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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, 2022

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	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
Blocks A & B, Portway Building, Granta Park Great Abington, Cambridge, United Kingdom	**CB21 6GS**
(Address of principal executive offices)	(Zip Code)

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

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

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

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

Indicate by check mark 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 1, 2022, the registrant had 29,676,127 ordinary shares, nominal value £0.01 per share, outstanding.

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SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS

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

- statements regarding the impact of the ongoing COVID-19 pandemic and its effects on our operations, research and development and clinical trials and potential disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- our ability to advance our product candidates into, and successfully complete, clinical trials;
- our reliance on the success of our product candidates in our *Bicycle*® Toxin Conjugate, or BTC™, *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™ and other pipeline programs;
- our ability to utilize our screening platform to identify and advance additional product candidates into clinical development;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- our ability to develop sales and marketing capabilities;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- our ability to operate our business without infringing the intellectual property rights and proprietary technology of third parties;
- costs associated with defending intellectual property infringement, product liability and other claims;
- regulatory development in the United States, the European Union, the United Kingdom and other jurisdictions;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;

- the amount of and our ability to satisfy interest and principal payments under our debt facility with Hercules Capital, Inc., or Hercules;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations or obtain additional grant funding;
- the rate and degree of market acceptance of any approved products;
- developments relating to our competitors and our industry, including competing therapies;
- our ability to effectively manage our anticipated growth;
- our ability to attract and retain qualified employees and key personnel;
- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance;
- business interruptions resulting from geo-political actions, including war or the perception that hostilities may be imminent, including, the ongoing war in Ukraine and terrorism, or natural disasters and public health epidemics; 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 on Form 10-Q 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, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 372,769	$ 438,680
Accounts receivable	10,000	1,000
Prepaid expenses and other current assets	9,454	7,965
Research and development incentives receivable	16,270	10,910
Total current assets	408,493	458,555
Property and equipment, net	16,815	3,123
Operating lease right-of-use assets	15,076	14,666
Other assets	5,098	3,448
Total assets	$ 445,482	$ 479,792
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 4,859	$ 2,721
Accrued expenses and other current liabilities	16,952	14,244
Deferred revenue, current portion	19,530	19,273
Total current liabilities	41,341	36,238
Long-term debt, net of discount	30,144	29,873
Operating lease liabilities, net of current portion	12,496	12,081
Deferred revenue, net of current portion	46,849	52,067
Other long-term liabilities	3,260	3,279
Total liabilities	134,090	133,538
Commitments and contingencies (Note 11)		
Shareholders' equity:		
Ordinary shares, £0.01 nominal value; 57,820,181 and 55,295,420 shares authorized at June 30, 2022 and December 31, 2021, respectively; 29,666,317 and 29,579,364 shares issued and outstanding at June 30, 2022 and December 31, 2021, respectively	385	384
Additional paid-in capital	584,152	567,637
Accumulated other comprehensive loss	(374)	(3,388)
Accumulated deficit	(272,771)	(218,379)
Total shareholders' equity	311,392	346,254
Total liabilities and shareholders' equity	$ 445,482	$ 479,792

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,	
	2022	2021	2022	2021
Collaboration revenues	$ 4,378	$ 1,785	$ 8,238	$ 3,593
Operating expenses:				
Research and development	19,854	11,722	34,138	21,415
General and administrative	11,824	7,340	28,783	15,479
Total operating expenses	31,678	19,062	62,921	36,894
Loss from operations	(27,300)	(17,277)	(54,683)	(33,301)
Other income (expense):				
Interest income	908	23	1,126	38
Interest expense	(883)	(819)	(1,701)	(1,341)
Total other income (expense), net	25	(796)	(575)	(1,303)
Net loss before income tax provision	(27,275)	(18,073)	(55,258)	(34,604)
Benefit from income taxes	(447)	(160)	(866)	(500)
Net loss	$ (26,828)	$ (17,913)	$ (54,392)	$ (34,104)
Net loss per share, basic and diluted	$ (0.90)	$ (0.74)	$ (1.84)	$ (1.48)
Weighted average ordinary shares outstanding, basic and diluted	29,648,564	24,052,168	29,626,974	23,047,745
Comprehensives loss:				
Net loss	$ (26,828)	$ (17,913)	$ (54,392)	$ (34,104)
Other comprehensive income (loss):				
Foreign currency translation adjustment	2,094	(255)	3,014	(313)
Total comprehensive loss	$ (24,734)	$ (18,168)	$ (51,378)	$ (34,417)

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

Bicycle Therapeutics plc
Condensed Consolidated Statements of Shareholders' Equity
(In thousands, except share data)
(Unaudited)

	Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Shareholders' Equity
	Shares	Amount				
Balance at December 31, 2021	29,579,364	$ 384	$ 567,637	$ (3,388)	$ (218,379)	$ 346,254
Issuance of ADSs upon exercise of share options	30,074	1	449	—	—	450
Issuance of ADSs upon vesting of restricted share units	35,000	—	—	—	—	—
Share-based compensation expense	—	—	10,198	—	—	10,198
Foreign currency translation adjustment	—	—	—	920	—	920
Net loss	—	—	—	—	(27,564)	(27,564)
Balance at March 31, 2022	29,644,438	385	578,284	(2,468)	(245,943)	330,258
Issuance of ADSs upon exercise of share options	21,879	—	195	—	—	195
Share-based compensation expense	—	—	5,673	—	—	5,673
Foreign currency translation adjustment	—	—	—	2,094	—	2,094
Net loss	—	—	—	—	(26,828)	(26,828)
Balance at June 30, 2022	29,666,317	$ 385	$ 584,152	$ (374)	$ (272,771)	$ 311,392
Balance at December 31, 2020	21,094,557	$ 266	$ 249,947	$ (3,193)	$ (151,560)	$ 95,460
Issuance of ADSs upon exercise of share options	63,545	1	283	—	—	284
Issuance of ADSs, net of commissions and offering expenses of $1.8 million	2,358,485	33	58,742	—	—	58,775
Share-based compensation expense	—	—	3,821	—	—	3,821
Foreign currency translation adjustment	—	—	—	(58)	—	(58)
Net loss	—	—	—	—	(16,191)	(16,191)
Balance at March 31, 2021	23,516,587	300	312,793	(3,251)	(167,751)	142,091
Issuance of ADSs upon exercise of share options	125,666	2	1,573	—	—	1,575
Issuance of ADSs, net of commissions and offering expenses of $0.4 million	482,299	7	13,970	—	—	13,977
Share-based compensation expense	—	—	2,575	—	—	2,575
Foreign currency translation adjustment	—	—	—	(255)	—	(255)
Net loss	—	—	—	—	(17,913)	(17,913)
Balance at June 30, 2021	24,124,552	$ 309	$ 330,911	$ (3,506)	$ (185,664)	$ 142,050

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

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

	Six Months Ended June 30,	
	2022	**2021**
Cash flows from operating activities:		
Net loss	$ (54,392)	$ (34,104)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation expense	15,871	6,396
Depreciation and amortization	1,039	665
Non-cash interest	271	223
Changes in operating assets and liabilities:		
Accounts receivable	(9,346)	5,544
Research and development incentives receivable	(6,850)	(4,982)
Prepaid expenses and other current assets	(2,418)	278
Operating lease right-of-use assets	1,343	(2,229)
Other assets	(1,616)	(554)
Accounts payable	1,341	2,225
Accrued expenses and other current liabilities	3,209	(603)
Operating lease liabilities	(789)	2,296
Deferred revenue	2,072	(1,549)
Other long-term liabilities	334	317
Net cash used in operating activities	(49,931)	(26,077)
Cash used in investing activities:		
Purchases of property and equipment	(14,555)	(794)
Net cash used in investing activities	(14,555)	(794)
Cash flows from financing activities:		
Proceeds from the issuance of ADSs, net of issuance costs	—	72,752
Proceeds from the exercise of share options and sale of ordinary shares	645	1,859
Proceeds from issuance of debt	—	15,000
Net cash provided by financing activities	645	89,611
Effect of exchange rate changes on cash and cash equivalents	(2,070)	8
Net (decrease) increase in cash and cash equivalents	(65,911)	62,748
Cash and cash equivalents at beginning of period	438,680	135,990
Cash and cash equivalents at end of period	$ 372,769	$ 198,738
Supplemental disclosure of cash flow information		
Cash paid for interest	$ 1,390	$ 1,074
Cash paid for income taxes	$ 749	$ 53
Cash paid for amounts included in the measurement of operating lease liabilities	$ 1,336	$ 200
Purchases of property and equipment included in accounts payable and accrued expenses	$ 1,209	$ 36
Non-cash impact right-of-use asset and operating lease liabilities	$ 3,120	$ —

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

Bicycle Therapeutics plc
Notes to Condensed Consolidated Financial Statements
(Unaudited)

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 is evaluating BT5528, a second-generation *Bicycle* Toxin Conjugate ("BTC") targeting Ephrin type-A receptor 2 ("EphA2"), in a Company-sponsored Phase I/II clinical trial, BT8009, a second-generation BTC™ targeting Nectin-4, in a Company-sponsored Phase I/II clinical trial, and BT7480, a *Bicycle* tumor-targeted immune cell agonist® ("*Bicycle* TICA™") targeting Nectin-4 and agonizing CD137, in a Company-sponsored Phase I/II clinical trial. In addition, BT1718, a BTC that is being developed to target tumors that express Membrane Type 1 matrix metalloproteinase, is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial sponsored and fully funded by the Centre for Drug Development of Cancer Research UK. The Company's discovery pipeline in oncology includes *Bicycle*-based systemic immune cell agonists and *Bicycle* TICAs. Beyond the Company's wholly-owned oncology portfolio, the Company is collaborating with biopharmaceutical companies and organizations in immuno-oncology, anti-infective, cardiovascular, ophthalmology, dementia, central nervous system, neuromuscular 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").

