Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(**Mark One**)

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

For the quarterly period ended June 30, 2019

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	NASDAQ Global Select Market
American Depositary Shares, each representing one ordinary share, nominal value £0.01 per share	BCYC	NASDAQ Global Select Market

* 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 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 (§ 232.405 of this chapter) 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, 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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of August 7, 2019, the registrant had 17,900,731 ordinary shares, nominal value £0.01 per share, outstanding.

Table of Contents

Forward-looking Information

This Quarterly Report on Form 10-Q contains forward-looking statements which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (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:

- 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 Conjugate ("BTC") program and our other pipeline programs;
- our ability to utilize our screening platform to identify and advance additional product candidates into clinical development;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- our ability to develop sales and marketing capabilities;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- our ability to operate our business without infringing the intellectual property rights and proprietary technology of third parties;
- cost associated with defending intellectual property infringement, product liability and other claims;
- regulatory development in the United States, under the laws and regulations of England and Wales, and other jurisdictions;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations or obtain additional grant funding;
- the rate and degree of market acceptance of any approved products;

- developments relating to our competitors and our industry, including competing therapies;
- our ability to effectively manage our anticipated growth;
- our ability to attract and retain qualified employees and key personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act;
- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance;

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 Quarterly Report on Form 10-Q, 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 II. Item 1A and elsewhere in this Quarterly Report on Form 10-Q. 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 Quarterly Report represents our views only as of the date of this quarterly 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.

PART I - FINANCIAL INFORMATION

Item 1. Financial Statements.

Bicycle Therapeutics plc
Condensed Consolidated Balance Sheets
(In thousands, except share and per share data)
(Unaudited)

	June 30, 2019	December 31, 2018
Assets		
Current assets:		
Cash	$ 108,536	$ 63,380
Accounts receivable	160	5,021
Prepaid expenses and other current assets	2,021	2,076
Research and development incentives receivable	9,735	6,292
Total current assets	120,452	76,769
Property and equipment, net	2,002	1,818
Operating lease right-of-use assets	2,386	—
Other assets	1,406	3,039
Total assets	$ 126,246	$ 81,626
Liabilities, convertible preferred shares and shareholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 2,569	$ 1,887
Accrued expenses and other current liabilities	5,859	7,032
Deferred revenue, current portion	1,012	10
Total current liabilities	9,440	8,929
Warrant liability	—	4,804
Deferred revenue, net of current portion	9,358	14,625
Operating lease liabilities	1,628	—
Other long-term liabilities	1,261	897
Total liabilities	21,687	29,255
Commitments and contingencies (Note 12)		
Series A convertible preferred shares, £0.01 nominal value; no shares and 3,000,001 shares authorized at June 30, 2019 and December 31, 2018, respectively; no shares and 2,800,001 shares issued and outstanding at June 30, 2019 and December 31, 2018, respectively	—	41,820
Series B1 convertible preferred shares, £0.01 nominal value: no shares and 4,690,485 shares authorized at June 30, 2019 and December 31, 2018, respectively; no shares and 3,947,198 shares issued and outstanding at June 30, 2019 and December 31, 2018, respectively	—	54,621
Series B2 convertible preferred shares, £0.01 nominal value: no shares and 1,403,633 shares authorized at June 30, 2019 and December 31, 2018, respectively; no shares and 1,323,248 shares issued and outstanding at June 30, 2019 and December 31, 2018, respectively	—	25,756
Shareholders' equity (deficit):		
Ordinary shares, £0.01 nominal value; 31,995,653 and 15,452,420 shares authorized at June 30, 2019 and December 31, 2018, respectively; 17,900,731 shares issued and outstanding at June 30, 2019; 898,678 shares issued and 814,728 shares outstanding at December 31, 2018 , respectively	226	10
Additional paid-in capital	193,178	1,857
Accumulated other comprehensive loss	(2,183)	(1,751)
Accumulated deficit	(86,662)	(69,942)
Total shareholders' equity (deficit)	104,559	(69,826)
Total liabilities, convertible preferred shares and shareholders' equity (deficit)	$ 126,246	$ 81,626

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

Bicycle Therapeutics plc
Condensed Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share data)
(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Collaboration revenues	$ 1,522	$ 1,661	$ 7,906	$ 4,469
Operating expenses:				
Research and development	6,537	4,917	12,813	8,626
General and administrative	2,973	1,702	6,375	3,690
Total operating expenses	9,510	6,619	19,188	12,316
Loss from operations	(7,988)	(4,958)	(11,282)	(7,847)
Other income (expense):				
Interest and other income	90	52	154	49
Other expense, net	(2,184)	(73)	(5,377)	(111)
Total other expense, net	(2,094)	(21)	(5,223)	(62)
Net loss before income tax provision	(10,082)	(4,979)	(16,505)	(7,909)
Provision for (benefit from) income taxes	135	—	215	(396)
Net loss	$ (10,217)	$ (4,979)	$ (16,720)	$ (7,513)
Net loss attributable to ordinary shareholders	$ (10,217)	$ (4,979)	$ (16,720)	$ (7,513)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.40)	$ (11.85)	$ (4.08)	$ (18.38)
Weighted average ordinary shares outstanding, basic and diluted	7,298,139	420,063	4,101,564	408,807
Comprehensives Loss:				
Net loss	$ (10,217)	$ (4,979)	$ (16,720)	$ (7,513)
Other comprehensive income (loss):				
Foreign currency translation adjustment	(1,512)	(2,657)	(432)	(861)
Total comprehensive loss	$ (11,729)	$ (7,636)	$ (17,152)	$ (8,374)

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

Bicycle Therapeutics plc
Condensed Consolidated Statements of Convertible Preferred Shares and Shareholders' Equity (Deficit)
(In thousands, except share and per share data)
(Unaudited)

	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, 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	—	—	—	—	—	—
Issuance of restricted share awards	—	—	—	—	—	—	27,304	1	103	—	—	104
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	3	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	—	—	172	—	—	172
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	1,080	—	1,080
Net loss	—	—	—	—	—	—	—	—	—	—	(6,503)	(6,503)
Balance at March 31, 2019	2,800,001	41,820	3,947,198	54,621	1,403,633	27,339	842,035	11	2,132	(671)	(76,445)	(74,973)
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	—	—	—	—	—	—	702,557	9	10,018	—	—	10,027
Issuance of ADSs in initial public offering, net of underwriting discounts, commissions and offering expenses of $8.4 million	—	—	—	—	—	—	4,637,666	59	56,469	—	—	56,528
Issuance of restricted share awards	—	—	—	—	—	—	56,643	1	292	—	—	293
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	14,301	—	21	—	—	21
Share-based compensation expense	—	—	—	—	—	—	—	—	612	—	—	612
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(1,512)	—	(1,512)
Net loss	—	—	—	—	—	—	—	—	—	—	(10,217)	(10,217)
Balance at June 30, 2019	—	$ —	—	$ —	—	$ —	17,900,731	$ 226	$ 193,178	$ (2,183)	$ (86,662)	$ 104,559
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 restricted share awards	—	—	—	—	—	—	35,725	1	53	—	—	54
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	9,002	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	—	—	198	—	—	198
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	1,796	—	1,796
Net loss	—	—	—	—	—	—	—	—	—	—	(2,534)	(2,534)
Balance at March 31, 2018	2,800,001	41,820	3,947,198	54,621	—	—	413,722	6	1,089	1,865	(50,630)	(47,670)
Issuance of restricted share awards	—	—	—	—	—	—	12,757	—	26	—	—	26
Issuance of ordinary shares upon exercise of share options	—	—	—	—	—	—	359	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	—	—	309	—	—	309
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(2,657)	—	(2,657)
Net loss	—	—	—	—	—	—	—	—	—	—	(4,979)	(4,979)
Balance at June 30, 2018	2,800,001	$ 41,820	3,947,198	$ 54,621	—	$ —	426,838	$ 6	$ 1,424	$ (792)	$ (55,609)	$ (54,971)

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

Bicycle Therapeutics plc
Condensed Consolidated Statements of Cash Flows
(In thousands, except share and per share data)
(Unaudited)

	Six Months Ended June 30,	
	2019	**2018**
Cash flows from operating activities:		
Net loss	$ (16,720)	$ (7,513)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation expense	1,181	587
Depreciation and amortization	443	355
Change in fair value of warrant liability	5,381	111
Changes in operating assets and liabilities:		
Accounts receivable	4,955	(1,539)
Research and development incentives receivable	(3,518)	(1,821)
Prepaid expenses and other current assets	(60)	(462)
Operating lease right-of-use assets	352	—
Other assets	(124)	(314)
Accounts payable	530	155
Accrued expenses and other current liabilities	(978)	(177)
Lease liabilities	(351)	—
Deferred revenue	(4,329)	(2,211)
Other long-term liabilities	429	263
Net cash used in operating activities	(12,809)	(12,566)
Cash used in investing activities:		
Purchases of property and equipment	(881)	(650)
Net cash used in investing activities	(881)	(650)
Cash flows from financing activities:		
Proceeds from issuance of series B2 convertible preferred shares, net of issuance costs	1,334	—
Proceeds from issuance of ADSs in initial public offering, net of issuance costs	57,768	—
Proceeds from the exercise of share options	21	—
Proceeds from the exercise of warrants	6	—
Net cash provided by financing activities	59,129	—
Effect of exchange rate changes on cash	(283)	(1,043)
Net increase (decrease) in cash	45,156	(14,259)
Cash at beginning of period	63,380	67,663
Cash at end of period	$ 108,536	$ 53,404
Supplemental disclosure of cash flow information		
Cash paid for income taxes	73	—
Initial public offering costs accrued but not paid	664	—
Cash paid for amounts included in the measurement of operating lease liabilities	447	—
Advance billings on deferred revenue included in accounts receivable	—	5,103
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 condensed consolidated financial statements

Bicycle Therapeutics plc
Notes to Unaudited Condensed 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 metalloprotease. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK. The Company is also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2 and Nectin-4, respectively, for oncology indications. The Company is currently conducting Investigational New Drug application-enabling activities for BT5528 and BT8009. The Company's discovery pipeline in oncology includes Bicycle-targeted innate immune activators, as well as T-cell modulators. Beyond oncology, the Company is collaborating with biopharmaceutical companies and organizations in therapeutic areas that include anti-bacterial, cardiovascular, hematology, ophthalmology, dementia and respiratory indications.

The accompanying condensed 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 condensed consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP").

Share capital reorganization

On May 9, 2019, the Company's board of directors and shareholders approved the reorganization of the Company's share capital (the "Share Capital Reorganization") 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. All issued and outstanding share and per share amounts of ordinary shares and share options included in the accompanying condensed consolidated financial statements have been adjusted to reflect this the Share Capital Reorganization for all periods presented. The number of ordinary shares that were issued to the holders of the Company's convertible preferred shares (Note 6) and warrants to subscribe for Series A and Series B1 convertible preferred shares (Note 7) in conjunction with the closing of the Company's initial public offering ("IPO") were adjusted accordingly, as well as the number of ordinary shares over which options and outstanding warrants have been granted.

On May 22, 2019, Bicycle Therapeutics Limited ("BTL") re-registered as a public limited company, and changed its name to Bicycle Therapeutics plc. The Company historically conducted its business through BTL and its wholly owned subsidiaries, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics Inc., and, therefore the historical consolidated financial statements previously presented the consolidated results of operations of BTL. Following the completion of the Company's re-registration in May 2019, the consolidated financial statements of BTL became the historical consolidated financial statements of the Company.

Initial public offering

On May 28, 2019, the Company completed its 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 $56.5 million, after deducting underwriting discounts and commissions of $4.5 million and offering expenses of $3.9 million. Upon the closing of the IPO, all of the Company's outstanding convertible preferred shares automatically converted into 11,647,529 ordinary shares, on a 1:1.429 basis. In addition, warrants to subscribe for Series A and Series B1 convertible preferred shares 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 condensed consolidated balance sheet.

Liquidity

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel and collaboration partners, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations, and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval prior to commercialization. Even if the Company's research and development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The accompanying condensed 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 sales of convertible preferred shares (Note 6) and proceeds received from its collaboration arrangements (Note 10), and most recently, with proceeds from the IPO completed in May 2019. The Company has incurred recurring losses since inception, including $16.7 million for the six months ended June 30, 2019. As of June 30, 2019, the Company had an accumulated deficit of $86.7 million. The Company expects to continue to generate operating losses in the foreseeable future. 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 interim condensed 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 substantial 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

The Company's significant accounting policies are disclosed in the audited consolidated financial statements for the year ended December 31, 2018 included in the Company's final prospectus for the IPO filed pursuant to Rule 424(b) under the Securities Act, with the Securities and Exchange Commission ("SEC"), on May 23, 2019. Since the date of such consolidated financial statements, there have been no changes to the Company's significant accounting policies, other than those disclosed below.

Unaudited Interim Financial Information

Certain information in the footnote disclosures of the financial statements has been condensed or omitted pursuant to the rules and regulations of the SEC. These condensed consolidated financial statements should be read in conjunction with the Company's audited consolidated financial statements and notes thereto for the year ended December 31, 2018 included in the Company's final prospectus for the IPO filed pursuant to Rule 424(b) under the Securities Act, with the SEC, on May 23, 2019.

The accompanying condensed consolidated balance sheet at June 30, 2019, condensed consolidated statements of operations and comprehensive loss, condensed consolidated statements of convertible preferred shares and shareholders' equity (deficit) for the three and six months ended June 30, 2019 and 2018, and the condensed consolidated statements of cash flows for the six months ended June 30, 2019 and 2018 and the related financial information disclosed in these notes are unaudited. The unaudited interim financial statements have been prepared on the same basis as the audited annual financial statements for the year ended December 31, 2018, and, in the opinion of management, reflect all adjustments, consisting of normal recurring adjustments, necessary for the fair presentation of the Company's financial position as of June 30, 2019, the results of its operations for the three and six months ended June 30, 2019 and 2018, and its cash flows for the six months ended June 30, 2019 and 2018. The results for the three and six months ended June 30, 2019 are not necessarily indicative of the results to be expected for the year ending December 31, 2019, any other interim periods, or any future year or period.

