it.

Lump sum payments

4.2 Bicycle shall, subject to the provisions of clause 5 (*Payment Terms*), pay to the Pepscan Payment Party the following lump sum payments in accordance with the following terms:

4.2.1 within five (5) Business Days of the Effective Date, Bicycle shall place €2 million (two million euros) into escrow ("**Escrow Sum**") in the third-party escrow account of [***] ("**Escrow Account Holder**"), as further detailed at **Annex 2** (*Escrow Details*). With regard to the Escrow Sum:

4.2.1.1 such Escrow Sum shall remain in escrow until Pepscan has executed the steps required to be taken by it to withdraw from the Proceedings in accordance with clause 6.2 below; and

4.2.1.2 thereafter, the Escrow Account Holder shall be ordered to pay the Escrow Sum to the Pepscan Payment Party within [***] of Pepscan's execution of the steps required to be taken by it to withdraw from the Proceedings; and

4.2.2 €1 million (one million euros) on the first anniversary of the Effective Date.

Milestone payments

4.3 Bicycle shall, in addition to the lump sum payments contemplated in clause 4.2 above and also subject to the provisions of clause 5 (*Payment Terms*), pay to the Pepscan Payment Party certain additional lump sum payments upon certain performance-based milestones related to the development and marketing of the Licensed Products, if and when achieved, as set out below.

BT1718

4.4 Subject to clauses 4.7 and 5 (*Payment Terms*), Bicycle shall pay to the Pepscan Payment Party the following:

4.4.1 [***] upon the [***] of BT1718;

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

4.4.2 [***] of BT1718 for either:

4.4.2.1 [***]; or

4.4.2.2 [***]; and

4.4.3 the following sales milestone payments:

4.4.3.1 [***] payable following the end of the Year in which cumulative Net Sales of [***] of BT1718 are achieved;

4.4.3.2 [***] payable following the end of the Year in which cumulative Net Sales of a further [***] of BT1718 are achieved; and

4.4.3.3 [***] payable following the end of the Year in which cumulative Net Sales of a further [***] of BT1718 are achieved.

THR149

4.5 Subject to clauses 4.7 and 5 (*Payment Terms*), Bicycle shall pay to the Pepscan Payment Party the following:

4.5.1 [***] on the [***] of THR149;

4.5.2 [***] on the [***] of THR149 for either:

4.5.2.1 [***]; or

4.5.2.2 [***]; and

4.5.3 the following sales milestone payments:

4.5.3.1 [***] payable following the end of the Year in which cumulative Net Sales of [***] of THR149 are achieved;

4.5.3.2 [***] payable following the end of the Year in which cumulative Net Sales of a further [***] of THR149 are achieved; and

4.5.3.3 [***] payable following the end of the Year in which cumulative Net Sales of a further [***] of THR149 are achieved.

4.6 For the avoidance of doubt:

4.6.1 the milestone payments pursuant to clauses 4.4.1, 4.4.2, 4.5.1, and 4.5.2 above shall be payable only once in relation to each Licensed Product, notwithstanding how many [***];

4.6.2 the applicable milestone payments under clauses 4.4 and 4.5 are due and payable, if Bicycle or any third party with the consent of Bicycle triggers a milestone pursuant to clauses 4.4.1, 4.4.2, 4.5.1, or 4.5.2, or if the Licensed Product Net Sales reach a milestone set out in clauses 4.4.3 or 4.5.3; and

4.6.3 each milestone payment payable pursuant to clauses 4.4.3 and 4.5.3, shall be payable only once on the achievement of the given volume of Net Sales.

4.7 For purposes of facilitating the payment by Bicycle to the Pepscan Payment Party of the relevant milestone payments contemplated in clauses 4.4 and 4.5 above, Bicycle shall report to Pepscan, by way of a written notice, the occurrence of the relevant milestones (each, a "**Milestone Notice**"), which serves to notify the Pepscan Payment Party of its obligation to issue the valid VAT invoices for the corresponding milestone payments in accordance with clause 5.4 below. In this regard:

4.7.1 Bicycle shall, with regard to each of the milestones provided for in clauses 4.4.1, 4.4.2, 4.5.1 and 4.5.2, provide to Pepscan a Milestone Notice within [***] of:

4.7.1.1 the occurrence of the milestone event giving rise to the payment obligation, where such milestone event is carried out by Bicycle; and

4.7.1.2 Bicycle receiving notification from a third party of the occurrence of the milestone event giving rise to the payment obligation, where such milestone event is carried out by the aforesaid third party with the consent of Bicycle, it being understood that Bicycle shall contractually commit third parties with which it enters a licence agreement for BT1718 and/or THR149 after the Effective Date to notify Bicycle of the occurrence of a milestone event [***]; and

4.7.2 Bicycle shall, with regard to each of the milestones provided for in clauses 4.4.3 and 4.5.3, provide to Pepscan a Milestone Notice within:

4.7.2.1 [***] of the end of the preceding Year where the Net Sales meet or exceed the relevant thresholds, in circumstances where Bicycle made the sales and received the income directly; and

4.7.2.2 in circumstances where sales of BT1718 and/or THR149 have been made by authorised Bicycle licensees, [***] of Bicycle receiving net sales reports from the aforesaid licensees, [***], which report the net sales of BT1718 and/or THR149 by such licensee during the preceding Year where the Net Sales meet or exceed the relevant thresholds,

and each Milestone Notice shall further include the value of the milestone payment amount due as well as a brief description of the milestone event. Such Milestone Notices shall be sent to the Pepscan Payment Party via e-mail to [***] or to such other address as may be communicated in writing by Pepscan to Bicycle from time to time, and such e-mail shall constitute written notice for the purposes of this clause 4.7.

5. PAYMENT TERMS

5.1 Each Bicycle Party shall be jointly and severally liable for all the payments to be made to Pepscan pursuant to clause 4 (*Financial Settlement Terms*).

5.2 Pepscan hereby nominates Pepscan Systems BV as the Pepscan Party that shall invoice and accept payments made by Bicycle in accordance with this Settlement and Licence Agreement for, and on behalf of, the Pepscan Parties ("**Pepscan Payment Party**"). For the avoidance of doubt:

5.2.1 upon payment by Bicycle of the payments to the Pepscan Payment Party in accordance with this Settlement and Licence Agreement, such payment shall fulfil Bicycle's payment obligation to all Pepscan Parties; and

5.2.2 it shall be incumbent upon the Pepscan Payment Party to distribute such payments amongst the Pepscan Parties, as may be determined by Pepscan.

5.3 All amounts payable by Bicycle to Pepscan under clause 4 (*Financial Settlement Terms*) shall, subject to and without prejudice to the provisions set out in **Annex 1** (*Net Sales*), be paid [***], and all amounts payable are [***] invoice.

5.4 The Pepscan Payment Party shall submit valid VAT invoices to Bicycle at [***], or such other e-mail address as may be communicated in writing by Bicycle to the Pepscan Payment Party from time to time, for all the amounts payable by Bicycle to Pepscan under clause 4 (*Financial Settlement Terms*), as follows:

5.4.1 with regard to the lump sum payments contemplated at clause 4.2 above, the Pepscan Payment Party shall submit valid VAT invoices to Bicycle within [***] from such lump sum amounts becoming due; and

5.4.2 with regard to the milestone payments contemplated in clauses 4.4 and 4.5 above, the Pepscan Payment Party shall submit valid VAT invoices to Bicycle within [***] from receipt of the relevant Milestone Notice in accordance with clause 4.7 above.

5.5 The Pepscan Payment Party shall ensure that each invoice issued in accordance with clause 4 (*Financial Settlement Terms*):

5.5.1 is calculated in accordance with this Settlement and Licence Agreement; and

5.5.2 contains such other information reasonably requested by Bicycle, including bank account details.

5.6 Bicycle shall pay each undisputed invoice submitted by the Pepscan Payment Party in accordance with clauses 5.4 and 5.5, within [***] of receipt. All payments shall be made by Bicycle in Euros by bank transfer to the account of the Pepscan Payment Party at a bank to be nominated in writing by the Pepscan Payment Party from time to time.

5.7 If Bicycle fails to make a payment due to Pepscan under this Settlement and Licence Agreement by the due date, then Bicycle shall pay interest on the overdue sum from the due date until payment of the overdue sum, whether before or after judgment. Interest under this clause will accrue at [***].

5.8 If Bicycle disputes a payment in good faith in accordance with clause 5.9, then the interest payable under clause 5.7 is only payable after the dispute is resolved, on sums found or agreed to be due, from [***] after the date upon which the dispute is resolved until payment.

5.9 If, following receipt of any invoice, Bicycle notifies Pepscan in writing of a good faith dispute concerning any of the amounts payable under such invoice (indicating in such notice the basis for its dispute), then:

5.9.1 where applicable, the Pepscan Payment Party shall issue two (2) replacement invoices, one in respect of the disputed amount and one in respect of the undisputed amount;

5.9.2 where applicable, Bicycle shall pay the invoice for the undisputed amount but shall be entitled to withhold the disputed amount pending resolution in accordance with the dispute resolution process contemplated in clause 13 (*Dispute Resolution*); and

5.9.3 upon resolution of the disputed amount, Bicycle shall pay any amounts determined or agreed to be payable to Pepscan by no later than the date which is [***] after the date upon which the disputed amount was resolved.

6. WITHDRAWAL OF PROCEEDINGS AND RELEASE

6.1 This Settlement and Licence Agreement comprises full and final settlement of the Pepscan Released Claims, Bicycle Released Claims and Released Contract Claims and without limitation on each Party's rights and obligations under this Settlement and Licence Agreement, as of the Effective Date and thereafter:

6.1.1 each Party (i) releases and forever discharges any and all of the Released Contract Claims and (ii) undertakes not, at any stage in the future, to commence or re-institute any proceedings relating to the Released Contract Claims against a Party;

6.1.2 Bicycle (i) releases and forever discharges any and all of the Bicycle Released Claims, and (ii) undertakes not, at any stage in the future, to commence or re-institute any proceedings or oppositions relating to the Bicycle Released Claims against Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners, unless Pepscan commences patent infringement proceedings based on a patent within the Pepscan Patents against Bicycle, its licensees, suppliers and/or collaboration, development and/or commercialisation partners, in which case Bicycle shall be allowed to counterclaim for invalidity against that patent; and

6.1.3 Pepscan (i) releases and forever discharges any and all of the Pepscan Released Claims, and (ii) undertakes not, at any stage in the future, to commence or re-institute any proceedings or oppositions relating to the Pepscan Released Claims against Bicycle, its licensees, suppliers and/or collaboration, development and/or commercialisation partners.

6.2 As soon as the Escrow Account Holder confirms that the Escrow Sum has been placed in escrow in accordance with the terms of clause 4.2.1.1 and in any event within [***] of such confirmation each Party shall withdraw from:

6.2.1 the Proceedings; and

6.2.2 the Bicycle Nullity Actions, and for purposes of the Inter Partes Reviews, the Parties shall jointly request authorisation from the PTAB to file joint motions to terminate proceedings and will file such motions, together with this Settlement and Licence Agreement under seal, upon authorisation from the PTAB.

7. NO ADMISSION

This Settlement and Licence Agreement is entered into for the purposes of compromise only. It is not and shall not be represented or construed by the Parties as an admission or as evidence of wrongdoing on the part of any Party or any other person or entity, nor as an acknowledgement of the existence or disclosure of any relevant know-how.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

8. COSTS

Each Party shall bear their own legal costs and expenses in relation to the Proceedings and the Bicycle Nullity Actions as well as the drafting, negotiation and implementation of this Settlement and Licence Agreement and any further agreements arising from it.