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. 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 U.S. dollar ("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 condensed consolidated statements of operations and comprehensive loss as incurred. The Company recorded foreign exchange gains of $0.7 million and $0.4 million during the three months ended June 30, 2019 and 2018, respectively, and foreign exchange gains of $0.4 million and $0.2 million for the six months ended June 30, 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 condensed consolidated statements of convertible preferred shares and shareholders' equity (deficit) as a component of accumulated other comprehensive income (loss).

Leases

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 condensed 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.

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 condensed 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 three and six months ended June 30, 2019, the Company recognized $0.1 and $0.2 million, respectively, as a reduction of research and development expense related to government grant arrangements. There were no grant proceeds recognized for the three and six month periods ended June 30, 2018.

Recently adopted accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"). This guidance revises existing practice related to accounting for leases under ASC Topic 840 Leases ("ASC 840"). ASU 2016-02 requires lessees to recognize most leases on their balance sheet as a right-of-use asset and a lease liability. The lease liability is equal to the present value of lease payments and the right-of-use asset is based on the lease liability, subject to adjustment such as for initial direct costs. For income statement purposes, the new standard retains a dual model similar to ASC 840, requiring leases to be classified as either operating or finance. For lessees, operating leases will result in straight-line expense (similar to current accounting by lessees for operating leases under ASC 840). In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842) Targeted Improvements*, which provides an additional transition method that allows entities to initially apply the new standard at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption without restating prior periods. The guidance is effective for annual reporting periods beginning after December 15, 2018 and interim periods within those fiscal years, and early adoption is permitted. The Company adopted the new standard on January 1, 2019 by applying the new lease requirements at the adoption date without restating prior periods. In connection with the adoption of ASU 2016-02 the Company recorded an impact of approximately $2.7 million on its unaudited condensed consolidated balance sheet to record right-of-use-assets and $2.6 million to record lease liabilities on January 1, 2019, which are primarily related to the lease of the Company's corporate headquarters in the

U.K. and the lease of its office and laboratory space in Lexington, Massachusetts. The adoption of ASU 2016-02 did not have a material impact on the Company's results of operations or cash flows.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation — Stock Compensation: Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07") to simplify the accounting for share-based payments to non-employees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The new guidance expands the scope of ASC 718, *Compensation — Stock Compensation*, to include share-based payments granted to non-employees in exchange for goods or services used or consumed in an entity's own operations and supersedes the guidance in ASC Topic 505-50, *Equity-Based Payments to Non-Employees*. The guidance is effective for public business entities in annual periods beginning after December 15, 2018 and interim periods within those years. Early adoption is permitted. The Company adopted the new standard on January 1, 2019. The adoption did not have a material impact on the Company's financial position, results of operations or cash flows.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles (Topic 350): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*, which aligns the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software. This standard also requires customers to amortize the capitalized implementation costs of a hosting arrangement that is a service contract over the term of the hosting arrangement. The Company early adopted this standard, as of April 1, 2019, on a prospective basis for applicable implementation costs. The adoption of this standard would not have had a material impact to historical accounting periods, but will impact implementation costs that are incurred for the remainder of 2019 and in future periods.

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. ASU 2016-13 is effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. Early adoption is permitted. 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.

3. Fair value of financial assets and liabilities

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 (Note 7). 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 outstanding warrant liability to additional paid-in-capital in the condensed consolidated balance sheet. As such, there is no warrant liability at June 30, 2019.

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis (in thousands):

	Fair Value Measurement as of December 31, 2018 using:			
	Level 1	Level 2	Level 3	Total
Liabilities:				
Warrant liability	$ —	$ —	$ 4,804	$ 4,804
	$ —	$ —	$ 4,804	$ 4,804

During the six months ended June 30, 2019 and the year ended December 31, 2018, there were no transfers between levels.

4. Property and equipment, net

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

	June 30, 2019	December 31, 2018
Laboratory equipment	$ 3,884	$ 3,356
Leasehold improvements	142	75
Computer equipment and software	225	221
Furniture and office equipment	116	99
	4,367	3,751
Less: Accumulated depreciation and amortization	(2,365)	(1,933)
	$ 2,002	$ 1,818

Depreciation expense was $0.2 million and $0.4 million for the three and six months ended June 30, 2019, and $0.2 million and $0.4 million for the three and six months ended June 30, 2018, respectively.

5. Accrued expenses and other current liabilities

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

	June 30, 2019	December 31, 2018
Accrued employee compensation and benefits	$ 1,161	$ 1,610
Accrued external research and development expenses	2,843	3,814
Income taxes payable	269	15
Accrued professional fees	753	1,494
Current portion of operating lease liabilities	594	—
Other	239	99
	$ 5,859	$ 7,032

6. Convertible preferred shares

The Company had issued Series A convertible preferred shares ("Series A Preferred Shares"), Series B1 convertible preferred shares ("Series B1 Preferred Shares"), and Series B2 convertible preferred shares ("Series B2 Preferred Shares") (collectively the "Preferred Shares").

On May 26, 2017 the Company completed the issue of 3,562,583 Series B1 Preferred Shares at a price per share of £11.2278, for gross cash proceeds of $51.9 million. In addition, on October 27, 2017, an additional unaffiliated investor subscribed for a further 384,615 Series B1 Preferred Shares at a price per share of £13.00, for gross cash proceeds of $6.6 million. These two transactions are collectively referred to as "the Series B1 Financing". In conjunction with the Series B1 Financing, the Company also issued warrants to subscribe for 743,287 Series B1 Preferred Shares to the subscribers of the Series B1 Preferred Shares (Note 7). The Company allocated a portion of the proceeds equal to the fair value of the warrants at the date of grant to the warrant liability, and the remaining amount was allocated to the Series B1 Preferred Shares.

On December 20, 2018, the Company completed the issue of 1,323,248 Series B2 preferred shares at a price per Series B2 preferred share of £15.55, for gross cash proceeds of $26.1 million (the "Series B2 Financing"). In conjunction with the Series B2 Financing, the existing holders of warrants to subscribe for Series B1 preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 preferred shares and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 preferred shares to the new investor. In conjunction with the Series B2 Financing, the Company designated all previously outstanding

Series B preferred shares as Series B1 preferred shares. On January 3, 2019, the Company completed the issue of 80,385 Series B2 preferred shares at a price per share of £15.55, for gross cash proceeds of $1.6 million.

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.

7. Warrant liability

On May 26, 2017, the Company issued 200,000 warrants to subscribe for Series A Preferred Shares at £0.01 each, which are exercisable at any time after May 26, 2017 provided that they have not otherwise lapsed in accordance with their terms. The warrants to subscribe for Series A Preferred Shares expire upon the earlier of (i) 10 years from their issuance date, or (ii) upon an IPO or exit unless an exercise delay notice is provided by the Series A warrant holder, in which case they will expire 12 months following an IPO or exit. On May 28, 2019, 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 holders of the remaining 80,000 warrants provided the Company with an exercise delay notice, which are exercisable into 114,320 ordinary shares following the completion of the IPO, as adjusted for the impact of the Share Capital Reorganization (Note 1).

On May 26, 2017, in conjunction with the issuance of 3,562,583 Series B1 Preferred Shares at a price per share of £11.2278, the Company issued 627,903 warrants to subscribe for Series B1 Preferred Shares with an exercise price of £0.01. In addition, on October 27, 2017, in conjunction with the issuance of 384,615 Series B1 Preferred Shares the Company issued a further 115,384 warrants to subscribe for Series B1 Preferred Shares with an exercise price of £0.01. In conjunction with the Series B2 Financing, the existing holders of warrants to subscribe for Series B1 preferred shares surrendered 194,911 warrants to subscribe for the same number of Series B1 preferred shares and the Company issued a further 194,911 warrants to subscribe for the same number of Series B1 preferred shares to the new investor. The transfer of warrants between investors did not have an impact to the valuation of the warrant liability, as this represents a transaction between shareholders and the Company did not issue any new instruments or change the rights and preferences of the underlying warrants to subscribe for Series B1 preferred shares.

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. The Company assessed this event as a modification to the terms of the Series B1 warrants and, remeasured the warrant liability immediately before and immediately after the modification, which resulted in an incremental change in fair value of $0.1 million, which is included in other expense for the six months ended June 30, 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 1).

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 (Note 3). 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 condensed consolidated balance sheet.

The following table provides a roll-forward of the fair values of the Company's warrant liability for which fair value was determined by Level 3 inputs (in thousands):

	Warrant Liability
Fair value at December 31, 2018	$ 4,804
Change in fair value of warrant liability recorded as other expense	5,381
Conversion of warrant liability to equity upon closing of IPO and exercise of warrants	(10,021)
Impact of exchange rates on translation of warrant liability to USD included in accumulated other comprehensive income (loss)	(164)
Fair value at June 30, 2019	$ —

The warrant liability in the table above consisted of the fair value of warrants to subscribe for Series A and Series B1 Preferred Shares (see Note 6) and, prior to the IPO, was based on significant inputs not observable in the market, which represent a Level 3 measurement within the fair value hierarchy. The Company's valuation of the warrants to subscribe for Series A and Series B1 Preferred Shares utilized the Black-Scholes option-pricing model, which incorporates assumptions and estimates to value the warrant liability. The Company assessed these assumptions and estimates on a quarterly basis prior to the closing of the IPO in May 2019.

The quantitative elements associated with the Company's Level 3 inputs impacting the fair value measurement of the warrant liability included the fair value per share of the underlying Series A and Series B1 preferred shares or ordinary shares at the time of final remeasurement, into which the warrants were exercisable, the remaining contractual term of the warrants, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares.

The most significant assumption in the Black-Scholes option-pricing model impacting the fair value of the warrant liability was the fair value of the Series A and Series B1 preferred shares, or ordinary shares at the time of final remeasurement, into which the warrant is exercisable as of each remeasurement date. Given the absence of an active market for the Company's equity securities prior to the IPO, the Company determined the fair value per share of the convertible preferred shares underlying the warrants by taking into consideration the implied value derived from an independent third-party valuation of the Company's ordinary shares, adjusted for certain restrictions on the exercise of the B1 warrants per their contractual terms. Assumptions related to the remaining term, risk-free interest rate, expected dividend yield and expected volatility did not have an impact to the fair value of the warrants because the exercise price of the warrants was £0.01, and the fair value of the warrant was equal to the difference between the exercise price and the fair value regardless of the assumptions. The Company historically had been a private company and lacked company-specific historical and implied volatility information of its shares. Therefore, it estimated its expected share volatility based on the historical volatility of publicly traded peer companies for a term equal to the remaining contractual term of the warrants. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the remaining contractual term of the warrants. The Company had estimated a 0% dividend yield based on the expected dividend yield and the fact that the Company has never paid or

declared dividends. The following table presents the unobservable inputs to the fair value measurement of the warrant liability:

	Remeasurement upon closing of the IPO on May 28, 2019		December 31, 2018	
	Series A Warrants	Series B1 Warrants	Series A Warrants	Series B1 Warrants(1)
Risk free rate	2.2%	2.1%	2.6%	2.5%
Expected dividend yield	—%	—%	—%	—%
Expected term (years)	8.0	5.8	8.4	6.25
Expected volatility	74.7%	78.2%	75.4%	79.6%
Exercise price	£ 0.01	£ 0.01	£ 0.01	£ 0.01
Fair value of preferred shares or ordinary shares underlying the warrant	$ 12.28	$ 12.28	$ 8.61	$ 4.15

(1) The fair value of the Series B1 preferred shares underlying the warrants to purchase Series B1 preferred shares at December 31, 2018 includes a 50% probability that the warrants will be not be exercisable prior to the IPO, based on their contractual terms. 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

8. Ordinary shares

Each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. 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, 2018 and June 30, 2019, the Company has not declared any dividends.

As of June 30, 2019 and December 31, 2018, the Company's authorized capital share consisted of 31,995,653 ordinary shares and 15,452,420 ordinary shares, respectively, with a nominal value of £0.01 per share.

9. Share-based compensation

Employee incentive pool

2019 Share Option Plan

In May 2019, the Company adopted the 2019 Share Option Plan (the "2019 Plan"), which became effective in conjunction with the IPO. The 2019 Plan provides for the grant of options to purchase ordinary shares, share appreciation rights, restricted shares, restricted share units, and other share-based awards to officers, employees, directors and other key persons (including consultants).

The Company has initially reserved 2,470,583 ordinary shares for future issuance under the 2019 Plan. The number of ordinary shares reserved for issuance of the 2019 Plan will automatically increase on the first day of January, commencing on January 1, 2020, in an amount equal to 4% of the total number of 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, subject to adjustment in the event of a share split, share dividend or other change in capitalization. As of June 30, 2019, there were 1,092,902 shares available for issuance under the 2019 Plan.

Share options issued under the 2019 Share Option Plan have a 10 year contractual life, and 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. The exercise price

of share options issued under the 2019 Share Option Plan shall not be 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 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 ("ESPP"), which became effective in conjunction with the IPO. The Company initially reserved 215,000 ordinary shares for future issuance under this plan. 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 falls 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 June 30, 2019, 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 condensed consolidated statements of operations and comprehensive loss (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Research and development expenses	$ 291	$ 171	$ 399	$ 298
General and administrative expenses	614	164	782	288
	$ 905	$ 335	$ 1,181	$ 587

Share options

The following table summarizes the Company's option activity since December 31, 2018:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2018	863,712	$ 1.01	8.75	$ 3,292
Granted	1,875,820	12.13		
Exercised	(14,304)	1.49		
Forfeited	(109,279)	1.61		
Outstanding as of June 30, 2019	2,615,949	$ 8.96	9.39	$ 8,313
Vested and expected to vest as of June 30, 2019	2,615,949	$ 8.96	9.39	$ 8,313
Options exercisable as of June 30, 2019	326,708	$ 3.03	8.27	$ 2,441

The weighted average grant-date fair value of share options granted during the six months ended June 30, 2019 and 2018 was $8.26 per share and $1.83 per share, respectively.

Total share-based compensation expense for share options granted was $0.6 million and $0.8 million for the three and six months ended June 30, 2019, respectively, and $0.3 million and $0.5 million, for the three and six months ended June 30, 2018, respectively. Expense for non-employee consultants for the three and six months ended June 30, 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 was $0.1 million and $0.1 million during the three and six months ended June 30, 2019, respectively, and was immaterial during the three and six months ended June 30, 2018.

The Company granted options for the purchase of an aggregate of 0 and 18,719 ordinary shares during the six months ended June 30, 2019 and 2018, respectively, for which 20% of the award vests upon the first anniversary of the vesting start date, 60% vests thereafter in 36 equal monthly installments, and 20% on the earlier of the fourth anniversary of the vesting start date, or the achievement of a specified revenue threshold from the Company's collaboration arrangements. 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 and $43,000 during the three and six months ended June 30, 2019, respectively, and $0.3 million and $0.5 million during the six months ended June 30, 2018 related to these awards, 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:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Risk-free interest rate	2.2%	1.3%	2.2%	1.3%
Expected volatility	78.0%	75.1%	78.1%	75.1%
Expected dividend yield	—	—	—	—
Expected term (in years)	5.83	6.07	5.85	6.07

As of June 30, 2019, total unrecognized compensation expense related to the unvested employee and director share-based awards was $15.9 million, which is expected to be recognized over a weighted average period of 3.0 years.

Restricted shares

The Company had granted restricted shares with service-based vesting conditions. Shares of unvested restricted shares may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. These restricted shares are subject to repurchase rights, for aggregate consideration of £1.00. Accordingly, the Company has recorded the proceeds from the issuance of restricted shares as a liability in the condensed consolidated balance sheets included as a component of accrued expenses and other current liabilities. The restricted share liability is reclassified into shareholders' equity (deficit) as the restricted shares vested.

The following table summarizes the Company's restricted ordinary share award activity since December 31, 2018:

	Shares	Weighted Average Grant-Date Fair Value
Unvested restricted ordinary shares as of December 31, 2018	83,947	$ 1.93
Issued	—	—
Forfeited	—	—
Vested	(83,947)	1.93
Unvested restricted ordinary shares as of June 30, 2019	—	$ —

In conjunction with the IPO in May 2019, the board of directors modified the vesting terms to accelerate vesting for all unvested restricted shares. As a result, the Company recorded incremental share based compensation expense of $0.2 million upon the modification of the restricted shares during the three and six month periods ended June 30, 2019.

Total share-based compensation for unvested restricted shares granted was $0.3 million and $0.4 million for the three and six months ended June 30, 2019, respectively, and $27,000 and $0.1 million for the three and six months ended June 30, 2018, respectively.

The fair value of employee restricted share awards vested, based on estimated fair values of the ordinary shares underlying the restricted share awards on the day of vesting, was and $0.6 million and $0.7 million during the three and six months ended June 30, 2019, respectively, and $34,000 and $0.1 million during the three and six months ended June 30, 2018, respectively

As of June 30, 2019, there was no unrecognized compensation cost related to the unvested employee and director restricted share awards.

10. Significant agreements

For the three and six months ended June 30, 2019 and 2018, the Company had collaboration agreements with AstraZeneca AB ("AstraZeneca"), Sanofi (formerly Bioverativ), Oxurion (formerly ThromboGenics) and the Dementia Discovery Fund. The following table summarizes the revenue recognized in the Company's condensed consolidated statements of operations and comprehensive loss from these arrangements (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Collaboration revenues				
AstraZeneca	$ 362	$ 391	$ 787	$ 691
Sanofi	57	1,093	6,016	2,219
Oxurion	—	177	—	1,559
Dementia Discovery Fund	103	—	103	—
Material transfer agreement	1,000	—	1,000	—
Total collaboration revenues	$ 1,522	$ 1,661	$ 7,906	$ 4,469

AstraZeneca Collaboration Agreement

Summary of Agreement — 2016 Agreement

In November 2016, the Company entered into a Research Collaboration Agreement (the "AstraZeneca Collaboration Agreement") with AstraZeneca. The collaboration is focused on the research and development of Bicycle peptides that bind to up to six biological targets. After discovery and initial optimization of such Bicycle peptides, AstraZeneca will be responsible for all research and development, including lead optimization and drug candidate selection. AstraZeneca has option rights, at drug candidate selection, which allow it to obtain development and exploitation license rights with regard to such drug candidate. The initial research obligation focuses on two targets within respiratory, cardiovascular and metabolic disease. AstraZeneca also has an option to nominate up to four additional targets at any point up to the second anniversary of the agreement ("Additional Four Target Option"). The exercise of this option right results in an option fee payable to the Company of $5.0 million and the research obligations and rights are consistent with the obligations and rights related to the initial two targets discussed below.

Under the AstraZeneca Collaboration Agreement, the Company is obligated to use commercially reasonable efforts to perform research activities on the initial two targets, under mutually agreed upon research plans. The research plans includes two discrete parts, on a research program by research program basis: (i) the Bicycle Research Term, which is focused on the generation of Bicycle peptide libraries using the Company's peptide drug discovery platform, to be screened against selected biological targets and optimization of promising compounds, with the goal of identifying compounds that meet the criteria set by the parties, and (ii) the AZ Research Term, during which AstraZeneca may select certain compounds and continue research activities on those compounds, at its sole expense, with the goal of identifying compounds that satisfy the relevant pharmacological and pharmaceutical criteria for clinical testing. AstraZeneca may, at its sole discretion, approve any compound to be progressed into drug development and, upon the selection of each drug candidate, AstraZeneca is to pay $8.0 million as an option fee, in order to obtain worldwide development and exploitation rights.

Each research program is to continue for an initial period of three years (the "Research Term"), including one year for the Bicycle Research Term and two for the AZ Research Term. AstraZeneca may extend the Research Term for each research program by twelve months (or fifteen months, if needed to complete certain toxicology studies). The Research Term for a specific program can be shorter if it is ceased due to a screening failure, a futility determination, abandonment by AstraZeneca, or upon selection of a drug candidate. AstraZeneca has certain substitution rights should a screening failure or futility determination be reached but is obligated to fund these additional efforts related to substitution.

Under the terms of the AstraZeneca Collaboration Agreement, the Company granted to AstraZeneca, for each research program, a right and license (with the right to sublicense) to certain background and platform intellectual property, for the duration of the applicable Research Term, to the extent necessary or useful for AstraZeneca to conduct the activities assigned to it in the applicable research plan, but for no other purpose.

The activities under the AstraZeneca Collaboration Agreement are governed by a joint steering committee ("JSC") formed by an equal number of representatives from the Company and AstraZeneca. The JSC oversees and reviews each research program. Among other responsibilities, the JSC monitors and reports on research progress and it is responsible to ensure open and frequent exchange between the parties regarding research program activities.

AstraZeneca is obligated to fund two full time equivalents ("FTE") during the Bicycle Research Term, for each research program, based on an agreed upon FTE reimbursement rate. Payment is made quarterly in advance of services being provided.

AstraZeneca has the option to obtain development and commercialization licenses associated with each designated drug candidate in return for a fee of $8.0 million per drug candidate. In addition, AstraZeneca is required to make certain milestone payments to the Company upon the achievement of specified development, regulatory and commercial milestones. More specifically, for each research program, the Company is eligible to receive up to $29.0 million in development milestone payments and up to $23.0 million in regulatory milestone payments. The Company is also eligible for up to $110.0 million in commercial milestone payments, on a research program by research program basis. Development milestone payments are triggered upon initiation of a defined phase of clinical research for a drug candidate. Regulatory milestone payments are triggered upon approval to market a product candidate by the United States Food and Drug Administration ("FDA") or other global regulatory authorities. Commercial milestone payments are triggered when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee. In addition, to the extent any of the product candidates covered by the licenses conveyed to AstraZeneca are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Royalty payments are subject to certain reductions, including in certain countries where AstraZeneca faces generic competition. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from AstraZeneca.

Either party may terminate the AstraZeneca Collaboration Agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. Either party may terminate the AstraZeneca Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. AstraZeneca may terminate the AstraZeneca Collaboration Agreement, entirely or on a licensed product by licensed product or country by country basis, for convenience.

Accounting Analysis

The Company has identified the following performance obligations:

(i) research license and the related research and development services during the Bicycle Research Term for the first target (the "Target One Research License and Related Services"),

(ii) research license and the related research and development services during the Bicycle Research Term for the second target (the "Target Two Research License and Related Services").

The Company concluded that the Additional Four Target Option is not a material right, as the option does not provide a discount that AstraZeneca otherwise would not have received. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract. The Company has concluded that the research license is not distinct from the research and development services during the Bicycle Research Term as AstraZeneca cannot obtain the benefit of the research license without the Company performing the research and development services. The services incorporate proprietary technology and unique skills and specialized expertise,

particularly as it relates to constrained peptide technology that is not available in the marketplace. As a result, for each research program, the research license has been combined with the research and development services into a single performance obligation.

The total transaction price was initially determined to be $1.2 million, consisting solely of research and development funding. The Company utilizes the most likely amount method to determine the amount of research and development funding to be received. Additional consideration to be paid to the Company upon the exercise of the license options by AstraZeneca or upon reaching certain milestones is excluded from the transaction price as they relate to option fees and milestones that can only be achieved subsequent to the option exercise or are outside of the initial contact term.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for the Target One Research License and Related Services and the Target Two Research License and Related Services are 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 will recognize revenue related to amounts allocated to the Research License and Related Services as the underlying services are performed over the one year Research Term using a proportional performance model over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected and will remeasure its progress towards completion at the end of each reporting period, which best reflects the progress towards satisfaction of the performance obligation.

In October 2017, AstraZeneca selected a replacement target for the first target, and as such a new Research Term was started related to the Target One Research License and Related Services. In addition, both programs were extended. The total transaction price under the arrangement increased to $2.0 million for the additional research and development funding to be received.

For the three months and six months ended June 30, 2019, the Company recognized $25,000 and $0.2 million, respectively, and for the three and six months ended June 30, 2018, the Company recognized $0.3 million and $0.6 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 June 30, 2019 and December 31, 2018, the Company recorded no deferred revenue and $24,000 of deferred revenue, respectively, in connection with the 2016 AstraZeneca Collaboration Agreement.

May 2018 AstraZeneca Option Exercise — Additional Four Targets

Under the AstraZeneca Collaboration Agreement, AstraZeneca was granted an option to nominate up to four additional targets at any point up to the second anniversary of the agreement ("Additional Four Target Option"). In May 2018, AstraZeneca made an irrevocable election to exercise the Additional Four Target Option. As a result, AstraZeneca is entitled to obtain research and development services with respect to Bicycle peptides that bind to up to four additional targets, along with license rights to those selected targets, in exchange for an option fee of $5.0 million, which was paid by AstraZeneca to the Company in January, 2019. AstraZeneca is obligated to fund two FTEs during the Bicycle Research Term, for each research program, based on an agreed upon FTE reimbursement rate. Payment is made quarterly in advance of services being provided. AstraZeneca has the option to obtain worldwide development and commercialization licenses associated with each designated drug candidate in return for a fee of $8.0 million per drug candidate, upon the selection of such drug candidate, after which AstraZeneca would be required to fund development and commercialization costs, and to pay regulatory and commercial milestone payments and royalties to 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 each research services option, including the underlying development and exploitation license options related to each respective target, results in a material right as the option exercise fee related to the development and exploitation license contains a discount that AstraZeneca would not have otherwise received.

The research license and the related research and development services related to the fourth, fifth and sixth targets are not performance obligations 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 determined to be $5.7 million at the inception of the arrangement, 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 is primarily based on the nature of the services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees AstraZeneca would pay to exercise the license options, the estimated value of the License Option using comparable transactions, and the probability that (i) AstraZeneca would opt into the target development, and (ii) the license options would be exercised by AstraZeneca. Based on the relative standalone selling price, the allocation of the transaction price to the separate performance obligations at the inception of the arrangement is as follows (in thousands):

Performance Obligations	Allocation of Transaction Price
Target Three Research License and Related Services	$ 650
Target 3 Material Right	1,504
Target 4 Material Right	1,204
Target 5 Material Right	1,165
Target 6 Material Right	1,127
	$ 5,650

The Company will recognize revenue related to amounts allocated to the Target Three Research License and Related Services as the underlying services are performed using a proportional performance model over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company will commence revenue recognition upon exercise of or upon expiry of the option. 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 six months ended June 30, 2019, the Company commenced research and development services related to the fourth target.

For the three and six months ended June 30, 2019, the Company recognized $0.3 million and $0.6 million of revenue, respectively, and for the three and six months ended June 30, 2018, the Company recognized $0.1 million and $0.1 million of revenue for the Target Three Research License and Related Service and research and development services for the fourth target related to the May 2018 AstraZeneca Option Exercise. As of June 30, 2019 and December 31, 2018, the Company recorded $4.7 million and $4.7 million of deferred revenue, respectively, in connection with the May 2018 AstraZeneca Option Exercise and related contracts.

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 will provide for research and development services focused on up to three collaboration programs; (i) Sickle cell disease, (ii) Hemophilia, and (iii) and a third program ("Program 3"), which is an optional program, to be defined. The Company will use its bicyclic peptide screening platform to perform research and development services for the programs and Sanofi has the ability to select a collaboration product for each program and obtain a license to develop and exploit the selected collaboration product for an additional option fee.

Under the Sanofi Collaboration Agreement, the Company is obligated to perform research activities on the initial two named collaboration programs, under mutually agreed upon research plans. The research and development services for each program consist of two stages. The first is an initial stage of screening for high affinity binders and affinity maturation of such binders to identify lead compounds led by the Company (the "BV Bicycle Research Term"). Upon the conclusion of the BV Bicycle Research Term, Sanofi can, at its sole discretion, select a certain number of collaboration compounds to move forward into the Joint Research Term. Upon selection of the collaboration compounds, Sanofi is required to pay an option fee. During the Joint Research Term, the Company and Sanofi will jointly conduct research and development activities which will include lead optimization of lead compounds, in preparation for lead collaboration product nomination ("Joint Research Term"). Sanofi may, at its sole discretion, approve any compound to be progressed into drug development and upon the selection of each collaboration product candidate, Sanofi shall pay $5.0 million as an option fee, in order to obtain worldwide development and exploitation rights for that collaboration product.