9. AUDIT RIGHTS

9.1 Pepscan shall be entitled to procure access to any of Bicycle's records to verify the achievement (or not) of the milestones under clauses 4.4 and 4.5 ("**Audit**"), provided that Pepscan shall only procure such Audit by appointing an external, reputable, independent and international firm of registered accountants that can cover both Europe and the United States of America and which have offices in both such jurisdictions ("**Auditors**") and Pepscan shall not conduct the Audit itself and/or with the assistance of any Pepscan personnel.

9.2 The Auditors shall be bound by confidentiality provisions consistent with those contemplated in clause 10 (*Confidentiality)* below, and Bicycle reserves the right to require the Auditors to enter into a separate confidentiality agreement directly with Bicycle prior to the Auditors commencing with the Audit. For the avoidance of doubt, Pepscan shall not be entitled to have any access to and/or have sight of Bicycle's records that are the subject of the Audit, and Pepscan shall therefore rely on the formal report issued by the Auditors following the completion of the Audit.

9.3 Pepscan shall provide at least [***] notice of its intention to procure an Audit, and any Audit shall be conducted by the Auditors during business hours.

9.4 Subject to Bicycle's confidentiality obligations, Bicycle shall provide the Auditors with all reasonable co-operation, access and assistance in relation to each Audit.

9.5 Pepscan shall use its reasonable endeavours to ensure that the conduct of each Audit does not unreasonably disrupt Bicycle and that individual Audits are co-ordinated with each other to minimise any disruption. The Parties agree that there shall be no more than one (1) Audit per Year.

9.6 Irrespective of the outcome of any Audit, the Parties shall bear their own costs and expenses incurred in respect of the conduct of Audits and their compliance with their obligation under this clause 9 (*Audit Rights*).

9.7 Each Bicycle Party shall, and shall procure that its sub-licensees with which it enters a licence agreement for BT1718 and/or THR149 after the Effective Date shall, keep true, complete, separate and detailed records and books containing all data reasonably required for the computation and verification of the achievement of the milestones set out in clauses 4.4 and 4.5. Within not more than [***] from the Effective Date, Bicycle shall request the same from any sub-licensees with which it entered a licence agreement for BT1718 and/0r THR149 before the Effective Date.

10. CONFIDENTIALITY

10.1 The terms of this Settlement and Licence Agreement and the negotiations which led to it are to remain confidential between the Parties (the "**Confidential Information**"), save that they may be disclosed:

10.1.1 by any Party with the prior written consent of the other Party;

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

10.1.2 subject to clause 10.3, by any Party to its respective professional advisers or auditors, to the extent necessary to enable them to perform their functions properly for such Party;

10.1.3 subject to clause 10.3, by any Party to: (i) potential acquirors (and their respective professional advisers), to the extent necessary to enable them to consider, evaluate, negotiate and/or advance a potential acquisition or transaction related to that Party; and (ii) financing sources (and their respective professional advisers), to the extent necessary to enable them to consider, evaluate, negotiate and/or advance a potential financing transaction related to that Party;

10.1.4 by any Party to the extent such disclosure is, in the reasonable opinion of such Party's legal counsel, required to be disclosed pursuant to law, regulation or a valid order of a court of competent jurisdiction or other governmental body of competent jurisdiction (including, for the avoidance of doubt, the U.S. Securities and Exchange Commission); provided that the Party intending to make the disclosure shall, to the extent legally permissible, first have given prompt written notice (and to the extent practicable, at least [***]) to the other Party and give the other Party a reasonable opportunity to take whatever action it deems necessary to protect its Confidential Information. If no protective order or other remedy is obtained, the Party making the disclosure shall furnish only that portion of Confidential Information which such Party is advised by counsel is legally required to be disclosed.

10.2 In the event that a given Party is required to make a disclosure pursuant to the above clause 10.1, the other Party will be permitted to disclose the same information should it wish to do so provided such disclosure shall be made under and/or pursuant to the same confidentiality protections (if any) under which the first Party made the disclosure, including as set out in clause 10.1.4.

10.3 To the extent that a Party discloses Confidential Information to the third parties contemplated in clauses 10.1.2 and/or 10.1.3 above (as applicable) ("**Authorised Persons**"), such disclosure shall be on a "need-to-know" basis and made solely for the purposes contemplated in clauses 10.1.2 and 10.1.3 (as applicable), and the Party disclosing the Confidential Information shall:

10.3.1 inform all such Authorised Persons that the Confidential Information is confidential and subject to the terms contemplated in this clause 10 (*Confidentiality*);

10.3.2 ensure that all such Authorised Persons are under a duty of confidentiality or otherwise enter into written confidentiality agreements with it on terms consistent with this clause 10 (*Confidentiality*); and

10.3.3 be responsible for all acts and omissions of Authorised Persons as though they were its own acts or omissions under this clause 10 (*Confidentiality*).

10.4 The Parties shall not use the Confidential Information other than as contemplated by this Settlement and Licence Agreement.

10.5 The provisions of this clause 10 (*Confidentiality*) shall not apply to any information which at the time of its disclosure was already generally available to the public other than by reason of a breach of the terms of this Settlement and Licence Agreement, or

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

otherwise becomes part of the public domain other than by reason of a breach of the terms of this Settlement and Licence Agreement.

10.6 Without prejudice to any other rights or remedies that any Party may have, each Party acknowledges and agrees that damages alone would not be an adequate remedy for any breach of the terms of this clause 10 (*Confidentiality*). Accordingly, each Party shall be entitled to the remedies of injunctions, specific performance or other equitable relief for any threatened or actual breach of this clause 10 (*Confidentiality*).

11. COMMUNICATION

11.1 Subject to clauses 10.1 and 11.2, a Party shall not make any public announcement or issue any media release relating to the execution or subject matter of this Settlement and Licence Agreement without the prior written consent of the other Party as to the form, content and timing of the announcement or release.

11.2 Included at **Annex 4** (*Communication Statement*) is an agreed form of wording that the Parties shall publicly communicate (including on their websites) the terms of this Settlement and Licence Agreement.

12. CHANGE OF CONTROL

12.1 If there is an acquisition of any of the Pepscan Parties or Bicycle Parties (as applicable) ("**Target**"), whether by a third party or an Affiliate of the Target ("**Acquirer**"), meaning the sale or other transfer of the entire issued share capital of the Target or any merger, scheme of arrangement or other similar transaction resulting in the Acquirer (or persons acting in concert with the Acquirer) holding (whether by one or a series of related transactions) all the shares in the Target, the Target undertakes to Bicycle or Pepscan (as applicable) that it shall not as a part of such sale or other transfer of the entire issued share capital or merger, scheme of arrangement or other similar transaction take any actions that would result in the Target ceasing to be bound by the rights and obligations under this Settlement and Licence Agreement.

12.2 Subject to clauses 12.3 and 12.5:

12.2.1 if there is a sale, transfer or other means of disposition (including by means of out-license) of all or substantially all of the business or assets of a Party ("**Transferor**") to a third party or an Affiliate, new entity or separate division of the Transferor, the Transferor undertakes that it shall: (i) transfer any and all of its rights and obligations under this Settlement and Licence Agreement to the successor in interest ("**Transferee**"); and (ii) procure that such Affiliate, new entity or separate division of the Transferor (as applicable) shall, for the purposes of clause 12.4 of this Settlement and Licence Agreement, grant to the other Party, as represented by any one entity of such Party, a power of attorney in the form contained in **Annex 5** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any such sale, transfer or other means of disposition pursuant to this clause 12.2.1; and

12.2.2 if there is a sale, transfer or other means of disposition (including by means of out-license) of any of the Pepscan Patents and/or the Pepscan Know-How by any Pepscan Party ("**Transferor**"), including a sale, transfer or other disposition (including by means of out-license) of one or more of the Pepscan Patents or the Pepscan Know-How to a third party or an Affiliate, new entity or separate division of the Transferor, the Transferor undertakes that it shall:

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

(i) ensure that the new owner of the Pepscan Patents and/or the Pepscan Know-How ("**Transferee**") shall be contractually bound to Bicycle by the rights and obligations of Pepscan under clauses 3 (*Grant of Licences*) and 6 (*Withdrawal of Proceedings and Release*); and (ii) procure that such Affiliate, new entity or separate division of the Transferor (as applicable) shall, for the purposes of clause 12.4 of this Settlement and Licence Agreement, grant to Bicycle, as represented by any one nominated Bicycle Party, a power of attorney in the form contained in **Annex 5** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any such sale, transfer or other means of disposition pursuant to this clause 12.2.2.

12.3 In the event that there is a sale, transfer or other disposition (including by means of out-license) by a Party ("**Transferor**") to an Affiliate, new entity or separate division ("**Affiliate Transferee**") pursuant to any of sub-clauses 12.2.1 or 12.2.2, and such Affiliate, new entity or separate division of the Transferor (as applicable) is subsequently sold or transferred by the applicable Affiliate Transferee to a third party, then the Transferor shall procure that the Affiliate Transferee either:

12.3.1 transfers such: (i) business or assets (and in each case any contracts); or (ii) Pepscan Patents and/or Pepscan Know-How (as applicable) back to the original Transferor (or another Affiliate of the original Transferor) and the applicable rights and obligations under this Settlement and Licence Agreement shall also be transferred back by the Affiliate Transferee to the original Transferor (or another Affiliate of the original Transferor). To the extent the transfer made pursuant to this clause is made to an Affiliate of the original Transferor and such Affiliate has not previously executed a power of attorney in accordance with clauses 12.2.1, 12.2.2 or 12.4 of this Settlement and Licence Agreement, then the Transferor shall procure that such Affiliate of the original Transferor shall, for the purposes of clause 12.4 of this Settlement and Licence Agreement, grant to the other Party, as represented by any one entity of such Party, a power of attorney in the form contained in **Annex 5** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any transfer back to the Affiliate of the original Transferor pursuant to this clause 12.3.1; or

12.3.2 undertake to ensure that, as applicable:

12.3.2.1 the new owner of the business or assets shall also be contractually bound by the rights and obligations under this Settlement and Licence Agreement; or

12.3.2.2 the new owner of the Pepscan Patents and/or Pepscan Know-How (as applicable) shall also be contractually bound to Bicycle by the rights and obligations under clauses 3 (*Grant of Licences*) and 6 (*Withdrawal of Proceedings and Release*).

12.4 In order to facilitate the transfer of rights and obligations set out in sub-clauses 12.2.1 and 12.2.2 and clause 12.3: (i) the other Party ("**Remaining Party**") agrees to do all acts and things, and provide the Transferor with all assistance (including the execution of any documentation), reasonably requested in writing by the Transferor, and which is necessary, in order to effect such transfer from the Transferor to the Transferee or Affiliate Transferee or new owner under clause 12.3.2 (as applicable), provided that such acts and assistance do not impose any additional obligations on the Remaining Party (other than the doing of such things and assistance); and (ii) each Party shall

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

simultaneously with the execution of this Settlement and Licence Agreement grant to the other a power of attorney in the form contained in **Annex 5** (*Power of Attorney*) of this Settlement and Licence Agreement (with the Party acting as the attorney, in each case, to be represented by any one entity of such Party) (and shall deliver the original of such power of attorney concurrently with execution this Settlement and Licence Agreement) so as to permit the Transferor to execute on its behalf any documentation required to perfect any transfer from the Transferor to the Transferee, or Affiliate Transferee, or new owner under clause 12.3.2 (as applicable), but not for any other purpose whatsoever.

12.5 The Transferor shall indemnify the Remaining Party and keep it indemnified from and against any and all liabilities, costs, expenses, damages and losses suffered or incurred by the Remaining Party arising as a result of any failure of the Transferor to secure the transfer of rights and obligations to the Transferee in accordance with the provisions of clause 12.2 or the Transferor's failure to comply with the terms of clause 12.3 (as applicable). The Remaining Party shall have an obligation to mitigate any loss, and shall not be entitled to recover any legal costs or costs for management time incurred in pursuing the indemnity set out in this clause 12.5. For the avoidance of doubt, if and to the extent that the failure of the Transferor to secure the transfer of rights and obligations to the Transferee, Affiliate Transferee or new owner pursuant to clause 12.3.2 (as applicable) in accordance with the provisions of clause 12.2 and clause 12.3 (as applicable) or the Transferor's failure to comply with the terms of clause 12.3 (as applicable) is a result of the Remaining Party's breach of clause 12.4, this indemnity may not be invoked by the Remaining Party.

12.6 Without prejudice to any other rights or remedies that each Party may have, each Party acknowledges and agrees that damages alone would not be an adequate remedy for any breach of the terms of this clause 12 (*Change of Control*). In particular, with regard to clause 12.4, the Parties recognise that significant damage shall be caused to the Transferor should the Remaining Party not provide the necessary assistance to the Transferor, as required in accordance with such clause 12.4. Accordingly, each Party shall be entitled to the remedies of injunctions, specific performance or other equitable relief for any threatened or actual breach of this clause 12 (*Change of Control*).

12.7 Each Party shall keep confidential the terms and existence of any transaction or potential transaction to be implemented by the other Party in accordance with the terms of this clause 12 (*Change of Control*), save that details of any such transaction or potential transaction may be disclosed in accordance with clauses 10.1.1, 10.1.2, 10.1.3 or 10.1.4.

13. DISPUTE RESOLUTION

13.1 Except as provided for in clause 13.6 any dispute arising out of or in connection with this Settlement and Licence Agreement including any question regarding its existence, validity or termination, shall be exclusively referred to and finally resolved by arbitration under the LCIA Rules, which Rules are deemed to be incorporated by reference into this clause 13.1.

13.2 The number of arbitrators shall be three.

13.3 The seat, or legal place, of arbitration shall be [***].

13.4 The language to be used in the arbitral proceedings shall be English.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

13.5 Arbitration conducted in accordance with this clause 13 (*Dispute Resolution*) shall be governed by and construed in accordance with the law of England and Wales.

13.6 Any application for equitable relief made by a Party pursuant to clauses 10.6 and 12.6 or any dispute relating to any such application, shall be subject to the exclusive jurisdiction of the courts of England and Wales.

14. ENTIRE AGREEMENT

14.1 Subject to clause 14.2, this Settlement and Licence Agreement constitutes the entire agreement between the Parties in relation to its subject matter and replaces and extinguishes all prior heads of terms, agreements, draft agreements, arrangements, undertakings, or collateral contracts of any nature made by the Parties, whether oral or written, relating to that subject matter.

14.2 Nothing in this Agreement shall exclude or restrict the liability of any Party arising out of fraud, fraudulent misrepresentation or fraudulent concealment.

15. NOTICES

15.1 Any notice to be given under this Settlement and Licence Agreement ("**Notice**") must be in writing, and delivered by courier or recorded first class post.

15.2 A Notice served under this Agreement will be deemed to be received upon the sooner of:

15.2.1 delivery of the Notice; or

15.2.2 if couriered or posted to a recipient in the same country as the sender, [***] and if sent to a recipient in a different country to the sender, [***].

15.3 The details of the Parties for the purpose of Notices relating to this Settlement and Licence Agreement are as follows:

Party	**Contact**	**Address**
BICYCLERD LIMITED	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLETX LIMITED	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLE THERAPEUTICS PLC	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLE THERAPEUTICS INC	[***], General Counsel	4 Hartwell Place, Lexington, MA, United States of America
PEPSCAN SYSTEMS BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPSCAN PRESTO BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

PEPSCAN THERAPEUTICS BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPSCAN HOLDING NV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPMAB BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands

15.4 Each Party may alter the above details which relate to it and shall promptly notify the other Party of any such change by a Notice in accordance with this clause 15 (*Notices*). The change will take effect [***] after the day on which the Notice of the change is deemed to be delivered in accordance with clause 15.2.

16. GOVERNING LAW

16.1 This Settlement and Licence Agreement and any non-contractual obligation arising out of or in connection to this Settlement and Licence Agreement, including any question regarding its existence, validity or termination, will be governed by and construed in accordance with the law of England and Wales.

16.2 For the avoidance of doubt, the PLA 2009, PLA 2010, and FSA, including any and all disputes between the Parties arising thereof or in connection therewith, remain to be governed by and construed in accordance with Dutch law.

17. GENERAL PROVISIONS

17.1 The Parties agree that no Party shall have, and each Party waives, any right to terminate all, or any part, of this Agreement, whether under contract, statute, tort, common law or otherwise.

17.2 Except in accordance with clause 12 (*Change of Control*), no Party shall assign, novate or transfer any rights or obligations under this Settlement and Licence Agreement without the prior written consent of the other Party.

17.3 No variation of this Settlement and Licence Agreement shall be effective unless made in writing and signed by or on behalf of each of the Parties.

17.4 In the event of any clause of this Settlement and Licence Agreement or any part of such clause being declared illegal, invalid or unenforceable by any court, authority or relevant arbitral panel of competent jurisdiction, that clause or part thereof shall be deemed not to form part of this Settlement and Licence Agreement, all other clauses or parts thereof contained in this Settlement and Licence Agreement shall remain in full force and shall not be affected thereby. The Parties shall negotiate in good faith to agree a replacement provision that, to the greatest extent possible, achieves the intended commercial result of the original provision.

17.5 The failure to exercise, or delay in exercising, a right, power or remedy provided by this Settlement and Licence Agreement or by law shall not constitute a waiver of that right, power or remedy. If a Party waives a breach of any provision of this Settlement and Licence Agreement this shall not operate as a waiver of a subsequent breach of that provision, or as a waiver of a breach of any other provision.

17.6 The rights, powers and remedies provided in this Settlement and Licence Agreement are cumulative and not exclusive of any rights, powers and remedies provided by the law, or otherwise.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

17.7 Nothing in this Settlement and Licence Agreement shall be deemed to constitute a partnership, collaboration or joint venture between the Parties, nor to create a relationship of principal and agent for any purpose between the Parties, nor to authorise any Party to make or enter into any commitments for or on behalf of the other Party except as expressly provided in this Settlement and Licence Agreement.

17.8 This Settlement and Licence Agreement may be entered into in any number of counterparts. Each counterpart shall, when signed, be regarded as an original, and all the counterparts together shall together constitute one and the same Settlement and Licence Agreement. This Agreement shall not take effect until it has been signed by the Parties. This Settlement and Licence Agreement may validly be executed by electronic signature (in an agreed form) and exchanged and delivered by e-mail.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

SIGNED FOR AND ON BEHALF OF
BICYCLE THERAPEUTICS PLC:

/s/ Kevin Lee……

Name/Position: Dr Kevin Lee, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLETX LIMITED:

/s/ Kevin Lee……

Name/Position: Dr Kevin Lee

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLERD LIMITED:

/s/ Kevin Lee ……

Name/Position: Dr Kevin Lee

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLE THERAPEUTICS INC.:

/s/ Lee Kalowski……

Name/Position: Lee Kalowski, President & CFO

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN SYSTEMS BV:

/s/ Hans de Backer……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN PRESTO BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN THERAPEUTICS BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN HOLDING NV:

/s/ Hans de Backer ……

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Name/Position: Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPMAB BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

ANNEX 1 – NET SALES

1. "**Net Sales**" shall mean the total product sales of each of the Licensed Products, made directly by Bicycle and any of its authorised licensees anywhere in the world. Net Sales shall be subject to the following deductions, [***].

2. In calculating the Net Sales, any disposal of a Licensed Product by Bicycle and, to the extent applicable, any of its authorised licensees:

   [***].

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

ANNEX 2 – ESCROW DETAILS

Escrow details:

[***]

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ANNEX 3 – LICENSED PRODUCTS

[Redacted content comprises approximately 2 pages.]

BT1718

[***]

THR149

[***]

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

ANNEX 4 – COMMUNICATION STATEMENT

Bicycle Therapeutics Announces Settlement of Patent Dispute with Pepscan Systems B.V.

CAMBRIDGE, England, & BOSTON – [TBD], 2020 – Bicycle Therapeutics plc (NASDAQ:BCYC), a clinical-stage biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (*Bicycle*®) technology, today announced that it has entered into a settlement and license agreement with Pepscan Systems B.V. regarding Bicycle's use of Pepscan's CLIPS peptide technology.

The companies have agreed to settle all intellectual property disputes worldwide. Under the terms of the settlement, Bicycle has been granted a license to use CLIPS peptide technology in the development of its product candidates BT1718 and THR-149. Bicycle will pay €3 million upfront, will pay €1 million on the first anniversary of the date of settlement, and will make potential additional payments to Pepscan based on achievement of specified clinical, regulatory and commercial milestones.

About Bicycle Therapeutics
Bicycle Therapeutics (NASDAQ: BCYC) is a clinical-stage biopharmaceutical company developing a novel class of medicines, referred to as *Bicycles*®, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making *Bicycles* attractive candidates for drug development. Bicycle's lead product candidate, BT1718, a *Bicycle* Toxin Conjugate (BTC) that targets MT1-MMP, is being investigated in an ongoing Phase I/IIa clinical trial in collaboration with the Centre for Drug Development of Cancer Research UK. Bicycle is also evaluating BT5528, a second-generation BTC targeting EphA2, in a Company-sponsored Phase I/II study. BT8009 is a BTC targeting Nectin-4, a well-validated tumor antigen, and is also currently being evaluated a Company-sponsored Phase I/II trial. Bicycle is headquartered in Cambridge, UK with many key functions and members of its leadership team located in Lexington, MA. For more information, visit bicycletherapeutics.com.

Forward-Looking Statements
This press release may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will" and variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding Bicycle's use of CLIPS peptide technology in the development of its product candidates BT1718 and THR-149, Bicycle's future payment obligations to Pepscan, and Bicycle's contemplated achievement of specified clinical, regulatory and commercial milestones. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking

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statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: risks to site initiation, clinical trial commencement, patient enrollment and follow-up, as well as to Bicycle's abilities to meet other anticipated deadlines and milestones, presented by the ongoing COVID-19 pandemic; uncertainties inherent in the initiation and completion of clinical trials by Bicycle or its collaboration partners and in the clinical development of Bicycle's product candidates; availability and timing of results from clinical trials; expectations for regulatory approvals to conduct trials or to market product; and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled "Risk Factors" in Bicycle's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 5, 2020, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

Investor and Media Contact:
Bicycle Therapeutics
Maren Killackey
maren.killackey@bicycletx.com
+1-617-203-8300

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Pepscan grants Bicycle Therapeutics a global CLIPS Technology license for product candidates BT1718 and THR-149

Lelystad, the Netherlands – [TBD] 2020 – Pepscan, the all-in-one peptide service provider with proprietary peptide constraining technologies, today announced that it has entered into a global agreement with Bicycle Therapeutics plc regarding the use of Pepscan's CLIPS peptide technology for the further development of Bicycle's product candidates BT1718 and THR-149.

As expert in constrained peptides, Pepscan developed a proprietary, highly versatile constraining technology to lock peptides into active conformations, called CLIPS (**C**hemical **Li**nkage of **P**eptides onto **S**caffolds). The CLIPS cyclization technology is known for its versatility and ease of application. CLIPS-peptides are recognized for their enhanced affinity, selectivity and proteolytic stability.

Peter Timmerman, CSO and inventor of the CLIPS technology: "We are proud to grant Bicycle a license for the continued use of the CLIPS technology for BT1718 and THR-149".

As part of the agreement, Pepscan and Bicycle have agreed to settle all intellectual property disputes worldwide.