Each research program shall continue for an initial period of three years (the "Research Term") unless a program is abandoned by Sanofi or extended for up to one year. The first year of each Research Term shall be the BV Bicycle Research Term and the remaining part of the Research Term, including any extensions of the Research Term, shall be the Joint Research Term.

Under the terms of the Sanofi Collaboration Agreement, the Company granted to Sanofi, for each collaboration program, a non-exclusive, sublicensable (through multiple tiers), worldwide license under certain intellectual property of the Company to conduct the activities assigned to Sanofi in the applicable research plan for the duration of the applicable Research Term, but for no other purpose.

The activities under the Sanofi Collaboration Agreement is governed by a joint steering committee ("JSC") formed by an equal number of representatives from the Company and Sanofi. The JSC oversees, review and recommends direction of each collaboration program and variations of or modifications to the research plans.

Under the terms of the Sanofi Collaboration Agreement, the Company received a $10.0 million up-front cash payment. Additionally, prior to the initiation of the research plan for each collaboration program, Sanofi made a non-refundable payment of $1.4 million for the Sickle cell program and $2.8 million for the Hemophilia program as payment for the Company's services during the BV Bicycle Research Term. During the Joint Research Term, Sanofi is obligated to fund a minimum of two FTE's based on an agreed upon FTE reimbursement rate and fund certain external costs incurred by the Company. Sanofi has the option to obtain development and commercialization licenses associated with each designated collaboration product candidate in return for a fee of $5.0 million per drug candidate. In addition, Sanofi would be required to make certain milestone payments to the Company upon the achievement of specified development, regulatory and commercial events. More specifically, for each collaboration program, the Company is eligible to receive between $47.5 million and $67.0 million in development milestone payments for the Sickle Cell and Hemophilia programs, respectively, and up to $104.0 million in regulatory milestone payments for each program. In addition, the Company is eligible for up to $55.0 million in commercial milestone payments, on a research program by research program basis. Development milestone payments are triggered upon initiation of a defined phase of clinical research for a collaboration product. Regulatory milestone payments are triggered upon approval to market a product candidate by the FDA or other global regulatory authorities. Commercial milestone payments are triggered when an approved collaboration product reaches certain defined levels of net sales by the licensee. In addition, to the extent any of the collaboration products covered by the licenses conveyed to Sanofi are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits to low double digits based on a percentage of net sales. Royalty payments are subject to certain reductions, including for instances where Sanofi faces generic competition in certain countries. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from Sanofi.

Under the terms of the Collaboration Agreement, Sanofi was also provided with an option to obtain screening services on the additional Program 3 target upon making an option fee payment of $5.0 million in addition to a non-refundable payment of $1.4 million as payment for the Company's services related to Program 3 during the BV Bicycle Research Term. The option expired in November 2018 unexercised.

Either party may terminate the Sanofi Collaboration Agreement if the other party has materially breached or defaulted in the performance of any of its material obligations and such breach or default continues after the specified cure period. Either party may terminate the Sanofi 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. Sanofi may 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 has identified the following four performance obligations associated with the Sanofi Collaboration Agreement:

(i) Research License and the related research and development services during the BV Bicycle Research Term for Sickle cell program (the "Sickle Cell Research License and Related Services"),

(ii) Research License and the related research and development services during the BV Bicycle Research Term for Hemophilia program (the "Hemophilia Research License and Related Services"),

(iii) Material right associated with the sickle cell program development and exploitation license option ("Sickle Cell License Option Material Right"), and

(iv) Material right associated with the hemophilia program development and exploitation license option ("Hemophilia License Option Material Right").

The Company concluded that the option to obtain screening services on the additional Program 3 target is not a material right, as the option does not provide a discount that Sanofi otherwise would not have received. The Company's participation in the JSC was assessed as immaterial in the context of the contract. Research license and the related research and development services related to the Joint Research Term are not performance obligations at the inception of the arrangement, as they are optional services that will be performed if Sanofi selects collaboration compounds for lead optimization. The amount paid by Sanofi for the services during the Joint Research Team do not reflect a discount that the customer would otherwise receive and do not provide the customer with material rights.

The total transaction price was initially determined to be $14.2 million, consisting of the $10.0 million upfront payment and non-refundable research and development funding of $4.2 million. The Company may receive reimbursement of FTE costs and external costs associated with work under the Joint Research Term, milestone payments during the Joint Research Term, as well as upon exercise of the license options. These variable amounts are excluded from the transaction price as they relate to fees and milestones that can only be achieved subsequent to the exercise of an option.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for the Research License and Related Services is primarily based on the nature of the services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees Sanofi would pay to exercise the license options, the estimated value of the license option using comparable transactions, and the probability that the license options would be exercised by Sanofi. Based on the relative standalone selling price, the allocation of the transaction price to the separate performance obligations at the inception of the arrangement is as follows (in thousands):

Performance Obligations	Allocation of Transaction Price
Sickle Cell Research License and Related Services	$ 1,405
Hemophilia Research License and Related Services	2,811
Sickle Cell License Option Material Right	5,286
Hemophilia License Option Material Right	4,698
	$ 14,200

The Company will recognize revenue related to amounts allocated to the Sickle Cell Research License and Related Services and the Hemophilia Research License and Related Services obligations as the underlying services are performed using a proportional performance model, over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company will commence revenue recognition when the underlying option is exercised or upon expiry of the option.

During the six months ended June 30, 2019, Sanofi extended the research and development services on both programs. The arrangement consideration increased to $14.9 million. On March 28, 2019, Sanofi notified the Company that it would not exercise the Sickle Cell License Option. As a result, the amount allocated to the Sickle Cell License Option Material Right of $5.3 million was recognized into revenue during the six months ended June 30, 2019.

The Company recognized $0.1 million and $6.0 million of collaboration revenue for the three and six months ended June 30, 2019, respectively, and $1.1 million and $2.2 million of collaboration revenue for the three and six months ended June 30, 2018, respectively, related to its collaboration with Sanofi. As of December 31, 2018 and June 30, 2019, the Company recorded deferred revenue of $9.9 million and $4.7 million, respectively, related to its collaboration with Sanofi, respectively.

Oxurion Collaboration Agreement

Summary of Agreement

In August 2013, the Company entered into a Research Collaboration and License Agreement with Oxurion (the "Oxurion Collaboration Agreement"). 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 is obligated to perform specified research activities in accordance with the research plan, which includes two stages. Stage I, now completed, focused on the screening of targets using the Company's Bicycle peptide discovery platform with the goal of identifying compounds that meet the criteria set by the parties, and Stage II, during which Oxurion has continued research activities on selected Bicycle peptides with the goal of identifying compounds for further development and commercialization. The Company is not obligated or expected to perform any research services during Stage II of the research plan.

The Company granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Oxurion Collaboration Agreement provided for an upfront payment of €1.0 million and potential additional research and development funding, at an agreed upon FTE rate, should the research effort require more than one FTE or the research plan be amended or extended by Oxurion. In addition, Oxurion is required to make certain milestone payments to the Company upon the achievement of specified research, development, regulatory and commercial events. More specifically, for each collaboration program, the Company is eligible to receive up to €8.3 million in research and development milestones of which €1.8 million has been received as of June 30, 2019. In addition, the Company is eligible to receive up to €16.5 million upon achievement of certain regulatory milestone payments (e.g. €5 million for granting first regulatory approval in either the United States or EU for the first indication). In addition, to the extent any of the collaboration products covered by the licenses granted to Oxurion are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from Oxurion.

Either party may terminate the Oxurion Collaboration Agreement if the other party has materially breached any of its material obligations and such breach continues after the specified cure period. Either party may terminate the Oxurion Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party that is not dismissed or otherwise disposed of within a specified time period. Oxurion may terminate the Oxurion Collaboration Agreement, entirely or on a program by program, licensed product by licensed product or country by country basis, for convenience upon not less than 90 days prior written notice to the Company.

In November 2017, the parties executed the First Deed of Amendment to the Oxurion Collaboration Agreement ("First Amendment"). The First Amendment confirms that THR-149 has been selected as a development compound under the Oxurion Collaboration Agreement and that Stage II of the research plan has been completed. The First Amendment provided for additional research services to be performed by the Company related to the identification of two additional compounds for Oxurion, in its discretion, to select as development compounds. As for the work under the Oxurion Collaboration Agreement, the Company will perform the work under Stage I of the research plan, which will be funded at a specified FTE rate, plus any direct out of pocket expenses, and Oxurion will be responsible for Stage II research and any development after the selection of a development compound. Additional milestones and royalties were added for the potential additional licensed compounds, consistent with those of the initial Oxurion Collaboration Agreement. The Company is not obligated or expected to perform any research services during Stage II of the research plan.

Accounting Analysis

Under the Oxurion Collaboration Agreement, all licenses were granted and research services to be provided by the Company were fully completed and revenue associated with those obligations was fully recognized prior to

January 1, 2016. Under the First Amendment, the Company has identified a single performance obligation associated with the performance of research services associated with Stage I of the research plan for which the Company will be reimbursed for its services at a specified FTE reimbursement rate plus out of pocket costs which will be recognized on a proportional performance basis as the associated FTE efforts and costs are incurred, which best reflects the progress towards satisfaction of the performance obligation. None of the unpaid development or regulatory milestones have been included in the transaction price, as all milestones are not considered probable at December 31, 2018 and June 30, 2019.

The Company recognized no revenue for the three and six months ended June 30, 2019, and $0.2 million and $1.6 million of revenue for the three and six months ended June 30, 2018, respectively, related to its agreements with Oxurion. As of June 30, 2019, the research services under the First Amendment were complete. The revenue recognized for the three and six months ended June 30, 2018 includes $1.2 million related to the achievement of developmental milestones during the advancement of the research by Oxurion into a Phase I clinical study. There was no deferred revenue recorded as of December 31, 2018 and June 30, 2019 in connection with the agreements with Oxurion.

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"). 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. The activities under the DDF Collaboration Agreement will be governed by a project advisory panel, composed of two representatives from each Party. 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 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.

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.

The Company recognized $0.1 million of revenue for both the three and six months ended June 30, 2019 and recorded deferred revenue of $1.0 million as of June 30, 2019 related to its collaboration with DDF.

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. The agreement has a term of 14 months after delivery of the Materials and data package, and may be terminated upon 45 days' notice by the recipient. At any point during the term of the agreement and continuing through two months after the completion of the permitted research, the recipient has the option to enter into good faith negotiations to obtain a license to the Company's background intellectual property and/or the Company's interest in the new substances or developments for the purpose of continued research and development of collaboration products. The Company recognized $1.0 million of revenue during the three and six months ended June 30, 2019 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):

	Balance at Beginning of Year	Additions	Deductions	Impact of Exchange Rates	Balance at End of Period
Period ended December 31, 2018					
Contract assets	$ —	$ 91	$ (91)	$ —	$ —
Contract liabilities:					
Deferred revenue					
Sanofi collaboration deferred revenue	14,467	—	(4,006)	(553)	9,908
AstraZeneca collaboration deferred revenue	—	5,350	(466)	(157)	4,727
Total deferred revenue	$ 14,467	$ 5,350	$ (4,472)	$ (710)	$ 14,635

	Balance at Beginning of Period	Additions	Deductions	Impact of Exchange Rates	Balance at End of Period
Period ended June 30, 2019					
Contract assets	$ —	$ 103	$ —	$ —	$ 103
Contract liabilities:					
Deferred revenue					
Sanofi collaboration deferred revenue	9,908	—	(5,286)	34	4,656
AstraZeneca collaboration deferred revenue	4,727	24	(35)	(14)	4,702
DDF collaboration deferred revenue	—	1,114	(103)	1	1,012
Total deferred revenue	$ 14,635	$ 1,138	$ (5,424)	$ 21	$ 10,370

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

The Sanofi deferred revenue balance at June 30, 2019 is comprised of $4.7 million allocated to the Hemophilia License Option Material Right, which will commence revenue recognition when the respective option is exercised at the end of Joint Research Term or when the option expires.

The AstraZeneca deferred revenue balance at June 30, 2019 includes $4.7 million allocated to the Target 3, Target 4, Target 5 and Target 6 Material Rights, which will commence revenue recognition when the respective option is exercised at the end of AZ Research Term or when the option expires. The remaining balance relates to research and development services billed in advance that will be recognized over the Bicycle Research Term.

During the three and six months ended June 30, 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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Revenue recognized in the period from:				
Revenue recognized based on proportional performance	$ (113)	$ (1,169)	$ (138)	$ (2,287)
Revenue recognized based on expiration of material rights	—	—	(5,286)	—
Total	$ (113)	$ (1,169)	$ (5,424)	$ (2,287)

Cancer Research UK

On December 13, 2016, the Company entered into a Clinical Trial and License Agreement with Cancer Research Technology Limited ("CRTL") and Cancer Research UK ("CRUK") (the "CRUK Agreement"). Pursuant to the CRUK Agreement, as amended in March 2017 and June 2018, CRUK's Centre for Drug Development will sponsor and fund a Phase Ia and Phase IIa clinical trial for the Company's lead product candidate, BT1718, a Bicycle Toxin Conjugate, in patients with advanced solid tumors.

CRUK is responsible to design, prepare, carry out and sponsor the clinical trial at its cost. The Company is responsible for supplying agreed quantities of GMP materials for the study, the supply of which has been completed. In the event that additional quantities are needed, the Company will provide CRUK with all reasonable assistance to complete the arrangements necessary for the generation and supply of such additional GMP materials but CRUK will be responsible for supplying and paying for such additional quantities of GMP materials.

The Company granted CRUK a license to its intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial the Company retains the right to continue the development of BT1718 during the clinical trial. Upon the completion of the Phase I/IIa clinical study, the Company has the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and the Company decides to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, the Company will assign or grant to CRTL an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case the Company will receive a mid to high double digit percentage of the net revenue depending on the stage of development when the license is granted). The CRUK Agreement contains additional future milestone payments upon the achievement of development and regulatory milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a high double digit percentage on net sales of products developed.