About Pepscan

Pepscan is the all-in-one peptide service provider, building on 25 years of experience in advancing and applying peptide expertise to facilitate clients in the development and (GMP) production of peptides. At its end-to-end facility in Lelystad, the Netherlands, Pepscan offers a range of patented technologies, phage display capabilities, a lead-optimization array platform, and production facilities for R&D- to GMP-grade peptides, including libraries and neoantigen vaccines. Among its patents is the CLIPS technology, which locks peptides into active conformations. With its epitope mapping service platform, Pepscan also supports biotech companies in developing their antibody pipelines. The underlying protein mimicry platform delivers binding insights, even in cases where other technologies fall short. For more information visit pepscan.com.

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ANNEX 5 – POWER OF ATTORNEY

Power of Attorney

This power of attorney is made on [DATE] 202[●] by [NAME OF REMAINING PARTY], a company incorporated in [PLACE OF INCORPORATION] with company number [NUMBER] whose registered office is [ADDRESS] (the "**Principal**").

RECITALS:

A. The Principal is [party to a OR required to execute this power of attorney pursuant to the terms of a] Settlement and Licence Agreement made on [DATE] 202[●] made between the Bicycle Parties and Pepscan Parties (each as defined therein) (the "**Settlement and Licence Agreement**").

B. Clauses 12.2 and 12.3 of the Settlement and Licence Agreement detail certain of the rights and obligations of the parties thereto in the event of:

(i) a sale, transfer or other means of disposition (including by means of out-license) of all or substantially all of the business or assets of a party to the Settlement and Licence Agreement to a third party or an Affiliate (as defined in the Settlement and Licence Agreement), new entity or separate division of the transferring party; and/or

(ii) a sale, transfer or other means of disposition (including by means of out-license) of any Pepscan Patents and/or the Pepscan Know-How by Pepscan (as defined in the Settlement and Licence Agreement) to a third party or an Affiliate, new entity or separate division of Pepscan; and/or

(iii) a sale, transfer or other disposition (including by means of out-license), by an Affiliate, new entity of separate division to a third party,

such events the "**Change of Control Events**" and the selling/transferring party in each case the "**Transferor**".

D. Upon the occurrence of a Change of Control Event, then: (i) in the case of a transfer pursuant to clause 12.2, the Transferor undertakes to transfer to the new owner of the business or assets or the Pepscan Patents and/or Pepscan Know-How (as applicable) the relevant rights and obligations of the Transferor under the Settlement and Licence Agreement; or (ii) in the case of a transfer pursuant to clause 12.3, the Transferor shall procure that the Affiliate Transferee (as defined in the Settlement and Licence Agreement) shall transfer to the new owner, the original Transferor (as defined in the Settlement and Licence Agreement) or another Affiliate of the original Transferor (as applicable) the business or assets or the Pepscan Patents and/or Pepscan Know-How (as applicable) and the relevant rights and obligations under the Settlement and Licence Agreement (collectively, a "**Transfer**").

D. In order to facilitate any Transfer pursuant to clauses 12.2 and 12.3, the Principal has agreed to do all acts and things and provide the Transferor with all assistance (including the execution of any documentation), reasonably requested in writing by the Transferor, and which is necessary to give effect the Transfer, subject to the terms of the Settlement and Licence Agreement.

E. Pursuant to clause 12.4 of the Settlement and Licence Agreement, the Principal has agreed to grant this power of attorney to permit the Transferor to execute on its behalf

any documentation required to perfect any Transfer (but not, for the avoidance of doubt, for any other purpose whatsoever).

1. APPOINTMENT AND POWERS

The Principal appoints [NAME OF TRANSFEROR], a company incorporated in [PLACE OF INCORPORATION] with company number [NUMBER] whose registered office is [ADDRESS] as its attorney (the "**Attorney**") and in the Principal's name or otherwise and on its behalf to:

1.1 consider, settle, approve, sign, execute, deliver and/or issue all agreements, documents, certificates and instruments (all whether as a deed or not) which the Attorney in its absolute discretion considers necessary or desirable in connection with the implementation of the Transfer immediately following the occurrence of a Change of Control Event including any document necessary to perfect or effect the Transfer (the "**Transfer Documents**"); and

1.2 take any steps or do anything which the Attorney in its absolute discretion considers necessary or desirable in connection with the implementation of the Transfer or the implementation and/or execution of the Transfer Documents,

provided, for the avoidance of doubt, that: (i) this power of attorney does not authorize the Attorney to consider, settle, approve, sign, execute, deliver and/or issue any agreements, documents, certificates and instruments (all whether as a deed or not) which seek to impose any additional obligations on the Principal in excess of those required by clause 12 (*Change of Control*) of the Settlement and Licence Agreement); and (ii) this power of attorney shall not be used for any other purposes whatsoever.

2. DELEGATION BY CORPORATE ATTORNEY

Where the Attorney is a corporation the Attorney may delegate one or more of the powers conferred on the Attorney by this power of attorney to a director or an officer (or directors or officers) appointed for that purpose by the board of directors of the Attorney by resolution or otherwise.

3. POWER BY WAY OF SECURITY

This power of attorney is given by way of security to secure the performance of obligations owed by the Principal to the Attorney under clause 12 (*Change of Control*) of the Settlement and Licence Agreement and shall be irrevocable save with the consent of the Attorney while that interest or obligation remains undischarged.

4. RATIFICATION

The Principal undertakes to ratify and confirm whatever the Attorney does or purports to do, provided that such acts are within the scope of this power of attorney and taken in good faith in the exercise of any power conferred by this power of attorney.

5. VALIDITY

The Principal declares that a person who deals with the Attorney in good faith may accept a written statement signed by that Attorney to the effect that this power of attorney has not been revoked as conclusive evidence of that fact.

6. INDEMNITY

6.1 Subject always to clause 6.2, the Principal undertakes to indemnify the Attorney against all liabilities, costs, expenses, damages and losses (including but not limited to any direct, indirect or consequential losses, loss of profit, loss of reputation and all interest, penalties and legal costs (calculated on a full indemnity basis and including any cost incurred in enforcing this indemnity) and all other reasonable professional costs and expenses) which the Attorney sustains or incurs in connection with any action taken within the scope of the powers conferred by this power of attorney and taken in good faith pursuant to the terms of this power of attorney.

6.2 The indemnity in clause 6.1 shall not cover the Attorney if and to the extent a claim under it results from the fraud, negligence or wilful misconduct of the Attorney.

7. GOVERNING LAW AND JURISDICTION

This power of attorney and any dispute or claim (including non-contractual disputes or claims) arising out of or in connection with it, its subject matter or its formation shall be governed by and construed in accordance with the law of England and Wales. It is irrevocably agreed that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim (including non-contractual disputes or claims) arising out of or in connection with this power of attorney or its subject matter or formation.

IN WITNESS of which this power of attorney has been executed and delivered as a deed on the date at the beginning of this power of attorney.

EXECUTED as a **DEED** on behalf of **[NAME OF REMAINING PARTY]** acting by:

....

(*print name of director*) in the presence of: (*signature of director*)

Signature of witness: .....

Name of witness: .....

Address of witness: .....

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

[***] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED.

Exhibit 10.24

Date: 20 November 2020

(1) BICYCLERD LIMITED

(2) BICYCLETX LIMITED

(3) BICYCLE THERAPEUTICS PLC

(4) BICYCLE THERAPEUTICS INC

(5) PEPSCAN SYSTEMS BV

(6) PEPSCAN PRESTO BV

(7) PEPSCAN THERAPEUTICS BV

(8) PEPSCAN HOLDING NV

(9) PEPMAB BV

SETTLEMENT AGREEMENT

TABLE OF CONTENTS

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

SETTLEMENT AGREEMENT

THIS AGREEMENT is made the 20th day of November 2020

BETWEEN

1. **BICYCLERD LIMITED**, formerly named Bicycle Therapeutics Limited, a company incorporated in England and Wales under registration number 06960780, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England;

2. **BICYCLETX LIMITED**, a company incorporated in England and Wales under registration number 11036101, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England;

3. **BICYCLE THERAPEUTICS PLC**, a company incorporated in England and Wales under registration number 11036004, whose registered office is at Building 900 Babraham Research Campus, Cambridge, England; and

4. **BICYCLE THERAPEUTICS INC**, a company incorporated in Delaware, United States of America, whose principal place of business is at 4 Hartwell Place, Lexington, MA, United States of America,

(each, a "**Bicycle Party**" and collectively, "**Bicycle**")

AND

1. **PEPSCAN SYSTEMS BV**, a company incorporated in The Netherlands under registration number 39060590, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

2. **PEPSCAN PRESTO BV**, a company incorporated in The Netherlands under registration number 39097142, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

3. **PEPSCAN THERAPEUTICS BV**, a company incorporated in The Netherlands under registration number 39097144, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad;

4. **PEPSCAN HOLDING NV**, a company incorporated in The Netherlands under registration number 39096665, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad; and

5. **PEPMAB BV**, a company incorporated in The Netherlands under registration number 62174169, whose registered office is at Zuidersluisweg 2, 8243RC Lelystad,

(each, a "**Pepscan Party**", and collectively, "**Pepscan**")

Unless stated otherwise, Bicycle and Pepscan shall each comprise a "**Party**" and together shall comprise the "**Parties**").

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

RECITALS

A. Whereas, Bicycle is the registered owner of the European patents EP 2 257 624, EP 2 474 613, and their counterparts, and further patents and patent applications of the patent family of PCT-application WO 2009 / 098 450.

B. Whereas, the Parties are in on-going opposition proceedings before the Technical Boards of Appeal of the European Patent Office, in respect of EP 2 257 624 and EP 2 474 613 (case numbers T1573/15 and T0973/17) (the "**Oppositions**").

C. Whereas, the Parties have agreed to settle their differences and have agreed terms for the full and final settlement of the disputes upon and subject to the terms and conditions set forth below, on a fully and effectively binding basis, in this Settlement Agreement.

IT IS AGREED:

1. DEFINITIONS AND INTERPRETATION

1.1 In this Settlement Agreement, unless the context otherwise requires:

1.1.1 "**Affiliate(s)**" means any entity from time to time which, directly or indirectly through one or more intermediaries, controls, is controlled by or is under common control with a Party. For the purposes of this definition, the term "control" means the beneficial ownership of more than 50% (fifty percent) of the issued share capital of a company or the legal power to direct or cause the direction of the general management of the company.

1.1.2 "**Bicycle Patents**" means the [***].

1.1.3 "**Bicycle Released Claims**" means any claim in an infringement, revocation or entitlement action, opposition, *inter partes* review, or in any other action relating to the misuse, misappropriation, validity or infringement of intellectual property rights, trade secrets or confidential information, including any claim for liability, right, demand and set-off (including any claims for interest, costs and disbursements), whether or not presently known to the Parties, their assignees, transferees, representatives, principals, officers or directors, and whether in law or equity, that Bicycle, its assignees, transferees, representatives, principals, officers or directors, ever had, may have or hereafter can, shall or may have against Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners prior to the Effective Date or in the future with regard to the Bicycle Patents solely with respect to Monocycles and/or Multicycles.

1.1.4 "**Bicycles**" means peptides comprising two (2) peptide loops connected to a scaffold, wherein the scaffold is attached by three (3) discrete covalent bonds each.

1.1.5 "**Business Day**" means any day which is not a Saturday or Sunday or a bank holiday in any part of the United Kingdom.

1.1.6 "**Effective Date**" means the terms as defined in clause 2 (*Effective Date*).

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

1.1.7 "**Monocycles**" means peptides comprising scaffolds which create only one (1) peptide loop, i.e., wherein the scaffolds are attached to a polypeptide by two (2) discrete covalent bonds each, irrespective of how they are obtained.

1.1.8 "**Multicycles**" means peptides comprising scaffolds which create more than two (2) peptide loops, *i.e.*, wherein the scaffolds are attached to a polypeptide by more than three (3) discrete covalent bonds each, provided that at least three (3) of the peptide loops effectively contribute to a prophylactic, therapeutic or other biotechnological effect of the molecule, but excluding any such peptide obtained by use of phage display. The limitation that at least three (3) peptide loops must contribute to a prophylactic, therapeutic or other biotechnology effect of the molecule does not apply to the screening phase as, inevitably, all kinds of (effective and non-effective) compounds are produced during screening.

1.1.9 "**Pepscan Payment Party**" means the term as defined in clause 4.2.

1.1.10 "**Pepscan Released Claims**" means any claim in an infringement, a revocation or entitlement action, opposition, *inter partes* review, or in any other action relating to the misuse, misappropriation, validity or infringement of intellectual property rights, trade secrets or confidential information, including any claim for liability, right, demand and set-off (including any claims for interest, costs and disbursements), whether or not presently known to the Parties, their assignees, transferees, representatives, principals, officers or directors, and whether in law or equity, that Pepscan, its assignees, transferees, representatives, principals, officers or directors, ever had, may have or hereafter can, shall or may have against Bicycle, its licensees, suppliers and/or collaboration, development and/or commercialisation partners prior to the Effective Date or in the future with regard to the Bicycle Patents.

1.1.11 "**Settlement Agreement**" means this settlement agreement together with any annexes to it.

1.2 In this Settlement Agreement, the terms "Bicycle" and "Pepscan" shall include each of the respective entities listed on the cover page, including each Affiliate thereof.

1.3 Where any consent is required from the Bicycle Parties or Pepscan Parties (as applicable) for purposes of this Settlement Agreement, such consent shall be given by BicycleRD Limited on behalf of the Bicycle Parties, and by Pepscan Systems BV on behalf of the Pepscan Parties.

1.4 The clause and Annex headings are for convenience only and shall not affect the interpretation of this Settlement Agreement.

1.5 References to "clauses" are to clauses in the main body of this Settlement Agreement, references to "Annexes" are to schedules of this Settlement Agreement and references to "paragraphs" are to paragraphs of the Annexes.

1.6 References to the singular include the plural and *vice versa*, and references to one gender include the other genders.

1.7 Any phrase introduced by the expressions "including", "include", "in particular" or any similar expression shall be construed as illustrative and shall not limit the sense of the words preceding those terms.

1.8 Any reference to a statute, statutory provision or subordinate legislation ("**legislation**") (except where the context otherwise requires): (i) shall be deemed to include any bye laws, licences, statutory instruments, rules, regulations, orders, notices, directions, consents or permissions made under that legislation; and (ii) shall be construed as referring to any legislation which replaces, re-enacts, amends or consolidates such legislation (with or without modification) at any time.

1.9 In the case of any inconsistency between any provision of the Annexes to this Settlement Agreement and any term of this Settlement Agreement, the latter shall prevail.

2. EFFECTIVE DATE

This Settlement Agreement shall take effect upon signature of it by the last of the Parties and such date shall comprise the Effective Date.

3. FINANCIAL SETTLEMENT TERMS

3.1 In consideration for Pepscan withdrawing from the Oppositions in accordance with the terms of clause 5.1 below, Bicycle shall, subject to the provisions of clause 4 (*Payment Terms*), pay to the Pepscan Payment Party the following lump sum payment in accordance with the following terms:

3.1.1 within five (5) Business Days of the Effective Date, Bicycle shall place €1 million (one million euros) into escrow ("**Escrow Sum**") in the third-party escrow account [***] ("**Escrow Account Holder**"), as further detailed at **Annex 1** (*Escrow Details*). With regard to the Escrow Sum:

3.1.1.1 such Escrow Sum shall remain in escrow until Pepscan has withdrawn from the Oppositions in accordance with clause 5.1 below; and

3.1.1.2 thereafter, the Escrow Account Holder shall be ordered to pay the Escrow Sum to the Pepscan Payment Party within [***] of Pepscan's withdrawal from the Oppositions.

3.1.2 For the avoidance of doubt, the payment contemplated in this clause 3 (*Financial Settlement Terms*) shall be the sole payment due and payable by Bicycle to Pepscan and no additional payments shall be made by Bicycle pursuant to this Settlement Agreement and the matters giving rise to it.

4. PAYMENT TERMS

4.1 Each Bicycle Party shall be jointly and severally liable for all the payments to be made to Pepscan pursuant to clause 3 (*Financial Settlement Terms*).

4.2 Pepscan hereby nominates Pepscan Systems BV as the Pepscan Party that shall invoice and accept payments made by Bicycle in accordance with this Settlement Agreement for, and on behalf of, the Pepscan Parties ("**Pepscan Payment Party**"). For the avoidance of doubt:

4.2.1 upon payment by Bicycle of the payments to the Pepscan Payment Party in accordance with this Settlement Agreement, such payment shall fulfil Bicycle's payment obligation to all Pepscan Parties; and

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

4.2.2 it shall be incumbent upon the Pepscan Payment Party to distribute such payments amongst the Pepscan Parties, as may be determined by Pepscan.

4.3 The sum payable by Bicycle to Pepscan under clause 3 (*Financial Settlement Terms*) shall, be paid [***], and all amounts payable are [***] invoice.

4.4 The Pepscan Payment Party shall, within [***] from such lump sum amount becoming due, submit valid VAT invoices to Bicycle at [***], or such other e-mail address as may be communicated in writing by Bicycle to the Pepscan Payment Party.

4.5 If Bicycle fails to make the payment due to Pepscan under this Settlement Agreement by the due date, then Bicycle shall pay interest on the overdue sum from the due date until payment of the overdue sum, whether before or after judgment. Interest under this clause will accrue at [***].

5. WITHDRAWAL OF OPPOSITIONS AND RELEASE

5.1 As soon as the Escrow Account Holder confirms that the Escrow Sum has been placed in escrow in accordance with the terms of clause 3.1.1 and in any event within [***] of such confirmation, Pepscan shall withdraw from the Oppositions.

5.2 As of the Effective Date and thereafter, Pepscan releases and forever discharges any and all of the Pepscan Released Claims and undertakes not, at any stage in the future, to commence or re-institute any proceedings or oppositions relating to the Pepscan Released Claims, against Bicycle, its licensees, suppliers and/or collaboration, development and/or commercialisation partners, unless Bicycle commences patent infringement proceedings based on a patent within the Bicycle Patents against Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners, in which case Pepscan shall be allowed to counterclaim for invalidity against that patent.

5.3 As of the Effective Date and thereafter, Bicycle releases and forever discharges any and all of the Bicycle Released Claims and undertakes not, at any stage in the future, to commence or re-institute any proceedings or oppositions relating to the Bicycle Released Claims against Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners, unless Pepscan is in breach of clause 5.2.

5.4 For the avoidance of doubt:

5.4.1 nothing in clause 5.3 may be construed as Bicycle giving consent to Pepscan, its licensees, suppliers and/or collaboration, development and/or commercialisation partners to make, dispose of, offer to dispose of use or import: (i) Bicycles; and/or (ii) phage display to identify Bicycles or Multicycles; and

5.4.2 Pepscan shall not disclose, publicise or disseminate any information concerning Bicycles that arise from screening or otherwise, nor use or transfer outside of Pepscan, any Bicycles that arise from screening or otherwise, to the extent (i) that the activity giving rise to the information or the Bicycle(s) would, absent the release and undertaking contained in clause 5.3, comprise infringement of any of the Bicycle Patents, or (ii) doing so would otherwise constitute an infringement or misappropriation of any of Bicycle's other intellectual property or other rights.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

6. NO ADMISSION

This Settlement Agreement is entered into for the purposes of compromise only. It is not and shall not be represented or construed by the Parties as an admission or as evidence of wrongdoing on the part of any Party or any other person or entity, nor as an acknowledgement of the existence or disclosure of any relevant know-how.

7. COSTS

Each Party shall bear their own legal costs and expenses in relation to, the Oppositions as well as the drafting, negotiation and implementation of this Settlement Agreement and any further agreements arising from it.

8. CONFIDENTIALITY

8.1 The terms of this Settlement Agreement and the negotiations which led to it are to remain confidential between the Parties (the "**Confidential Information**"), save that they may be disclosed:

8.1.1 by any Party with the prior written consent of the other Party;

8.1.2 subject to clause 8.3, by any Party to its respective professional advisers or auditors, to the extent necessary to enable them to perform their functions properly for such Party;

8.1.3 subject to clause 8.3, by any Party to: (i) potential acquirors (and their respective professional advisers), to the extent necessary to enable them to consider, evaluate, negotiate and/or advance a potential acquisition or transaction related to that Party; and (ii) financing sources (and their respective professional advisers), to the extent necessary to enable them to consider, evaluate, negotiate and/or advance a potential financing transaction related to that Party;

8.1.4 by any Party to the extent such disclosure is, in the reasonable opinion of such Party's legal counsel, required to be disclosed pursuant to law, regulation or a valid order of a court of competent jurisdiction or other governmental body of competent jurisdiction (including, for the avoidance of doubt, the U.S. Securities and Exchange Commission); provided that the Party intending to make the disclosure shall, to the extent legally permissible, first have given prompt written notice (and to the extent practicable, at least [***] notice) to the other Party and give the other Party a reasonable opportunity to take whatever action it deems necessary to protect its Confidential Information. If no protective order or other remedy is obtained, the Party making the disclosure shall furnish only that portion of Confidential Information which such Party is advised by counsel is legally required to be disclosed.

8.2 In the event that a given Party is required to make a disclosure pursuant to the above clause 8.1, the other Party will be permitted to disclose the same information should it wish to do so provided such disclosure shall be made under and/or pursuant to the same confidentiality protections (if any) under which the first Party made the disclosure, including as set out in clause 8.1.4.

8.3 To the extent that a Party discloses Confidential Information to the third parties contemplated in clauses 8.1.2 and/or 8.1.3 above (as applicable) ("**Authorised Persons**"), such disclosure shall be on a "need-to-know" basis and made solely for the

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purposes contemplated in clauses 8.1.2 and 8.1.3 (as applicable), and the Party disclosing the Confidential Information shall:

8.3.1 inform all such Authorised Persons that the Confidential Information is confidential and subject to the terms contemplated in this clause 8 (*Confidentiality*);

8.3.2 ensure that all such Authorised Persons are under a duty of confidentiality or otherwise enter into written confidentiality agreements with it on terms consistent with this clause 8 (*Confidentiality*); and

8.3.3 be responsible for all acts and omissions of Authorised Persons as though they were its own acts or omissions under this clause 8 (*Confidentiality*).

8.4 The Parties shall not use the Confidential Information other than as contemplated by this Settlement Agreement.

8.5 The provisions of this clause 8 (*Confidentiality*) shall not apply to any information which at the time of its disclosure was already generally available to the public other than by reason of a breach of the terms of this Settlement Agreement, or otherwise becomes part of the public domain other than by reason of a breach of the terms of this Settlement Agreement.

8.6 Without prejudice to any other rights or remedies that any Party may have, each Party acknowledges and agrees that damages alone would not be an adequate remedy for any breach of the terms of this clause 8 (*Confidentiality*). Accordingly, each Party shall be entitled to the remedies of injunctions, specific performance or other equitable relief for any threatened or actual breach of this clause 8 (*Confidentiality*).

9. CHANGE OF CONTROL

9.1 If there is an acquisition of any of the Pepscan Parties or Bicycle Parties (as applicable) ("**Target**"), whether by a third party or an Affiliate of the Target ("**Acquirer**"), meaning the sale or other transfer of the entire issued share capital of the Target or any merger, scheme of arrangement or other similar transaction resulting in the Acquirer (or persons acting in concert with the Acquirer) holding (whether by one or a series of related transactions) all the shares in the Target, the Target undertakes to Bicycle or Pepscan (as applicable) that it shall not as a part of such sale or other transfer of the entire issued share capital or merger, scheme of arrangement or other similar transaction take any actions that would result in the Target ceasing to be bound by the rights and obligations under this Settlement Agreement.