The CRUK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity generates its revenue from the sale of tobacco products or is an affiliate of such party). CRUK may terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met, in which case, if the study is terminated by CRUK prior to the completion of the Phase 1a dose escalation portion of the study for such reasons or if CRUK refuses release of any additional quantities of GMP materials or if the parties cannot agree upon a plan to supply the additional quantities of GMP materials, the Company will be obligated to refund fifty percent of the costs and expenses incurred or committed by CRUK to perform the clinical trial. If the study is terminated by CRUK for an insolvency event, a material breach by the Company, or if the Company is acquired by an entity that generates its revenue from the sale of tobacco products or is an affiliate of such party, the Company will reimburse CRUK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case where the Company is acquired by an entity that generates its revenue from the sale of tobacco products or is an affiliate of such party, CRUK will not be obliged to grant a license to the Company in respect of the results of the clinical trial and the Company will assign or grant to CRT an exclusive license to develop and commercialize the product without CRT being required to make any payment to the Company.

The Company concluded that the costs incurred by CRUK is a liability in accordance with ASC 730, *Research and Development*, as the payment is not based solely on the results of the research and development having future economic benefit. As such, the Company recorded a liability of $1.3 million and $0.8 million at June 30, 2019 and December 31, 2018, respectively, which is recorded in other long-term liabilities in the condensed consolidated balance sheets. The liability is recorded as incremental research and development expense in the statements of operations and comprehensive loss.

11. Income Taxes

During the three and six months ended June 30, 2019, the Company recorded an income tax provision of $0.1 million and $0.2 million, respectively. During the three and six months ended June 30, 2018, the Company recorded an income tax provision of $0 and an income tax benefit of $0.4 million, respectively. The Company is subject to United Kingdom corporate taxation. Due to the nature of its business, the Company has generated losses

since inception and has therefore not paid United Kingdom corporation tax. The Company's income tax provision in 2019 is mainly the result of profits of Bicycle Therapeutics Inc. in the U.S. from an intercompany service arrangement, which is partially offset by research credits benefitted in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement. The Company's income tax benefit recorded in 2018 is mainly the result of deferred tax assets benefitted in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement. The benefit from income taxes for the six months ended June 30, 2018 is limited to the total tax benefit the Company expects to realize for the respective year, since the Company incurred losses in the respective year to date periods that exceeds the expected annual loss.

The 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 States deferred tax assets and has not provided a valuation allowance against the net deferred tax assets in the United States. The Company recorded a valuation allowance against all of its U.K. deferred tax assets as of June 30, 2019 and December 31, 2018.

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 from 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 provision for (benefit from) income taxes shown on the condensed 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.

12. Commitments and Contingencies

Leases

In September 2015, the Company entered into a tenancy agreement for office and laboratory space in Building 260 Babraham Research Campus, Cambridge, U.K. for a period of two years, beginning on October 1, 2015. The annual rent was approximately $0.2 million plus service charges. In October 2017, this agreement was extended until January 2018 with annual rent of approximately $0.2 million.

In 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 condensed consolidated balance sheets. With the adoption of ASU 2016-02, 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 condensed consolidated balance sheets. With the adoption of ASC 2016-02, 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 future minimum lease payments due under the Company's operating leases as of December 31, 2018 were as follows (in thousands):

Year Ending December 31,	
2019	888
2020	901
2021	915
2022	483
2023	—
	$ 3,187

Prior to the adoption of ASU 2016-02 and for the three and six months ended June 30, 2018, the Company recognized rent expense on a straight-line basis over the lease period and recorded deferred rent for rent expense incurred but not yet paid. During the three and six months ended June 30, 2018, the Company recognized total rent expense of $0.2 million and $0.5 million, respectively.

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 condensed consolidated statement of operations and comprehensive loss are as follows (in thousands):

	Three Months Ended June 30, 2019	Six Months Ended June 30, 2019
Operating lease cost	$ 224	$ 449
Variable lease cost	87	167
Total lease cost	$ 311	$ 616
Weighted-average remaining operating lease term (years)	3.1	3.1
Weighted-average discount rate	8.50%	8.50%

The following table summarizes the maturities of the Company's operating leases as of June 30, 2019 (in thousands):

Year Ending December 31,	
2019	$ 555
2020	862
2021	764
2022	443
2023	—
Present value adjustment	(402)
Total lease liabilities	$ 2,222
Less: current lease liabilities	(594)
Long term lease liabilities	$ 1,628

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 filed a complaint in the District Court of The Hague against Pepscan Systems B.V. ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement entered into with Pepscan in 2009 and 2010 ("PLA"). In response, Pepscan counterclaimed for injunctive relief and unquantified damages. The Company is vigorously prosecuting its claims and defending against those of Pepscan. The Company does not believe that a loss is probable or estimable at this time, and as such, the Company has not recorded a liability related to the Pepscan litigation as of June 30, 2019 and December 31, 2018. Should the Company not be successful in maintaining its rights to Pepscan's patent or in the Company's alternative demand that the patent be invalidated, commercialization of the Company's lead product could be delayed. As the Pepscan patent expires prior to the expected commercialization date of the product, the Company does not believe that the legal proceedings could have a material adverse effect on the Company's business and operating results.

Founder Royalty arrangements

At the time BicycleRD Limited was organized, BicycleRD Limited entered into a royalty agreement with its founders and initial investors (the "Founder Royalty Agreement"). Pursuant to the Founder Royalty Agreement, the Company will pay a royalty rate in the low single digit percentages on net product sales to its founders and initial investors, for a period of 10 years from the first commercial sale on a country by country basis. No royalties have been earned or paid under the royalty arrangements to date.

In accordance with the terms of the Founder Royalty Agreement, as amended in May 2017, the parties amended the terms of the royalty arrangements to limit the future royalties payments to net sales on future products that could be generated under the collaboration with Oxurion and AstraZeneca, in exchange for the issuance of warrants to subscribe for 200,000 Series A Preferred Shares.

Indemnification obligations

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has indemnification obligations towards members of its board of directors that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification arrangements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnification obligations. The Company is not aware of any claims under indemnification arrangements, and therefore it has not accrued any liabilities related to such obligations in its condensed consolidated financial statements as of June 30, 2019 and December 31, 2018.

13. 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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Numerator:				
Net loss attributable to ordinary shareholders	$ (10,217)	$ (4,979)	$ (16,720)	$ (7,513)
Denominator:				
Weighted average ordinary shares outstanding, basic and diluted	7,298,139	420,063	4,101,564	408,807
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.40)	$ (11.85)	$ (4.08)	$ (18.38)

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:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2019	2018	2019	2018
Convertible preferred shares (as converted to ordinary shares)	—	9,641,740	—	9,641,740
Warrants to subscribe for convertible preferred shares (as adjusted to reflect the impact of the share capital reorganization and issuance of bonus shares (Note 1))(1)(2)	114,320	1,347,953	114,320	1,347,953
Restricted ordinary shares	—	123,735	—	123,735
Options to purchase ordinary shares	2,615,949	971,079	2,615,949	971,079
	2,730,269	12,084,507	2,730,269	12,084,507

(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 June 30, 2019, 80,000 warrants are outstanding which are exercisable into 114,320 ordinary shares.

14. Benefit plans

The Company established a defined-contribution savings plan under Section 401(k) of the United States Internal Revenue 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 three months ended June 30, 2019 and 2018 the Company made contributions totaling $25,000 and $19,000, respectively, to the 401(k) Plan. During the six months ended June 30, 2019 and 2018, the Company made contributions totaling $0.1 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 contributes each year amounts of up to 12% of their annual base salary ("U.K Plan"). During the three months ended June 30, 2019 and 2018, the Company made contributions totaling $0.1 million and $0.1 million, respectively, to the U.K. Plan. During the six months ended June 30, 2019 and 2018, the Company made contributions totaling $0.2 million and $0.1 million, respectively, to the U.K. Plan.

15. Related party transactions

The Company has entered into a Founder Royalty Agreement with its founders and initial investors (Note 12). No royalties have been earned or paid under the Founder Royalty Agreement to date.

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 $50,000 a during the three and six months ended June 30, 2019 and 2018, respectively.

16. Geographic information

The Company operates in two geographic regions: the United States and the United Kingdom. Information about the Company's long-lived assets, including operating lease right-of-use assets, held in different geographic regions is presented in the table below (in thousands):

	June 30, 2019	December 31, 2018
United States	$ 1,853	$ 498
United Kingdom	2,535	1,320
	$ 4,388	$ 1,818

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

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations.

You should read the following discussion and analysis of our financial condition and results of operations together with our unaudited condensed consolidated financial statements and the related notes appearing elsewhere in this Quarterly Report on Form 10-Q and our audited financial statements and related notes for the year ended December 31, 2018 included in our final prospectus for our initial public offering filed pursuant to Rule 424(b) under the Securities Act of 1933, as amended, with the Securities and Exchange Commission, on May 23, 2019. Some of the information contained in this discussion and analysis or set forth elsewhere in this report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks, uncertainties and assumptions. Factors that might cause future results to differ materially from those projected in the forward-looking statements include, but are not limited to, those set forth under the heading "Risk Factors" in Part II, Item 1A of this report.

Overview

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

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

Our initial internal programs are focused on oncology indications with high unmet medical need. Our lead product candidate, BT1718, is a *Bicycle* Toxin Conjugate, or BTC. This *Bicycle* is being developed to target tumors that express Membrane Type 1 matrix metalloprotease, or MT1-MMP. MT1-MMP is expressed in approximately 76% to 96% of the ovarian, bladder, endometrial and triple negative breast cancer samples we have tested, depending on cancer type. The *Bicycle* is chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. BT1718 is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial in collaboration with, and fully funded by, the Centre for Drug Development of Cancer Research UK, or CRUK. The Phase I part of the clinical trial commenced in early 2018 and this part of the trial remains ongoing. As of August 7, 2019, six cohorts of patients have been dosed and evaluated on the twice-weekly schedule, with doses ranging from 0.6 mg/m^2 to 9.6 mg/m^2. Four cohorts in the once-weekly schedule have been dosed and evaluated with doses ranging from 9.6 mg/m^2 to 25 mg/m^2. The escalation is ongoing, and we have not observed dose limiting toxicities in the once weekly escalation. We expect to report preliminary data from the Phase I part of this clinical trial in the second half of 2019.

We are also developing BT5528 and BT8009, which are BTCs targeting Ephrin type-A receptor 2, or EphA2, and Nectin-4, respectively, for oncology indications. BT5528 and BT8009 are being investigated for safety, activity and to establish a rationale for therapeutic use in preclinical studies. We are currently conducting Investigational New Drug application, or IND, -enabling activities for BT5528 and BT8009. Our discovery pipeline in oncology includes *Bicycle*-targeted innate immune activators as well as T-cell modulators.

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

Financial Overview

Since our inception, we have devoted substantially all of our resources to developing our *Bicycle* platform and our lead product candidates, BT1718, BT5528 and BT8009, conducting research and development of our product candidates and preclinical programs, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of ADS's and ordinary shares, convertible preferred shares, as well as proceeds received from upfront payments, research and development payments, and development milestone payments from our collaboration agreements with Oxurion, AstraZeneca and Sanofi, and DDF. From our inception in 2009 through June 30, 2019, we have received gross proceeds of $193.0 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering, as well as $29.2 million of cash payments under our collaboration revenue arrangements, including $4.1 million from Oxurion, $8.0 million from AstraZeneca, $14.9 million from Sanofi and $1.1 million from DDF. 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 $10.2 million and $16.7 million for the three and six months ended June 30, 2019, respectively. As of June 30, 2019, we had an accumulated deficit of $86.7 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;
- progress the preclinical and clinical development of BT5528 and BT8009;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, commercial and scientific personnel;
- acquire or in-license other products and technologies;
- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and
- add operational, financial and management information systems and personnel, including personnel to support our research and development programs, any future commercialization efforts, and our 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.

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.

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 AstraZeneca, Sanofi, Oxurion, and DDF, including amounts that are recognized related to upfront payments, milestone payments, option exercise payments, and amounts due to us for research and development services. In the future, revenue may include additional milestone payments, option exercise payments, and royalties on any net product sales under our collaborations. We expect that any revenue we generate will fluctuate from period to period as a result of the timing and amount of license, research and development services, and milestone and other payments. We do not expect Sanofi will select a candidate for additional development under the hemophilia program, and therefore, we expect that previously deferred revenue related to the Sanofi collaboration arrangement will be recognized into revenue upon termination of the collaboration agreement.

Expenses

Research and Development Expenses

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

- employee-related expenses including salaries, benefits, and share-based compensation expense;
- expenses incurred under agreements with third parties that conduct research and development, preclinical activities, clinical activities and manufacturing on our behalf;
- the cost of consultants;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical study materials and clinical trial materials;
- costs related to compliance with regulatory requirements; and

- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other operating costs.

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

U.K. research and development tax credits and government grant funding are recorded as an offset to research and development expense.

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

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

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

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

- completing research and preclinical development of our product candidates, including conducting future clinical trials of BT1718;
- progressing the preclinical and clinical development of BT5528 and BT8009;
- establishing an appropriate safety profile with IND-enabling studies to advance our preclinical programs into clinical development;
- identifying new product candidates to add to our development pipeline;
- successful enrollment in, and the initiation and completion of clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with others;
- establishing commercial manufacturing capabilities or making arrangements with third party manufacturers;
- the development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials;
- addressing any competing technological and market developments, as well as any changes in governmental regulations;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how, as well as obtaining and maintaining regulatory exclusivity for our product candidates;
- continued acceptable safety profile of the drugs following approval; and
- attracting, hiring and retaining qualified personnel.

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

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, corporate and business development and administrative functions. General and administrative expenses also include professional fees for legal, patent, accounting, auditing,

tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

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

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

Other Income (Expense)

Interest and Other Income

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

Other Expense, net

Other expense, net consists 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.

Provision For (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 provision for (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 has generated taxable income in certain periods based on intercompany service arrangements.

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

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

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

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.