9.2 Subject to clauses 9.3 and 9.5:

9.2.1 if there is a sale, transfer or other means of disposition (including by means of out-license) of all or substantially all of the business or assets of a Party ("**Transferor**") to a third party or an Affiliate, new entity or separate division of the Transferor, the Transferor undertakes that it shall: (i) transfer any and all of its rights and obligations under this Settlement Agreement to the successor in interest ("**Transferee**"); and (ii) procure that such Affiliate, new entity or separate division of the Transferor (as applicable) shall, for the purposes of clause 9.4 of this Settlement Agreement, grant to the other Party, as represented by any one entity of such Party, a power of attorney in the form contained in **Annex 2** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any such sale, transfer

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or other means of disposition pursuant to this clause 9.2.1; and

9.2.2 if there is a sale, transfer or other means of disposition (including by means of out-license) of any of the Bicycle Patents by any Bicycle Party ("**Transferor**"), including a sale, transfer or other disposition (including by means of out-license) of one or more of the Bicycle Patents to a third party or an Affiliate, new entity or separate division of the Transferor, the Transferor undertakes that it shall: (i) ensure that the new owner of the Bicycle Patents ("**Transferee**") shall be contractually bound to Pepscan by the rights and obligations of Bicycle under clause 5 (*Withdrawal of Oppositions and Release*); and (ii) procure that such Affiliate, new entity or separate division of the Transferor (as applicable) shall, for the purposes of clause 9.4 of this Settlement Agreement, grant to Pepscan, as represented by any one nominated Pepscan Party, a power of attorney in the form contained in **Annex 2** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any such sale, transfer or other means of disposition pursuant to this clause 9.2.2.

9.3 In the event that there is a sale, transfer or other disposition (including by means of out-license) by a Party ("**Transferor**") to an Affiliate, new entity or separate division ("**Affiliate Transferee**") pursuant to any of sub-clauses 9.2.1 or 9.2.2, and such Affiliate, new entity or separate division of the Transferor (as applicable) is subsequently sold or transferred by the applicable Affiliate Transferee to a third party, then the Transferor shall procure that the Affiliate Transferee either:

9.3.1 transfers such: (i) business or assets (and in each case any contracts); or (ii) the Bicycle Patents (as applicable) back to the original Transferor (or another Affiliate of the original Transferor) and the applicable rights and obligations under this Settlement Agreement shall also be transferred back by the Affiliate Transferee to the original Transferor (or another Affiliate of the original Transferor). To the extent the transfer made pursuant to this clause is made to an Affiliate of the original Transferor and such Affiliate has not previously executed a power of attorney in accordance with clauses 9.2.1, 9.2.2 or 9.4 of this Settlement Agreement, then the Transferor shall procure that such Affiliate of the original Transferor shall, for the purposes of clause 9.4 of this Settlement Agreement, grant to the other Party, as represented by any one entity of such Party, a power of attorney in the form contained in **Annex 2** (*Power of Attorney*) and deliver the original of such power of attorney concurrently with the execution of any transfer back to the Affiliate of the original Transferor pursuant to this clause 9.3.1; or

9.3.2 undertake to ensure that, as applicable:

9.3.2.1 the new owner of the business or assets shall also be contractually bound by the rights and obligations under this Settlement Agreement; or

9.3.2.2 the new owner of the Bicycle Patents shall also be contractually bound to Pepscan by the rights and obligations under clause 5 (*Withdrawal of Oppositions and Release*).

9.4 In order to facilitate the transfer of rights and obligations set out in sub-clauses 9.2.1 and 9.2.2 and clause 9.3: (i) the other Party ("**Remaining Party**") agrees to do all acts and things, and provide the Transferor with all assistance (including the execution of any documentation), reasonably requested in writing by the Transferor, and which is

necessary, in order to effect such transfer from the Transferor to the Transferee or Affiliate Transferee or new owner under clause 9.3.2 (as applicable), provided that such acts and assistance do not impose any additional obligations on the Remaining Party (other than the doing of such things and assistance); and (ii) each Party shall simultaneously with the execution of this Settlement Agreement grant to the other a power of attorney in the form contained in **Annex 2** (*Power of Attorney*) of this Settlement Agreement (with the Party acting as the attorney, in each case, to be represented by any one entity of such Party) (and shall deliver the original of such power of attorney concurrently with execution this Settlement Agreement) so as to permit the Transferor to execute on its behalf any documentation required to perfect any transfer from the Transferor to the Transferee, or Affiliate Transferee, or new owner under clause 9.3.2 (as applicable), but not for any other purpose whatsoever.

9.5 The Transferor shall indemnify the Remaining Party and keep it indemnified from and against any and all liabilities, costs, expenses, damages and losses suffered or incurred by the Remaining Party arising as a result of any failure of the Transferor to secure the transfer of rights and obligations to the Transferee in accordance with the provisions of clause 9.2 or the Transferor's failure to comply with the terms of clause 9.3 (as applicable). The Remaining Party shall have an obligation to mitigate any loss, and shall not be entitled to recover any legal costs or costs for management time incurred in pursuing the indemnity set out in this clause 9.5. For the avoidance of doubt, if and to the extent that the failure of the Transferor to secure the transfer of rights and obligations to the Transferee, Affiliate Transferee or new owner pursuant to clause 9.3.2 (as applicable) in accordance with the provisions of clause 9.2 and clause 9.3 (as applicable) or the Transferor's failure to comply with the terms of clause 9.3 (as applicable) is a result of the Remaining Party's breach of clause 9.4, this indemnity may not be invoked by the Remaining Party.

9.6 Without prejudice to any other rights or remedies that each Party may have, each Party acknowledges and agrees that damages alone would not be an adequate remedy for any breach of the terms of this clause 9 (*Change of Control*). In particular, with regard to clause 9.4, the Parties recognise that significant damage shall be caused to the Transferor should the Remaining Party not provide the necessary assistance to the Transferor, as required in accordance with such clause 9.4. Accordingly, each Party shall be entitled to the remedies of injunctions, specific performance or other equitable relief for any threatened or actual breach of this clause 9 (*Change of Control*).

9.7 Each Party shall keep confidential the terms and existence of any transaction or potential transaction to be implemented by the other Party in accordance with the terms of this clause 9 (*Change of Control*), save that details of any such transaction or potential transaction may be disclosed in accordance with clauses 8.1.1, 8.1.2, 8.1.3 or 8.1.4.

10. DISPUTE RESOLUTION

10.1 Except as provided for in clause 10.6 any dispute arising out of or in connection with this Settlement Agreement including any question regarding its existence, validity or termination, shall be exclusively referred to and finally resolved by arbitration under the LCIA Rules, which Rules are deemed to be incorporated by reference into this clause 10.1.

10.2 The number of arbitrators shall be three.

10.3 The seat, or legal place, of arbitration shall be [***].

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

10.4 The language to be used in the arbitral proceedings shall be English.

10.5 Arbitration conducted in accordance with this clause 10 (*Dispute Resolution*) shall be governed by and construed in accordance with the law of England and Wales.

10.6 Any application for equitable relief made by a Party pursuant to clauses 8.6 and 9.6 or any dispute relating to any such application, shall be subject to the exclusive jurisdiction of the courts of England and Wales.

11. ENTIRE AGREEMENT

11.1 Subject to clause 11.2, this Settlement Agreement constitutes the entire agreement between the Parties in relation to its subject matter and replaces and extinguishes all prior heads of terms, agreements, draft agreements, arrangements, undertakings, or collateral contracts of any nature made by the Parties, whether oral or written, relating to that subject matter.

11.2 Nothing in this Agreement shall exclude or restrict the liability of any Party arising out of fraud, fraudulent misrepresentation or fraudulent concealment.

12. NOTICES

12.1 Any notice to be given under this Settlement Agreement ("**Notice**") must be in writing and delivered by courier or recorded first class post.

12.2 A Notice served under this Agreement will be deemed to be received upon the sooner of:

12.2.1 delivery of the Notice; or

12.2.2 if couriered or posted to a recipient in the same country as the sender, [***] and if sent to a recipient in a different country to the sender, [***].

12.3 The details of the Parties for the purpose of Notices relating to this Settlement Agreement are as follows:

Party	**Contact**	**Address**
BICYCLERD LIMITED	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLETX LIMITED	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLE THERAPEUTICS PLC	[***], General Counsel	Building 900 Babraham Research Campus, Cambridge, England, CB22 3AT
BICYCLE THERAPEUTICS INC	[***], General Counsel	4 Hartwell Place, Lexington, MA, United States of America
PEPSCAN SYSTEMS BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

PEPSCAN PRESTO BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPSCAN THERAPEUTICS BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPSCAN HOLDING NV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands
PEPMAB BV	CEO	Zuidersluisweg 2, 8243RC Lelystad, The Netherlands

12.4 Each Party may alter the above details which relate to it and shall promptly notify the other Party of any such change by a Notice in accordance with this clause 12 (*Notices*). The change will take effect [***] after the day on which the Notice of the change is deemed to be delivered in accordance with clause 12.2.

13. GOVERNING LAW

This Settlement Agreement and any non-contractual obligation arising out of or in connection to this Settlement Agreement, including any question regarding its existence, validity or termination, will be governed by and construed in accordance with the law of England and Wales.

14. GENERAL PROVISIONS

14.1 The Parties agree that no Party shall have, and each Party waives, any right to terminate all, or any part, of this Agreement, whether under contract, statute, tort, common law or otherwise.

14.2 Except in accordance with clause 9 (*Change of Control*), no Party shall assign, novate or transfer any rights or obligations under this Settlement Agreement without the prior written consent of the other Party.

14.3 No variation of this Settlement Agreement shall be effective unless made in writing and signed by or on behalf of each of the Parties.

14.4 In the event of any clause of this Settlement Agreement or any part of such clause being declared illegal, invalid or unenforceable by any court, authority or relevant arbitral panel of competent jurisdiction, that clause or part thereof shall be deemed not to form part of this Settlement Agreement, all other clauses or parts thereof contained in this Settlement Agreement shall remain in full force and shall not be affected thereby. The Parties shall negotiate in good faith to agree a replacement provision that, to the greatest extent possible, achieves the intended commercial result of the original provision.

14.5 The failure to exercise, or delay in exercising, a right, power or remedy provided by this Settlement Agreement or by law shall not constitute a waiver of that right, power or remedy. If a Party waives a breach of any provision of this Settlement Agreement this shall not operate as a waiver of a subsequent breach of that provision, or as a waiver of a breach of any other provision.

14.6 The rights, powers and remedies provided in this Settlement Agreement are cumulative and not exclusive of any rights, powers and remedies provided by the law, or otherwise.

14.7 Nothing in this Settlement Agreement shall be deemed to constitute a partnership, collaboration or joint venture between the Parties, nor to create a relationship of

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principal and agent for any purpose between the Parties, nor to authorise any Party to make or enter into any commitments for or on behalf of the other Party except as expressly provided in this Settlement Agreement.

14.8 This Settlement Agreement may be entered into in any number of counterparts. Each counterpart shall, when signed, be regarded as an original, and all the counterparts together shall together constitute one and the same Settlement Agreement. This Agreement shall not take effect until it has been signed by the Parties. This Settlement Agreement may validly be executed by electronic signature (in an agreed form) and exchanged and delivered by e-mail.

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

SIGNED FOR AND ON BEHALF OF
BICYCLE THERAPEUTICS PLC:

/s/ Kevin Lee……

Name/Position: Dr Kevin Lee, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLETX LIMITED:

/s/ Kevin Lee ……

Name/Position: Dr Kevin Lee

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLERD LIMITED:

/s/ Kevin Lee ……

Name/Position: Dr Kevin Lee

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
BICYCLE THERAPEUTICS INC.:

/s/ Lee Kalowski ……

Name/Position: Lee Kalowski, President & CFO

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN SYSTEMS BV:

/s/ Hans de Backer……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN PRESTO BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN THERAPEUTICS BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPSCAN HOLDING NV:

/s/ Hans de Backer ……

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Name/Position: Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

SIGNED FOR AND ON BEHALF OF
PEPMAB BV:

/s/ Hans de Backer ……

Duly represented hereto by: Pepscan Holding NV,
Johannes Wilhelmus Jacobus Henricus de Backer, CEO

Date: 20/11/2020

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

ANNEX 1 – ESCROW DETAILS

Escrow details:

[***]

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

ANNEX 2 – POWER OF ATTORNEY

Power of Attorney

This power of attorney is made on [DATE] 202[●] by [NAME OF REMAINING PARTY], a company incorporated in [PLACE OF INCORPORATION] with company number [NUMBER] whose registered office is [ADDRESS] (the "**Principal**").

RECITALS:

A. The Principal is [party to a OR required to execute this power of attorney pursuant to the terms of a] Settlement Agreement made on [DATE] 202[●] made between the Bicycle Parties and Pepscan Parties (each as defined therein) (the "**Settlement Agreement**").

B. Clauses 9.2 and 9.3 of the Settlement Agreement detail certain of the rights and obligations of the parties thereto in the event of:

(i) a sale, transfer or other means of disposition (including by means of out-license) of all or substantially all of the business or assets of a party to the Settlement Agreement to a third party or an Affiliate (as defined in the Settlement Agreement), new entity or separate division of the transferring party; and/or

(ii) a sale, transfer or other means of disposition (including by means of out-license) of any Bicycle Patents by Bicycle (as defined in the Settlement Agreement) to a third party or an Affiliate, new entity or separate division of Bicycle; and/or

(iii) a sale, transfer or other disposition (including by means of out-license), by an Affiliate, new entity of separate division to a third party,

such events the "**Change of Control Events**" and the selling/transferring party in each case the "**Transferor**".

D. Upon the occurrence of a Change of Control Event, then: (i) in the case of a transfer pursuant to clause 9.2, the Transferor undertakes to transfer to the new owner of the business or assets and/or Bicycle Patents (as applicable) the relevant rights and obligations of the Transferor under the Settlement Agreement; or (ii) in the case of a transfer pursuant to clause 9.3, the Transferor shall procure that the Affiliate Transferee (as defined in the Settlement Agreement) shall transfer to the new owner, the original Transferor (as defined in the Settlement Agreement) or another Affiliate of the original Transferor (as applicable) the business or assets and/or Bicycle Patents (as applicable) and the relevant rights and obligations under the Settlement Agreement (collectively, a "**Transfer**").

D. In order to facilitate any Transfer pursuant to clauses 9.2 and 9.3, the Principal has agreed to do all acts and things and provide the Transferor with all assistance (including the execution of any documentation), reasonably requested in writing by the Transferor, and which is necessary to give effect the Transfer, subject to the terms of the Settlement Agreement.

E. Pursuant to clause 9.4 of the Settlement Agreement, the Principal has agreed to grant this power of attorney to permit the Transferor to execute on its behalf any

documentation required to perfect any Transfer (but not, for the avoidance of doubt, for any other purpose whatsoever).

1. APPOINTMENT AND POWERS

The Principal appoints [NAME OF TRANSFEROR], a company incorporated in [PLACE OF INCORPORATION] with company number [NUMBER] whose registered office is [ADDRESS] as its attorney (the "**Attorney**") and in the Principal's name or otherwise and on its behalf to:

1.1 consider, settle, approve, sign, execute, deliver and/or issue all agreements, documents, certificates and instruments (all whether as a deed or not) which the Attorney in its absolute discretion considers necessary or desirable in connection with the implementation of the Transfer immediately following the occurrence of a Change of Control Event including any document necessary to perfect or effect the Transfer (the "**Transfer Documents**"); and

1.2 take any steps or do anything which the Attorney in its absolute discretion considers necessary or desirable in connection with the implementation of the Transfer or the implementation and/or execution of the Transfer Documents,

provided, for the avoidance of doubt, that: (i) this power of attorney does not authorize the Attorney to consider, settle, approve, sign, execute, deliver and/or issue any agreements, documents, certificates and instruments (all whether as a deed or not) which seek to impose any additional obligations on the Principal in excess of those required by clause 9 (*Change of Control*) of the Settlement Agreement); and (ii) this power of attorney shall not be used for any other purposes whatsoever.

2. DELEGATION BY CORPORATE ATTORNEY

Where the Attorney is a corporation the Attorney may delegate one or more of the powers conferred on the Attorney by this power of attorney to a director or an officer (or directors or officers) appointed for that purpose by the board of directors of the Attorney by resolution or otherwise.

3. POWER BY WAY OF SECURITY

This power of attorney is given by way of security to secure the performance of obligations owed by the Principal to the Attorney under clause 9 (*Change of Control*) of the Settlement Agreement and shall be irrevocable save with the consent of the Attorney while that interest or obligation remains undischarged.

4. RATIFICATION

The Principal undertakes to ratify and confirm whatever the Attorney does or purports to do, provided that such acts are within the scope of this power of attorney and taken in good faith in the exercise of any power conferred by this power of attorney.

5. VALIDITY

The Principal declares that a person who deals with the Attorney in good faith may accept a written statement signed by that Attorney to the effect that this power of attorney has not been revoked as conclusive evidence of that fact.

6. INDEMNITY

6.1 Subject always to clause 6.2, the Principal undertakes to indemnify the Attorney against all liabilities, costs, expenses, damages and losses (including but not limited to any direct, indirect or consequential losses, loss of profit, loss of reputation and all interest, penalties and legal costs (calculated on a full indemnity basis and including any cost incurred in enforcing this indemnity) and all other reasonable professional costs and expenses) which the Attorney sustains or incurs in connection with any action taken within the scope of the powers conferred by this power of attorney and taken in good faith pursuant to the terms of this power of attorney.

6.2 The indemnity in clause 6.1 shall not cover the Attorney if and to the extent a claim under it results from the fraud, negligence or wilful misconduct of the Attorney.

7. GOVERNING LAW AND JURISDICTION

This power of attorney and any dispute or claim (including non-contractual disputes or claims) arising out of or in connection with it, its subject matter or its formation shall be governed by and construed in accordance with the law of England and Wales. It is irrevocably agreed that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim (including non-contractual disputes or claims) arising out of or in connection with this power of attorney or its subject matter or formation.

IN WITNESS of which this power of attorney has been executed and delivered as a deed on the date at the beginning of this power of attorney.

EXECUTED as a **DEED** on behalf of **[NAME OF REMAINING PARTY]** acting by:

....

(*print name of director*) in the presence of: (*signature of director*)

Signature of witness: .....

Name of witness: .....

Address of witness: .....

[***] = Certain confidential information contained in this document, marked by brackets, has been omitted because it is both (i) not material and (ii) would be competitively harmful if publicly disclosed.

THIS DEED is made **BETWEEN**:

(1) **BICYCLETX LIMITED** a company incorporated under the laws of England and Wales with company number 11036101 and its registered office at Building 900, Babraham Research Campus, Babraham, Cambridgeshire, CB22 3AT, United Kingdom (the "***BicycleTX***"); and

(2) [**EXECUTIVE NAME**] of [executive address] (the "***Executive***"),

together, the "Parties".

RECITALS:

(A) The Parties entered into a Service Agreement on [DATE], as amended and/or amended and restated from time to time (the "***Service Agreement***").

(B) The Service Agreement provides that the Executive's salary be denominated in USD and converted and paid in GBP.

(C) The Parties wish to amend the Service Agreement so that the Executive's salary shall be calculated and paid in GBP, effective on and from 1 January 2021.

IT IS AGREED as follows:

1. The Parties hereby agree that the Service Agreement shall be amended such that, effective on and from 1 January 2021, the Executive's salary shall be established and paid in GBP and that Executive's Salary on and from 1 January 2021 (subject to review in accordance with the terms of the Service Agreement) shall be GBP[●].

2. Save as provided herein, the terms of the Service Agreement shall remain in full force and effect.

[*Remainder of page intentionally blank*]

Executed and delivered as a Deed by **BICYCLETX LIMITED** acting by a director:

_____ (Director)

on:____day of_____2021

in the presence of:

_____

Witness Name: Witness

Address:

_____

Executed and delivered as a Deed by:
[**EXECUTIVE NAME**]:

_____

Name:

on:____day of_____2021

in the presence of:

_____

Witness Name: Witness

Address:

Exhibit 10.28

FIRST AMENDMENT TO LOAN AND SECURITY AGREEMENT

THIS FIRST AMENDMENT TO LOAN AND SECURITY AGREEMENT (this "Amendment"), dated as of March 10, 2021, is entered into by and among BICYCLE THERAPEUTICS PLC, a public limited company organized under the laws of England and Wales ("Parent"), BICYCLETX LIMITED, a private company limited by shares organized under the laws of England and Wales ("BicycleTx"), BICYCLERD LIMITED, a private company limited by shares organized under the laws of England and Wales ("BicycleRD"), BICYCLE THERAPEUTICS INC., a Delaware corporation ("Bicycle US") and each of Parent's Subsidiaries that delivers a Joinder Agreement pursuant to Section 7.13 of the Loan Agreement (hereinafter collectively referred to as "Borrowers" and each, "Borrower"), the several banks and other financial institutions or entities from time to time parties to the Loan Agreement (as defined below) (collectively, referred to as the "Lenders") and HERCULES CAPITAL, INC., a Maryland corporation, in its capacity as administrative agent and collateral agent for the Lenders (in such capacity, "Agent").

Borrowers, Lenders and Agent are parties to that certain Loan and Security Agreement, dated as of September 30, 2020 (the "Existing Loan Agreement"; and the Existing Loan Agreement, as amended by this Amendment and as further amended, restated, supplemented or otherwise modified from time to time, the "Loan Agreement"). Borrowers have requested that the Lenders agree to certain amendments to the Loan and Security Agreement. Lenders have agreed to such request, subject to the terms and conditions hereof.

Accordingly, the parties hereto agree as follows:

SECTION 1 Definitions; Interpretation.

(a) **Terms Defined in Loan Agreement**. All capitalized terms used in this Amendment (including in the recitals hereof) and not otherwise defined herein shall have the meanings assigned to them in the Loan Agreement.

(b) **Rules of Construction**. The rules of construction that appear in Section 1.3 of the Loan Agreement shall be applicable to this Amendment and are incorporated herein by this reference.

SECTION 2 Amendments to the Loan Agreement.

(a) Upon satisfaction of the conditions set forth in Section 3 hereof, the Existing Loan Agreement is hereby amended as follows:

(i) New Definition. The following definition is added to Section 1.1 in its proper alphabetical order:

"First Amendment Effective Date" means March 10, 2021.

(ii) Amended and Restated Definitions. The following definitions are hereby amended and restated as follows:

"Amortization Date" means August 1, 2023; provided, however, if the Interest Only Extension Conditions are satisfied, then February 1, 2024.

"Interest Only Extension Conditions" shall mean satisfaction of each of the following events: (a) no default or Event of Default shall have occurred; and (b) Borrower has achieved the Performance Milestone on or prior to July 31, 2023.

(iii) Section 2.2. Section 2.2(a)(ii) is hereby amended and restated as follows:

(ii) Subject to the terms and conditions of this Agreement, the Lenders will severally (and not jointly) make in an amount not to exceed its respective Tranche 1B Commitment, and Borrowers agree to draw, a Term Loan Advance of Fifteen Million and 00/100 Dollars

($15,000,000) on the First Amendment Effective Date (the "Tranche 1B Advance" and together with the Tranche 1A Advance, each a "Tranche 1 Advance").