Results of Operations

Comparison of the Three Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the three months ended June 30, 2019 and 2018:

	Three Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Collaboration revenues	$ 1,522	$ 1,661	$ (139)
Operating expenses:			
Research and development	6,537	4,917	1,620
General and administrative	2,973	1,702	1,271
Total operating expenses	9,510	6,619	2,891
Loss from operations	(7,988)	(4,958)	(3,030)
Other income (expenses):			
Interest and other income	90	52	38
Other expense	(2,184)	(73)	(2,111)
Total other expense, net	(2,094)	(21)	(2,073)
Net loss before income tax provision	(10,082)	(4,979)	(5,103)
Provision for (benefit from) income taxes	135	—	135
Net loss	$ (10,217)	$ (4,979)	$ (5,238)

Collaboration Revenues

Collaboration revenues decreased by $0.1 million in the three months ended June 30, 2019, compared to the three months ended June 30, 2018, primarily due to an decrease in Sanofi revenue of $1.0 million as the BV Bicycle Research Term was substantially complete in the second quarter 2019, and $0.2 million under our collaboration agreement with Oxurion due to research services performed in 2018 pursuant to an amendment to the collaboration agreement that did not recur in the current year. The amounts were offset by revenue of $1.0 million for delivery of materials under a Material Transfer Agreement, and $0.1 million of revenue from a collaboration arrangement with DDF which was entered into in May 2019.

Research and Development Expenses

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

	Three Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
BT1718 (MT1)	$ 299	$ 378	$ (79)
BT5528 (EphA2)	1,441	925	516
BT8009 (Nectin-4)	941	120	821
Other discovery and platform related expense	2,912	2,279	633
Employee and contractor related expenses	2,457	1,862	595
Facility expenses	355	338	17
Research and development incentives	(1,868)	(985)	(883)
Total research and development expenses	$ 6,537	$ 4,917	$ 1,620

Research and development expense increased by $1.6 million in the three months ended June 30, 2019 compared to the three months ended June 30, 2018, primarily due to an increase of $1.9 million in direct program spend, including increases of $0.5 million and $0.8 million in the BT5528 and BT8009 programs, respectively, as we nominated candidates for these development programs in 2018, as well as other unallocated discovery and platform. Additionally, there was a $0.6 million increase in personnel-related expenses attributable to headcount increases. These expenses were offset by an increase in the research and development tax credit reimbursement of $0.9 million, due to the corresponding increase in research and development spending in the United Kingdom.

We begin to separately track program expenses at candidate nomination, at which point we will accumulate all costs to support that program to date. Through June 30, 2019, since the candidate nominations of BT1718, BT5528 and BT8009, we have incurred approximately $12.4 million, $6.8 million and $4.8 million of direct expenses for the development of these programs, respectively.

General and Administrative Expenses

General and administrative expenses were $3.0 million for the three months ended June 30, 2019, compared to $1.7 million for the three months ended June 30, 2018. The increase of $1.3 million primarily reflected increases of $0.8 million in personnel related costs, including $0.2 million in salary and bonus expense due to an increase in headcount and $0.4 million in share-based compensation expense, as well as $0.6 million in professional fees, including legal, human resources, marketing and consulting costs and $0.2 million in other general and administrative cost, including insurance expense, to support operations as a public company. These amounts were offset by an increase in gains from the effect of foreign exchange rates of $0.3 million during the three months ended June 30, 2019 compared to the three months ended June 30, 2018.

Other Expense, net

Other expense, net increased by $2.1 million during the three months ended June 30, 2019, compared to the three months ended June 30, 2018, primarily due to additional expense of $2.1 million associated with changes in the fair value of the warrant liability and final re-measurement upon completion of the IPO.

Comparison of the Six Months Ended June 30, 2019 and 2018

The following table summarizes our results of operations for the six months ended June 30, 2019 and 2018:

	Six Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
Collaboration revenues	$ 7,906	$ 4,469	$ 3,437
Operating expenses:			
Research and development	12,813	8,626	4,187
General and administrative	6,375	3,690	2,685
Total operating expenses	19,188	12,316	6,872
Loss from operations	(11,282)	(7,847)	(3,435)
Other income (expenses):			
Interest and other income	154	49	105
Other expense, net	(5,377)	(111)	(5,266)
Total other expense, net	(5,223)	(62)	(5,161)
Net loss before income tax provision	(16,505)	(7,909)	(8,596)
Provision for (benefit from) income taxes	215	(396)	611
Net loss	$ (16,720)	$ (7,513)	$ (9,207)

Collaboration Revenues

Collaboration revenues increased by $3.4 million in the six months ended June 30, 2019 compared to the six months ended June 30, 2018, primarily due to an increase of $3.8 million of revenue from our collaboration with Sanofi, including the recognition of $5.3 million of revenue related amounts that were allocated to a material right that were recognized upon Sanofi's exercise of its right to terminate the sickle cell program, offset by a decrease in research services revenue as the BV Bicycle Research Term was substantially complete in the second quarter 2019. Additionally, revenue increased by $1.0 million for delivery of materials under a Material Transfer Agreement, and $0.1 million of revenue from a collaboration arrangement with DDF which was entered into in May 2019. This was offset by a decrease of $1.6 million of revenue under our collaboration agreement with Oxurion primarily due to revenue recognized of $1.2 million for certain development milestones achieved during the six months ended June 30, 2018 that did not recur in the six months ended June 30, 2019.

Research and Development Expenses

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

	Six Months Ended June 30,		
	2019	2018	Change
	(in thousands)		
BT1718 (MT1)	$ 747	$ 553	$ 194
BT5528 (EphA2)	2,227	1,281	946
BT8009 (Nectin-4)	2,028	401	1,627
Other discovery and platform related expense	5,972	3,982	1,990
Employee and contractor related expenses	4,702	3,516	1,186
Facility expenses	655	713	(58)
Research and development incentives	(3,518)	(1,820)	(1,698)
Total research and development expenses	$ 12,813	$ 8,626	$ 4,187

Research and development expense increased by $4.2 million in the six months ended June 30, 2019 compared to the six months ended June 30, 2018, primarily due to increases of $0.9 million and $1.6 million in the BT5528 and BT8009 program spending, respectively, due to increased spending for these development programs in

2019 related to IND-enabling preclinical studies. In addition, the overall increase in research and development expense includes a $2.0 million in other unallocated discovery and platform related expense, and an increase of $1.2 million in employee and contractor related expenses due to an increase in headcount as we expanded our operations in the United States and the United Kingdom. These expenses were offset by a decrease in facilities-related expenses of $0.1 million, as well as increases in research and development tax credit reimbursement of $1.7 million, due to the corresponding increase in research and development spending in the United Kingdom.

General and Administrative Expenses

General and administrative expenses were $6.4 million for the six months ended June 30, 2019, compared to $3.7 million for the six months ended June 30, 2018. The increase of $2.7 million primarily reflected an increase of $1.3 million in personnel related costs, as well as an increase of $1.4 million in professional fees, including legal, human resources, marketing and consulting costs and $0.2 million in other general and administrative cost, including insurance expense, to support operations as a public company. These amounts were partially offset by an increase in gains from the effect of foreign exchange rates of $0.3 million during the six months ended June 30, 2019 compared to the six months ended June 30, 2018.

Other Expense, net

Other expense, net increased by $5.2 million during the six months ended June 30, 2019, compared to the six months ended June 30, 2018, primarily due to additional expense associated with changes in the fair value of the warrant liability and final re-measurement upon completion of the IPO.

Liquidity and Capital Resources

From our inception through June 30, 2019, we have not generated any revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We do not expect to generate significant revenue from sales of any products for several years, if at all.

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

From our inception in 2009 through June 30, 2019, we have received gross proceeds of $193.0 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering, as well as $29.2 million of cash payments under our collaboration revenue arrangements including $4.1 million from Oxurion, $8.0 million from AstraZeneca, $14.9 million from Sanofi, and $1.1 million from DDF.

Cash Flows

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

	Six Months Ended June 30,	
	2019	2018
	(in thousands)	
Net cash used in operating activities	$ (12,809)	$ (12,566)
Net cash used in investing activities	(881)	(650)
Net cash provided by financing activities	59,129	—
Effect of exchange rate changes on cash	(283)	(1,043)
Net increase (decrease) in cash	$ 45,156	$ (14,259)

Operating Activities

Net cash used in operating activities for the six months ended June 30, 2019 included our net loss of $16.7 million, net cash used by changes in our operating assets and liabilities of $3.1 million and non-cash charges of $7.0 million, which included share-based compensation expense of $1.2 million and depreciation and amortization of $0.4 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 six months ended June 30, 2019 consisted primarily of a decrease in accounts receivable of $5.0 million primarily due to a payment received from AstraZeneca for its exercise of the Additional Four Target Option, a decrease in deferred revenue of $4.3 million primarily related to revenue recognized under the Sanofi Collaboration arrangement, an increase in research and development incentives receivable of $3.5 million, and a decrease in accrued expenses and other current liabilities of $1.0 million, offset by an increase in accounts payable of $0.5 million and other long-term liabilities of $0.4 million.

Net cash used in operating activities for the six months ended June 30, 2018 included our net loss of $7.5 million, net cash used by changes in our operating assets and liabilities of $6.1 million and non-cash charges of $1.1 million, which included share-based compensation expense of $0.6 million and depreciation and amortization of $0.4 million and changes in the fair value of the warrant liability of $0.1 million. Net changes in our operating assets and liabilities for the six months ended June 30, 2018 consisted primarily of an increase in accounts receivable of $1.5 million primarily due to amounts earned for development milestones achieved under our Oxurion collaboration arrangement, an increase in research and development incentives receivable of $1.8 million, and a decrease in deferred revenue of $2.2 million, primarily due to the recognition of revenue related to the Sanofi Collaboration arrangement.

Investing Activities

During the six months ended June 30, 2019 and 2018, we used $0.9 million and $0.7 million, respectively, of cash in investing activities for purchases of property and equipment consisting primarily of laboratory equipment.

Financing Activities

During the six months ended June 30, 2019, net cash provided by financing activities was $59.1 million, primarily consisting of net proceeds from the sale of our IPO of $57.8 million, and net proceeds from our Series B2 convertible preferred shares issued in January 2019 of $1.3 million.

During the six months ended June 30, 2018, the Company did not use or receive cash from financing activities.

Funding Requirements

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

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

- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, commercial and scientific personnel;

- acquire or in-license other products and technologies;

- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and

- add operational, financial and management information systems and personnel, including personnel to support our research and development programs, any future commercialization efforts, and our 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.

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

- the scope, progress, results, and costs of drug discovery, preclinical development, laboratory testing, and clinical trials for the product candidates we may develop;

- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;

- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;

- the costs, timing and outcome of regulatory review of our product candidates;

- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;

- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;

- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, and distribution, for any product candidates for which we receive marketing approval;

- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

- the success of our collaborations with AstraZeneca, Oxurion, Sanofi and other partners;

- 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. 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

During the six months ended June 30, 2019, there were no material changes to our contractual obligations and commitments from those described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Contractual Obligations and Commitments" in our final prospectus for our initial public offering filed pursuant to Rule 424(b) under the Securities Act of 1933, as amended, with the Securities and Exchange Commission, on May 23, 2019.

Critical Accounting Policies and Significant Judgments and Estimates

Our financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. Our critical accounting policies are described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Significant Judgments and Estimates" in our final prospectus for our IPO filed pursuant to Rule 424(b) under the Securities Act of 1933, with the SEC, on May 23, 2019. If actual results or events differ materially from the estimates, judgments and assumptions used by us in applying these policies, our reported financial condition and results of operations could be materially affected. There have been no significant changes to our critical accounting policies from those described in our final prospectus for our IPO filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on May 23, 2019, other than as follows:

Share-Based Compensation

In May 2019, we adopted the 2019 Share Option Plan (the "2019 Plan"), which became effective in conjunction with the IPO. The 2019 Plan provides for the grant of options to purchase ordinary shares, share appreciation rights, restricted shares, restricted share units, and other share-based awards to offers, employees, directors and other key persons (including consultants). Share options issued under the 2019 Share Option Plan have a 10 year contractual life, and 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. The exercise price of share options issued under the 2019 Share Option Plan shall not be less than the fair value of ordinary shares as of the date of grant.

Prior to the IPO, we 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 are in the form of share options, the options may have been granted pursuant bilateral EMI option award agreements in the form approved by the board of directors. Such agreements provide for the grant of potentially tax-favored Enterprise Management Incentive, or EMI, options, to our U.K. employees, directors and consultants. Options issued pursuant to such

agreements have an exercise price of £0.01 per share. The exercise price for share options granted to U.S. employees have an exercise price that is not less than the fair value of ordinary shares as determined by the board of directors as of the date of grant. Exercise prices of our options to subscribe for ordinary shares are in British Pound Sterling.

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

We have granted awards that include both a service condition, that vest over time, and a performance condition, to 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.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation — Stock Compensation: Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07") to simplify the accounting for share-based payments to nonemployees by aligning it with the accounting share-based payments to employees, with certain exceptions. We adopted the new standard on January 1, 2019. Prior to the adoption, compensation expense for share-based awards granted to non-employee consultants was recognized over the period during which services are rendered by such consultants until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards was remeasured using the then-current fair value of our ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model, as applicable. Under the new guidance, 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 our ordinary shares, less any applicable purchase price.

The fair value of each share option is estimated using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the fair value of ordinary shares, the expected share price volatility, the expected term of the award, the risk-free interest rate, and expected dividends. See Note 9 to our condensed consolidated financial statements appearing in the accompanying Form 10-Q for further detail.

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

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities.

Emerging Growth 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, 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 permit 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.

Item 3. Quantitative and Qualitative Disclosure About Market Risk

Interest Rate Sensitivity

As of June 30, 2019, we had cash of $108.5 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in interest-bearing savings accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

As of June 30, 2019, we had no debt outstanding and are therefore not subject to interest rate risk related to debt.

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 $0.7 million and $0.4 million during the three months ended June 30, 2019 and 2018, respectively, and foreign exchange gains of $0.4 million and $0.2 million for the six months ended June 30, 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 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rule 13a-15(e) of the Securities Exchange Act of 1934, as amended, or the Exchange Act) as of the end of the period covered by this report. Based on that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures as of the end of the period covered by this report were not effective for the reasons set forth below.

In connection with the preparation of our consolidated financial statements for the year ended December 31, 2018, we identified an error in our previously reported financial statements due to a material weakness in our internal

control over financial reporting related to the valuation of our warrant liability. The material weakness is attributable to a deficiency in the design and operating effectiveness of our review of the respective third party valuation reports. Specifically, the findings relate to our internal control infrastructure that existed as of December 31, 2017 and September 30, 2018 where we did not design or implement sufficient processes, controls or other review processes to ensure that the liquidation preferences of our Series A and Series B1 warrants per our articles of association were properly reflected as an input in the valuations during the year ended December 31, 2017, or for the nine month periods ended September 30, 2018 as previously reported. As a result, the consolidated financial statements for those periods required restatement.

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

Changes in Internal Control over Financial Reporting

Other than the changes intended to remediate the material weakness noted above, no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended June 30, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. 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. We are also party to litigation in the District Court of The Hague against Pepscan Systems B.V., or Pepscan, to contest the right of Pepscan to terminate a non-exclusive patent license agreement we entered into with Pepscan in 2009 and 2010. Although the results of litigation and claims cannot be predicted with certainty, as of June 30, 2019, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 1A Risk Factors.

Investing in our American Depositary Shares, or ADSs, involves a high degree of risk. The following information about these risks, together with the other information appearing elsewhere in this Quarterly Report on Form 10-Q, including our unaudited condensed 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 $16.7 million for the six months ended June 30, 2019. In addition, our accumulated deficit as of June 30, 2019 was $86.7 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 lead product candidate, BT1718, and our other product candidates in our *Bicycle* Toxin Conjugate, or BTC, program;
- initiate and continue research, preclinical and clinical development efforts for any future product candidates;
- seek to discover and develop additional product candidates and further expand our clinical product pipeline;
- seek marketing and regulatory approvals for any product candidates that successfully complete clinical trials;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- expand our research and development infrastructure, including hiring and retaining additional personnel, such as clinical, quality control and scientific personnel;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize products for which we obtain marketing approval, if any;
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization and help us comply with our obligations as a public company; and
- add equipment and physical infrastructure to support our research and development.

Our ability to become and remain profitable depends on our ability to generate revenue. Generating product revenue will depend on our or any of our collaborators' ability to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. Successful commercialization will require achievement of key milestones, including completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our collaborators, may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We and any collaborators may never succeed in these activities and, even if we do, or any collaborators

do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our revenue to date has been primarily generated from our research collaborations with AstraZeneca, Sanofi, Oxurion, and DDF. There can be no assurance that we will generate revenue from these collaborations in the future.

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

Our limited operating history may make it difficult for 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. 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. For example, in the six months ended June 30, 2019, we used $12.8 million in net cash for our operating activities and in the year ended December 31, 2018, we used $26.1 million, in net cash for our operating activities, substantially all of which related to research and development activities. We expect our expenses to increase in connection with our ongoing activities, particularly as we initiate new clinical trials of, initiate new research and preclinical development efforts for and seek marketing approval for, our current product candidates or any future product candidates. In addition, if we obtain marketing approval for any of our product candidates, we may incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of a collaborator. Furthermore, 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 $108.5 million as of June 30, 2019, will enable us to fund our operating expenses and capital expenditure requirements for at least the next twelve months. Our estimate may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

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

Raising additional capital may cause dilution to our existing shareholders 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.

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

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

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

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

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

- successfully complete preclinical studies and clinical trials;
- receive regulatory approvals from the FDA, the EMA and other similar regulatory authorities;
- establish and maintain collaborations with third parties for the development and/or commercialization of our product candidates, or otherwise build and maintain strong development, sales, distribution and marketing capabilities that are sufficient to develop products and launch commercial sales of any approved products;
- obtain coverage and adequate reimbursement from payors such as government health care systems and insurance companies and achieve commercially attractive levels of pricing;
- secure acceptance of our product candidates from physicians, health care payors, patients and the medical community;

- produce, through a validated process, in manufacturing facilities inspected and approved by regulatory authorities, including the FDA, sufficiently large quantities of our product candidates to permit successful commercialization;

- manage our spending as expenses increase due to clinical trials and commercialization; and

- obtain and enforce sufficient intellectual property rights for any approved products and product candidates.

Of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a new drug application, or NDA, to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market our product candidates, any such approval may be subject to limitations on the indicated uses or patient populations for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot 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 do not have experience with *Bicycles* and may require evidence of safety and efficacy that goes beyond what we and our collaborators have included in our development plans. In such a case, development of *Bicycle* product candidates may be more costly or time-consuming than expected, and our candidate products and those of our collaboration partners may not prove to be viable.

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

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

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

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

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

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

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

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

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

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

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

conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

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

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

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of protocols related to our novel approach;
- our inability to locate qualified local consultants, physicians and partners; and

- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

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

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

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

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

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

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

We may employ companion diagnostics to help us more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics are subject to regulation by the FDA and comparable foreign regulatory authorities as medical devices and require separate regulatory approval prior to commercialization. We do not develop companion diagnostics internally and thus we will be dependent on the sustained cooperation and effort of our third-party collaborators in developing and obtaining approval for these companion diagnostics. There can be no guarantees that we will successfully find a suitable collaborator to develop companion diagnostics. We and our collaborators may encounter difficulties in developing and obtaining approval for the companion diagnostics, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by our collaborators to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates. In addition, our collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics, and both they and we may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community. If such companion diagnostics fail to gain market acceptance, our ability to derive revenues from sales of any products, if approved, will be adversely affected. In addition, the diagnostic company with whom we contract may decide to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our product candidates or our relationship with such diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another

diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

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

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

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

Our product candidates are currently undergoing safety testing in the form of Phase I/IIa clinical trials. None of our products have completed this testing to date. While our current and future product candidates will undergo safety testing to the extent possible and, where applicable, under such conditions discussed with regulatory authorities, not all adverse effects of drugs can be predicted or anticipated. Unforeseen side effects could arise either during clinical development or, if such side effects are 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 or any other of our product candidates are safe in humans.

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

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any collaborators, may need to recall the product, or be required to change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

- regulatory authorities may require the addition of labeling statements, such as a boxed warning or a contraindication;
- we, or any collaborators, may be required to create a medication guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

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

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

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

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

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

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

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

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our

products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

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

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

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

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

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

For example, we may seek a Breakthrough Therapy Designation for one or more of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, if preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

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

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

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

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

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

that we intend to charge for our products is also subject to approval. We do not have experience in obtaining reimbursement or pricing approvals in international markets.

Obtaining marketing approvals and compliance with regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries outside of the United Kingdom and the United States. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Pursuant to Article 50 of the Treaty on European Union, the United Kingdom will cease to be an EU Member State either on the effective date of a withdrawal agreement (entry into such a withdrawal agreement will require U.K. parliamentary approval) or, failing that, two years following the United Kingdom's notification of its intention to leave the European Union, or the Brexit Date, unless the European Council (together with the United Kingdom) unanimously decides to extend the two year period. On March 29, 2017, the United Kingdom formally notified the European Council of its intention to leave the European Union. It is unclear how long it will take to negotiate a withdrawal agreement, but it appears likely that Brexit will continue to involve a process of lengthy negotiations between the United Kingdom and EU Member States to determine the future terms of the United Kingdom's relationship with the European Union. For example, in March 2018, the United Kingdom reached a provisional agreement, or the Withdrawal Agreement, with the European Union on transitional arrangements following Brexit (which are intended to enable the United Kingdom to remain within the EU single market and customs union for a transitional period through 2020), but this Withdrawal Agreement needs to be formally agreed as part of the withdrawal arrangements currently under negotiation. Given that no formal withdrawal arrangements have been agreed, there have been several extensions to the Brexit Date and the United Kingdom has yet to formally leave the European Union. On April 11, 2019, the European Union granted the United Kingdom a further extension to the Brexit Date until October 31, 2019. The purpose of this extension is to allow for the ratification of the Withdrawal Agreement by the U.K. House of Commons. If the Withdrawal Agreement is ratified, the United Kingdom will leave the European Union earlier than October 31, 2019. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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

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

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

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. Varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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

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

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

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

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

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

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

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

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell

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

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

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

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

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

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

- restrictions on the labeling, distribution, marketing or manufacturing of the product, withdrawal of the product from the market, or product recalls;
- untitled and warning letters, or holds on clinical trials;

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

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

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

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

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

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

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

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

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

We have never commercialized a product, and even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting products based on our *Bicycle* peptides in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

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

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

Even if a product candidate displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our

efforts to educate the medical community and payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors, particularly due to the novelty of our *Bicycle* approach. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

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

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

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

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

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

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

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as the CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for novel products such as ours, as there is no body of established practices and precedents for these new products. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is: (1) a covered benefit under its health plan; (2) safe, effective and medically necessary; (3) appropriate for the specific patient; (4) cost-effective; and (5) neither experimental nor investigational. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Even if we obtain coverage for a given

product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Third-party payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the approved drugs for a particular indication.

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

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

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

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

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

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

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

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

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

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

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, or Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or

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

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

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

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

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

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

members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives;

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

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

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

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive 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, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Healthcare legislative reform measures 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, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs 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. The second Executive Order terminates 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 June 24, the U.S. Supreme Court granted certiorari to hear an appeal of the decision, which will be heard in the fall of 2019. The 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, two 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." On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. 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." In December 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. 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 Cuts and Jobs Act of 2017, the remaining provisions of the Affordable Care Act are invalid as well. While the Texas District Court Judge, as well as the Trump Administration and the Centers for Medicare & Medicaid Services, or CMS, have stated that the ruling will have no immediate effect. A Fifth Circuit US Court of Appeals hearing to determine whether certain states and the House of Representatives have standing to appeal the lower court decision was conducted on July 9, 2019, but it is unclear when a Court will render its decision on this hearing, and what effect it will have on the status of the Affordable Care Act and the impact on our business.

In December 2018, the CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk

adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS published a final rule that will give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. 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 2027 unless additional Congressional action is taken. 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 Trump administration's budget proposal for fiscal years 2019 and 2020 contained further drug price control measures that could be enacted during the budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. Congress and the Trump administration have each indicated that it will continue to seek new legislative, administrative and executive measures, including the President's issuance of future executive orders, to control drug costs. 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.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

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

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

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

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

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

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting

damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

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

Risks Related to Our International Operations

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

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

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;

- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

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

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

Legal, political and economic uncertainty surrounding the planned exit of the United Kingdom, from the European Union may be a source of instability in international markets, create significant currency fluctuations, adversely affect our operations in the United Kingdom and pose additional risks to our business, revenue, financial condition, and results of operations.

On June 23, 2016, the United Kingdom held a referendum in which a majority of the eligible members of the electorate voted for the United Kingdom to leave the European Union. The United Kingdom's withdrawal from the European Union is commonly referred to as Brexit. Pursuant to Article 50 of the Treaty on European Union, the United Kingdom will cease to be an EU Member State either on the effective date of a withdrawal agreement (entry into such a withdrawal agreement will require U.K. parliamentary approval) or, failing that, two years following the

United Kingdom's notification of its intention to leave the European Union, or the Brexit Date, unless the European Council (together with the United Kingdom) unanimously decides to extend the two year period. On March 29, 2017, the United Kingdom formally notified the European Council of its intention to leave the European Union. It is unclear how long it will take to negotiate a withdrawal agreement, but it appears likely that Brexit will continue to involve a process of lengthy negotiations between the United Kingdom and EU Member States to determine the future terms of the United Kingdom's relationship with the European Union. For example, in March 2018, the United Kingdom reached a provisional agreement, or the Withdrawal Agreement, with the European Union on transitional arrangements following Brexit (which are intended to enable the United Kingdom to remain within the EU single market and customs union for a transitional period through 2020), but this Withdrawal Agreement needs to be formally agreed as part of the withdrawal arrangements currently under negotiation. Given that no formal withdrawal arrangements have been agreed, there have been several extensions to the Brexit Date and the United Kingdom has yet to formally leave the European Union. On April 11, 2019, the European Union granted the United Kingdom a further extension to the Brexit Date until October 31, 2019. The purpose of this extension is to allow for the ratification of the Withdrawal Agreement by the U.K. House of Commons. If the Withdrawal Agreement is ratified, the United Kingdom will leave the European Union earlier than October 31, 2019.

On May 24, 2019, the U.K. Prime Minister Theresa May, announced that she would formally resign from the role of Prime Minister on June 7, 2019. On July 23, 2019, Boris Johnson was elected the new Prime Minister, and he may choose to attempt to renegotiate the Withdrawal Agreement, or leave the European Union on October 31, 2019 with no formal withdrawal arrangements in place.

The lack of clarity over which EU laws and regulations will continue to be implemented in the United Kingdom after Brexit (including financial laws and regulations, tax and free trade agreements, intellectual property rights, data protection laws, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws) may negatively impact foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict access to capital.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union after Brexit may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise) beyond the date of Brexit.

These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the United Kingdom's financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility.

If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the European Economic Area, or EEA, overall could be diminished or eliminated. The long-term effects of Brexit will depend on any agreements (or lack thereof) between the United Kingdom and the European Union and, in particular, any arrangements for the United Kingdom to retain access to EU markets either during a transitional period or more permanently.

Such a withdrawal from the European Union is unprecedented, and it is unclear how the United Kingdom's access to the European single market for goods, capital, services and labor within the European Union, or single market, and the wider commercial, legal and regulatory environment, will impact our U.K. operations and customers. Our U.K. operations service customers in the United Kingdom as well as in other countries in the European Union and EEA and these operations could be disrupted by Brexit, particularly if there is a change in the United Kingdom's relationship to the single market.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of the United Kingdom's withdrawal from the European Union, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may

result in increased trade barriers that could make our doing business in the European Union and the EEA more difficult. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the United Kingdom, or what, if any, role the EMA may have in the approval process. Even prior to any change to the United Kingdom's relationship with the European Union, the announcement of Brexit has created economic uncertainty surrounding the terms of Brexit and its consequences could adversely impact customer confidence resulting in customers reducing their spending budgets on our solutions, which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our ADSs.