(b) **References Within Existing Loan Agreement**. Each reference in the Existing Loan Agreement to "this Agreement" and the words "hereof," "herein," "hereunder," or words of like import, shall mean and be a reference to the Existing Loan Agreement as amended by this Amendment.

SECTION 3 Conditions of Effectiveness. The effectiveness of Section 2 of this Amendment shall be subject to the satisfaction of each of the following conditions precedent:

(a) Borrowers shall have paid (i) all invoiced costs and expenses then due in accordance with Section 5(e), and (ii) all other fees, costs and expenses, if any, due and payable as of the date hereof under the Loan Agreement.

(b) Agent shall have received:

(i) this Amendment, executed by Agent, Lenders and Borrowers;

(ii) an irrevocable Advance Request for a Tranche 1B Advance in the amount of Fifteen Million and 00/100 Dollars ($15,000,000) executed by Parent on behalf of the Borrowers;

(iii) certified copy of resolutions of each Borrower's Board of Directors evidencing approval of this Amendment and other transactions evidenced hereby; and

(iv) such other documents as Agent may reasonably request.

(c) On the date hereof, after giving effect to the amendment of the Existing Loan Agreement contemplated hereby, there exist no Events of Default or events that with the passage of time would result in an Event of Default.

SECTION 4 Representations and Warranties. To induce Agent and Lenders to enter into this Amendment, each Borrower hereby confirms, as of the date hereof, that (a) the representations and warranties made by it in Section 5 of the Loan Agreement and in the other Loan Documents are true and correct in all material respects; *provided*, *however*, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof provided, further, that to the extent such representations and warranties by their terms expressly relate only to a prior date such representations and warranties shall be true and correct as of such prior date; (b) there has not been and there does not exist a Material Adverse Effect; (c) that the information included in the Perfection Certificate delivered to Agent on the Closing Date remains true and correct; (d) Agent has and shall continue to have valid, enforceable and perfected first-priority liens, subject only to Permitted Liens, on and security interests in the Collateral and all other collateral heretofore granted by Borrowers to Agent, pursuant to the Loan Documents or otherwise granted to or held by Agent; (e) the agreements and obligations of Borrowers contained in the Loan Documents and in this Amendment constitute the legal, valid and binding obligations of Borrowers, enforceable against Borrowers in accordance with their respective terms, except as the enforceability thereof may be limited by bankruptcy, insolvency or other similar laws of general application affecting the enforcement of creditors' rights or by the application of general principles of equity; (f) the execution, delivery and performance of this Amendment by Borrowers will not violate any law, rule, regulation, order, contractual obligation or organizational document of Borrowers and will not result in, or require, the creation or imposition of any lien, claim or encumbrance of any kind on any of its properties or revenues; and (g) no Event of Default has occurred and is continuing.

SECTION 5 Miscellaneous.

(a) **Loan Documents Otherwise Not Affected; Reaffirmation; No Novation.**

(i) Except as expressly amended pursuant hereto or referenced herein, the Existing Loan Agreement and the other Loan Documents shall remain unchanged and in full force and effect and are hereby ratified

and confirmed in all respects. Lenders' and Agent's execution and delivery of, or acceptance of, this Amendment shall not be deemed to create a course of dealing or otherwise create any express or implied duty by any of them to provide any other or further amendments, consents or waivers in the future.

(ii) Each of the Borrowers hereby expressly (1) reaffirms, ratifies and confirms its Secured Obligations under the Existing Loan Agreement and the other Loan Documents, (2) reaffirms, ratifies and confirms the grant of security under Section 3.1 of the Existing Loan Agreement, (3) reaffirms that such grant of security in the Collateral secures all Secured Obligations under the Existing Loan Agreement, including without limitation any Term Loans funded on or after the date hereof, as of the date hereof, and with effect from (and including) the date hereof, such grant of security in the Collateral: (x) remains in full force and effect notwithstanding the amendments expressly referenced herein; and (y) secures all Secured Obligations under the Existing Loan Agreement, as amended by this Amendment, and the other Loan Documents, and (4) agrees that the Existing Loan Agreement and each other Loan Document shall remain in full force and effect following any action contemplated in connection herewith.

(iii) This Amendment is not a novation and the terms and conditions of this Amendment shall be in addition to and supplemental to all terms and conditions set forth in the Loan Documents. Nothing in this Amendment is intended, or shall be construed, to constitute an accord and satisfaction of Borrowers' Secured Obligations under or in connection with the Existing Loan Agreement and any other Loan Document or to modify, affect or impair the perfection or continuity of Agent's security interest in, (on behalf of itself and Lenders) security titles to or other liens on any Collateral for the Secured Obligations.

(b) **Conditions**. For purposes of determining compliance with the conditions specified in Section 3, Lenders that have signed this Amendment shall be deemed to have consented to, approved or accepted or to be satisfied with, each document or other matter required thereunder to be consented to or approved by or acceptable or satisfactory to Lenders unless Agent shall have received notice from Lenders prior to the date hereof specifying its objection thereto.

(c) **Release**. In consideration of the agreements of Agent and Lenders contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each Borrower, on behalf of itself and its successors, assigns, and other legal representatives, hereby fully, absolutely, unconditionally and irrevocably releases, remises and forever discharges Agent and Lenders, and its successors and assigns, and its present and former shareholders, affiliates, subsidiaries, divisions, predecessors, directors, officers, attorneys, employees, agents and other representatives (Agent, Lenders and all such other persons being hereinafter referred to collectively as the "Releasees" and individually as a "Releasee"), of and from all demands, actions, causes of action, suits, covenants, contracts, controversies, agreements, promises, sums of money, accounts, bills, reckonings, damages and any and all other claims, counterclaims, defenses, rights of set-off, demands and liabilities whatsoever of every name and nature, known or unknown, suspected or unsuspected, both at law and in equity, which Borrower, or any of its successors, assigns, or other legal representatives may now or hereafter own, hold, have or claim to have against the Releasees or any of them for, upon, or by reason of any circumstance, action, cause or thing whatsoever which arises at any time on or prior to the day and date of this Amendment for or on account of, or in relation to, or in any way in connection with the Loan Agreement, or any of the other Loan Documents or the transactions thereunder or related thereto. Each Borrower waives the provisions of California Civil Code section 1542, which states:

> A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS THAT THE CREDITOR OR RELEASING PARTY DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE AND THAT, IF KNOWN BY HIM OR HER, WOULD HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR OR RELEASED PARTY.

Each Borrower understands, acknowledges and agrees that the release set forth above may be pleaded as a full and complete defense and may be used as a basis for an injunction against any action, suit or other proceeding which may be instituted, prosecuted or attempted in breach of the provisions of such release. Each Borrower agrees that no fact, event, circumstance, evidence or transaction which could now be asserted or which may hereafter be discovered shall affect in any manner the final, absolute and unconditional nature of the release set forth above. The provisions of this section shall survive payment in full of the Secured Obligations, full performance of all the terms of this Amendment and the other Loan Documents.

(d) **No Reliance**. Borrowers hereby acknowledge and confirm to Agent and Lenders that each such Borrower is executing this Amendment on the basis of its own investigation and for its own reasons without reliance upon any agreement, representation, understanding or communication by or on behalf of any other Person.

(e) **Costs and Expenses**. Borrowers agree to pay to Agent on the date hereof the out-of-pocket costs and expenses of Agent and Lenders party hereto, and the fees and disbursements of counsel to Agent and Lenders party hereto in connection with the negotiation, preparation, execution and delivery of this Amendment and any other documents to be delivered in connection herewith on the date hereof.

(f) **Binding Effect**. This Amendment binds and is for the benefit of the successors and permitted assigns of each party.

(g) **Governing Law.** This Amendment and the other Loan Documents shall be governed by, and construed and enforced in accordance with, the laws of the State of California, excluding conflict of laws principles that would cause the application of laws of any other jurisdiction.

(h) **Complete Agreement; Amendments**. This Amendment and the Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements with respect to such subject matter. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of this Amendment and the Loan Documents merge into this Amendment and the Loan Documents.

(i) **Severability of Provisions.** Each provision of this Amendment is severable from every other provision in determining the enforceability of any provision.

(j) **Counterparts**. This Amendment may be executed in any number of counterparts and by different parties on separate counterparts, each of which, when executed and delivered, is an original, and all taken together, constitute one Amendment. Delivery of an executed counterpart of a signature page of this Amendment by facsimile, portable document format (.pdf) or other electronic transmission will be as effective as delivery of a manually executed counterpart hereof.

(k) **Loan Documents**. This Amendment and the documents related thereto shall constitute Loan Documents.

(l) **Electronic Execution of Certain Other Documents**. The words “execution,” “execute”, “signed,” “signature,” and words of like import in or related to any document to be signed in connection with this Amendment and the transactions contemplated hereby (including without limitation assignments, assumptions, amendments, waivers and consents) shall be deemed to include electronic signatures, the electronic matching of assignment terms and contract formations on electronic platforms approved by Agent, or the keeping of records in electronic form, each of which shall be of the same legal effect, validity or enforceability as a manually executed signature or the use of a paper-based recordkeeping system, as the case may be, to the extent and as provided for in any applicable law, including the Federal Electronic Signatures in Global and National Commerce Act, the California Uniform Electronic Transaction Act, or any other similar state laws based on the Uniform Electronic Transactions Act.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the parties hereto have duly executed this Amendment, as of the date first above written.

BORROWERS:

BICYCLE THERAPEUTICS PLC

Signature: /s/ Kevin Lee

Print Name: Kevin Lee

Title: Director; Chief Executive Officer

BICYCLETX LIMITED

Signature: /s/ Kevin Lee

Print Name: Kevin Lee

Title: Director

BICYCLERD LIMITED

Signature: /s/ Kevin Lee

Print Name: Kevin Lee

Title: Director

BICYCLE THERAPEUTICS INC.

Signature: /s/ Lee Kalowski

Print Name: Lee Kalowski

Title: President

[SIGNATURES CONTINUE ON THE NEXT PAGE]

AGENT:

HERCULES CAPITAL, INC.

Signature: /s/ Jennifer Choe

Print Name: Jennifer Choe

Title: Associate General Counsel

LENDERS:

HERCULES CAPITAL, INC.

Signature: /s/ Jennifer Choe

Print Name: Jennifer Choe

Title: Associate General Counsel

HERCULES CAPITAL FUNDING TRUST 2019-1

Signature: /s/ Jennifer Choe

Print Name: Jennifer Choe

Title: Associate General Counsel

[Signature Page to First Amendment to Loan and Security Agreement]

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-231718, 333-237054, 333-240993) and Form S-3 (No. 333-238996) of Bicycle Therapeutics plc of our report dated March 11, 2021 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Cambridge, United Kingdom
March 11, 2021

Exhibit 31.1

CERTIFICATION

I, Kevin Lee, certify that:

1. I have reviewed this Annual Report on Form 10-K of Bicycle Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2021

By: /s/ Kevin Lee
Kevin Lee, Ph.D., MBA
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Lee Kalowski, certify that:

1. I have reviewed this Annual Report on Form 10-K of Bicycle Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2021

By: /s/ Lee Kalowski
Lee Kalowski, MBA
Chief Financial Officer and President

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Kevin Lee, Chief Executive Officer of Bicycle Therapeutics plc (the "Company"), and Lee Kalowski, Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 11, 2021

IN WITNESS WHEREOF, the undersigned have set their hands hereto as of the 11th day of March, 2021.

/s/ Kevin Lee	/s/ Lee Kalowski
Kevin Lee, Ph.D., MBA	Lee Kalowski, MBA
Chief Executive Officer	Chief Financial Officer

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Bicycle Therapeutics plc under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.