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

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

Risks Related to Our Dependence on Third Parties

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

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

Under our collaborations with AstraZeneca, Sanofi, 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 CRUK, CRUK's Centre for Drug Development is sponsoring and funding a Phase I/IIa clinical trial of our lead product candidate, BT1718, in patients with advanced solid tumors. We depend on these collaborators to develop and, where applicable, commercialize products based on *Bicycle* peptides, and the success of their efforts directly impacts the milestones and royalties we will receive. We cannot 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; and

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

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

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

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

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

- disagreements with respect to the ownership of intellectual property rights or scope of licenses;
- disagreements with respect to the scope of any reporting obligations;
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities, or to permit public disclosure of these activities; and
- disputes with respect to a collaborator's or our development or commercialization efforts with respect to our products and product candidates.

For example, we are involved in ongoing litigation with Pepscan Systems B.V., or Pepscan, related to a non-exclusive patent license agreement that we entered into with Pepscan in 2009. Pursuant to the patent license agreement, we licensed rights related to the scaffold used for *Bicycles* contained in certain of our product candidates, including our lead product candidate, BT1718. The agreement required us to enter into a framework services agreement with Pepscan for Pepscan to provide certain *Bicycles* not produced by us. In 2010, we entered into such a framework services agreement. In 2014, we terminated the framework services agreement in accordance with its terms. Subsequently, in 2016, Pepscan terminated the patent license agreement. We instituted proceedings in the District Court of The Hague to contest the right of Pepscan to terminate the patent license agreement. In response, Pepscan claimed, among other things, that the termination of the framework services agreement and alleged breach by us of confidentiality obligations constituted grounds for the termination of the patent license agreement. In a preliminary judgement delivered in April 2018, the District Court of the Hague rejected Pepscan's claim that it was entitled to terminate the patent license agreement on the basis of a breach of a purported exclusive supply obligation. The District Court of the Hague reserved for further proceedings the question of whether Pepscan was entitled to terminate the patent license agreement on the basis of allegations that we had breached our confidentiality obligations. The District Court of the Hague gave us an opportunity to submit proof to the contrary through written evidence and further hearings.

In July 2018, Pepscan appealed the decision of the District Court of the Hague and the proceedings before the District Court of the Hague have been stayed pending a decision in the appeal brought by Pepscan. The appeal hearing has been scheduled in November 2019. While we intend to vigorously defend ourselves the appeal and any further proceedings, there can be no assurance that we will prevail. Our failure to successfully defend our use of the patent rights in question would delay the timing of our ability to commercialize our product candidates, including our lead product candidate BT1718, which could have a material adverse effect on our business and operating results.

In addition, in January 2013, Pepscan filed a notice of opposition in respect of European patent 2 257 624, which is a foundational patent that is directed to our technology platform. In April 2015, Pepscan filed a notice of opposition in respect of European patent 2 474 613, which is a divisional patent that is directed to extensions of our technology platform. As of June 30, 2019, no final decision has been issued by the European Patent Office. If we are unable to prevail against these challenges, our intellectual property estate may be materially harmed, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections.

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

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

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators, academic partners, regulatory affairs consultants and third-party CROs, to conduct our preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to engage with regulatory authorities and monitor and manage data for our ongoing preclinical and clinical programs. For example, CRUK currently sponsors and funds the Phase I/IIa clinical trial of our lead product candidate, BT1718, in patients with advanced

solid tumors. We also utilize CROs to perform toxicology studies related to our preclinical activities. While we will have agreements governing the activities of such third parties, we will control only certain aspects of their activities and have limited influence over their actual performance. Given the breadth of clinical therapeutic areas for which we believe *Bicycles* may have utility, we intend to continue to rely on external service providers rather than build internal regulatory expertise.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Because we rely on third parties to manufacture our product candidates, and because we collaborate with various organizations and academic institutions on the development of our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

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

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

Risks Related to Our Intellectual Property

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on research, manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. As of June 30, 2019, our intellectual property portfolio includes three patent families covering novel scaffolds, 11 patent families directed to our platform technology, 63 patent families covering bicyclic peptides and related conjugates, and six patent families directed to clinical indications and other properties of development assets.

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 parties review and equivalent proceedings in foreign jurisdictions. An adverse determination in any of the foregoing proceedings could result in the revocation or cancellation of, or amendment to, our patents in such a way that they no longer cover our products or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our products and product candidates. Such a loss of patent protection could have a material adverse impact on our business.

For example, in January 2013, Pepscan filed a notice of opposition in respect of European patent 2 257 624, which is a foundational patent that is directed to our technology platform. In April 2015, Pepscan filed a notice of opposition in respect of European patent 2 474 613, which is a divisional patent that is directed to extensions of our technology platform. As of June 30, 2019, no final decision has been issued by the European Patent Office. If we are unable to prevail against these challenges, our intellectual property estate may be materially harmed, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections.

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

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

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

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

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

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. The terms of one or more licenses that we enter into the future may not provide us with the ability to maintain or prosecute patents in the portfolio, and must therefore rely on third parties to do so.

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

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are

obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

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

Changes in either the patent laws or the interpretation of the patent laws in the United States or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. When implemented, the Leahy-Smith Act included several significant changes to U.S. patent law that impacted how patent rights could be prosecuted, enforced and defended. In particular, the Leahy-Smith Act also included provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allowed third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed new regulations and procedures governing the administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. It remains unclear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business.

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

We cannot 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.

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

product candidates, including our lead product candidate BT1718 would be impaired, which could have a material adverse effect on our business and operating results.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our products candidates, including interference and post-grant proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the composition, use or manufacture of our product candidates. We cannot guarantee that any of our patent searches or analyses including, but not limited to, the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based intellectual property rights that exist now or arise in the future. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use or manufacture. The scope of protection afforded by a patent is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

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

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

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

could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

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

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

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

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

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

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

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

In connection with our efforts to build our product candidate pipeline, we may enter into license agreements in the future. We expect that such license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market any product that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could

negatively impact the value of the product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms.

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

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

Risks Related to Employee Matters and Managing Growth

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

As of June 30, 2019, we had 62 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. For example, in 2018, we were the target of a cyber-attack. The cyber-attack comprised a phishing incident where two email accounts were accessed that resulted in the automatic forwarding of emails, to an unauthorized third party. Promptly after discovery of this cyber-attack, we performed a third-party investigation and determined that no further action was required under either U.S. or state law. This incident was reported to the U.K. information commissioners' office, who deemed no further action was required under GDPR regulations. The 2018 cyber-attack did not have a material impact to our business or financial condition. While we believe we responded appropriately, including implementing remedial measures to stop this cyber-attack and with the goal of preventing similar ones in the future, there can be no assurance that we will be successful in these remedial and preventative measures or successfully mitigating the effects of future cyber-attacks. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to respond appropriately to such breaches and to implement further data protection measures.

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

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

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

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

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

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

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (1) FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities, (2) manufacturing standards, (3) federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, and (4) laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, bribery and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee or collaborator misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. In 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 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, the trading price of our ADSs has ranged from $14.91 to $7.56. 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;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;

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

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

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.

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 June 30, 2019, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 67.8% 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 will 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, the approval of certain significant corporate transactions and amendments to our Articles of Association. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that 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 11,308,853 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 and the lock-up agreement signed in connection with our IPO.

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. 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.

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

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

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

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

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

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

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;
- not being required to comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

- 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.

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

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

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

Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm . However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

We have historically been a private limited company, and as such, have not historically been subject to the reporting requirements of Section 404 or an audit performed in accordance with auditing standards issued by the PCAOB.

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

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

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

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

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

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

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

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.

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

On December 22, 2017, President Trump signed into law the TCJA, which makes significant changes to the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation and other changes that may impact our operations, in particular the operations of our wholly owned U.S. subsidiary, Bicycle Therapeutics Inc. We urge investors to consult with their legal and tax advisers regarding the implications of the TCJA on an investment in our ordinary shares or ADSs.

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

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

We believe that we were not a CFC in the 2018 taxable year and we do not expect to be a CFC in the current taxable year. However, the determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. U.S. Holders (as defined below) 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:

1. An individual who is a citizen or individual resident of the United States;

2. 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;

3. an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

4. 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 PFIC, there could be adverse U.S. federal income tax consequences to U.S. holders.

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

Based on our analysis of our income, assets, activities and market capitalization, we believe that we were a PFIC in the 2018 taxable year. We have not yet determined our PFIC status for the current taxable year, but we may be a PFIC. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how we spend the cash we raise in any offering.

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

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 U.K., 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 those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

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

qualifying loss-making SME business can receive through R&D relief in any one year will be capped at three times the company's total PAYE and NICs liability for that year.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- all shareholders must be given the same information;

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

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

- misleading, inaccurate or unsubstantiated statements made in documents or to the media must be publicly corrected immediately;

- actions during the course of an offer by the offeree company, which might frustrate the offer are generally prohibited unless shareholders approve these plans. Frustrating actions would include, for example, lengthening the notice period for directors under their service contract or agreeing to sell off material parts of the target group;

- stringent and detailed requirements are laid down for the disclosure of dealings in relevant securities during an offer, including the prompt disclosure of positions and dealing in relevant securities by the parties to an offer and any person who is interested (directly or indirectly) in 1% or more of any class of relevant securities; and

- employees of both the offeror and the offeree company and the trustees of the offeree company's pension scheme must be informed about an offer. In addition, the offeree company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

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

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. The principal differences include the following:

- under English law and our articles of association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings;

- under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. However, that the voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank;

- under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise;

- under English law and our articles of association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the articles of association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other significant transactions;

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

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

- the quorum requirement for a shareholders' meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder 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.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.

Set forth below is information regarding shares of equity securities sold, and options granted, by us during the three months ended June 30, 2019 that were not registered under the Securities Act.

Recent Sales of Unregistered Equity Securities

On May 28, 2019, upon the closing of our IPO, all shares of our then-outstanding convertible preferred shares automatically converted into 11,647,529 ordinary shares, and 702,557 ordinary shares were issued upon the exercise of warrants to subscribe for Series A and Series B1 convertible preferred shares in conjunction with the IPO. The issuance of such ordinary shares was exempt from the registration requirements of the Securities Act, pursuant to Section 3(a)(9) of the Securities Act, involving an exchange of securities exchanged by the issuer with its existing security holders exclusively where no commission or other remuneration is paid or given directly or indirectly for soliciting such exchange. No underwriters were involved in this issuance of shares.

During the period between April 1, 2019 and June 30, 2019, we issued to certain of our employees and advisors, options to purchase an aggregate of 1,753,504 ordinary shares at an exercise price of $12.74 per share. We deemed these issuances to be exempt from registration under the Securities Act either in reliance on Rule 701 and/or Regulation S of the Securities Act as sales and offers under compensatory benefit.

Use of Proceeds from Initial Public Offering

On May 28, 2019, we completed our initial public offering of 4,333,333 ADSs at a 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 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 became effective on May 22, 2019.

We received aggregate net proceeds from the offering of approximately $56.5 million, after deducting underwriting discounts and commissions of $4.5 million and offering expenses of $3.9 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning ten percent 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. We invested the net proceeds from our IPO in interest bearing cash accounts.

Item 3. Defaults Upon Senior Securities.

Not Applicable

Item 4. Mine Safety Disclosures.

Not Applicable.

Item 5. Other Information.

None.

Item 6. Exhibits.

Exhibit 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).
10.1	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).
10.2	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).
10.3	2019 Share Option Plan (Incorporated by reference to Exhibit 99.4 to the Registration Statement on Form S-8 (File No. 333-231718), filed with the Securities and Exchange Commission on May 23, 2019).
10.4	Form of Non-Plan Share Option Contract 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).
10.5	Form of Non-Plan Share Option Contract 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).
10.6	Employment Agreement between the Registrant and Kevin Lee, Ph.D., MBA, dated May 15, 2019 (Incorporated by reference to Exhibit 10.7 to Amendment No. 2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 15, 2019).
10.7	Employment Agreement between the Registrant and Lee Kalowski, MBA, effective May 28, 2019 (Incorporated by reference to Exhibit 10.8 Amendment No. 2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 15, 2019).
10.8	Employment Agreement between the Registrant and Michael Skynner, Ph.D., dated May 15, 2019 (Incorporated by reference to Exhibit 10.9 Amendment No. 2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 15, 2019).
10.9	Employment Agreement between the Registrant and Nicholas Keen, Ph.D., effective May 28, 2019 (Incorporated by reference to Exhibit 10.10 to Amendment No. 2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 15, 2019).
10.10	Form of Deed of Indemnity between the Registrant and each of its directors (Incorporated by reference to Exhibit 10.12 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).

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 Calculation Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed herewith.

#The certification attached as Exhibit 32.1 accompanying this Quarterly Report on Form 10-Q is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company. 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 this Quarterly Report on Form 10-Q, irrespective of any general incorporation language contained in such filing.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

BICYCLE THERAPEUTICS PLC

Date: August 8, 2019

By: /s/ Kevin Lee

Kevin Lee, Ph.D., MBA
Chief Executive Officer

(Principal Executive Officer)

Date: August 8, 2019

By: /s/ Lee Kalowski

Lee Kalowski, MBA
Chief Financial Officer and President

(Principal Financial and Accounting Officer)

Exhibit 31.1

CERTIFICATION 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

I, Kevin Lee, certify that:

1. I have reviewed this Form 10-Q 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)) 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) 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

   (c) 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: August 8, 2019

By: /s/ Kevin Lee

Kevin Lee, Ph.D., MBA
Chief Executive Officer

Exhibit 31.2

CERTIFICATION 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

I, Lee Kalowski, certify that:

1. I have reviewed this Form 10-Q 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)) 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) 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

   (c) 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: August 8, 2019

By: /s/ Lee Kalowski

Lee Kalowski, MBA
Chief Financial Officer and President

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

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 Quarterly Report on Form 10-Q for the period ended June 30, 2019, to which this Certification is attached as Exhibit 32.1 (the "Periodic 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 Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: August 8, 2019

IN WITNESS WHEREOF, the undersigned have set their hands hereto as of the 8th day of August, 2019.

By: /s/ Kevin Lee
Kevin Lee, Ph.D., MBA
Chief Executive Officer

By: /s/ Lee Kalowski
Lee Kalowski, MBA
Chief Financial Officer and President

"This certification accompanies the Form 10-Q 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-Q), irrespective of any general incorporation language contained in such filing."