Liquidity

As of June 30, 2022, the Company had cash and cash equivalents of $372.8 million.

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 the sale of its ordinary shares and American Depositary Shares ("ADSs"), including in its initial public offering ("IPO") completed in May 2019 and follow-on offering completed in October 2021, offerings pursuant to its at-the-market offering program ("ATM"), and prior to its IPO, offerings of its convertible preferred shares, as well as proceeds received from its collaboration arrangements (Note 9) and proceeds from a loan agreement with Hercules Capital, Inc. ("Hercules") (Note 6). The Company has incurred recurring losses since inception, including net losses of $26.8 million and $54.4 million for the three and six months ended June 30, 2022, respectively, and $17.9 million and $34.1 million for the three and six months ended June 30, 2021, respectively. As of June 30, 2022, the Company had an accumulated deficit of $272.8 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 these 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 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 one or more of 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.

The Company is subject to risks common to companies in the biotechnology industry and in light of the ongoing COVID-19 pandemic, including but not limited to, risks of delays in initiating or continuing research programs and clinical trials, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, if approved, 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.

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, 2021 included in the Company's Annual Report on Form 10-K for the year ended December 31, 2021, which was filed with the Securities and Exchange Commission (the "SEC"), on March 1, 2022 (the "2021 Annual Report"). 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.

Use of estimates

The preparation of condensed consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the condensed consolidated financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these condensed consolidated financial statements include, but are not limited to, the accrual for research and development expenses, revenue recognition, share-based compensation expense, valuation of right-of-use assets and liabilities, and income taxes, including the valuation allowance for deferred tax assets. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. Estimates are periodically reviewed in light of reasonable changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates or assumptions.

Significant risks and uncertainties

In 2020, with the global spread of the ongoing COVID-19 pandemic, the Company established a cross-functional task force and implemented business continuity plans designed to address and mitigate the impact of the ongoing COVID-19 pandemic on the Company's business. While the Company continues to experience limited financial impacts at this time, the Company has not disbanded this task force and continues to monitor the evolving pandemic and its potential effects on the Company's business, financial condition, results of operations and growth prospects.

Unaudited interim financial information

Certain information in the footnote disclosures of these financial statements has been condensed or omitted pursuant to the rules and regulations of the SEC. These unaudited 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, 2021 included in the Company's 2021 Annual Report.

The accompanying condensed consolidated balance sheet as of June 30, 2022, condensed consolidated statements of operations and comprehensive loss, condensed consolidated statements of shareholders' equity, and condensed consolidated statements of cash flows for the three and six months ended June 30, 2022 and 2021, 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, 2021, and, in the opinion of management, reflect all adjustments, consisting of normal recurring adjustments, necessary for the fair statement of the Company's financial position as of June 30, 2022, and the results of its operations and its cash flows for the three and six months ended June 30, 2022 and 2021. The results for the three and six months ended June 30, 2022 are not necessarily indicative of the results to be expected for the year ending December 31, 2022, any other interim periods, or any future year or period.

Accounts receivable

As of June 30, 2022, accounts receivable consists of amounts due under the collaboration agreement between BicycleTx Limited and Genentech, Inc. ("Genentech"). The Company makes judgments as to its ability to collect outstanding receivables and estimates credit losses at the reporting date resulting from the inability of its customers to make required payments. Provisions are made based upon a specific review of all significant outstanding invoices and the overall quality and age of those invoices. To date, the Company has not had any write-offs of bad debt, and the Company did not have an allowance for credit losses as of June 30, 2022.

Government grants

From time to time, the Company may enter into arrangements with governmental entities for the purpose of obtaining funding for research and development activities. The Company is reimbursed for costs incurred that are associated with specified research and development activities included in the grant application approved by the government authority. 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, and accrued but unpaid grant income is included in other current assets. The Company analyzes each arrangement on a case-by-case basis, and income is recognized when the Company concludes that it has reasonable assurance that it will comply with the conditions attached to the grant and the expenses have been incurred. There are no significant performance criteria other than to maintain satisfactory progress on the specified project, and there are no significant acceptance or recapture provisions associated with the government grants for the three and six month periods ended June 30, 2022 and 2021, respectively. For the three and six months ended June 30, 2022, the Company recognized $0.4 million and $0.8 million, respectively, and for the three and six months ended June 30, 2021, the Company recognized $0.8 million and $1.9 million, respectively, as a reduction of research and development expense related to government grant arrangements. As of June 30, 2022, the Company has approximately $1.7 million of government grant funding remaining for future cost reimbursement through February of 2024.

Recently adopted accounting pronouncements

In June 2016, the FASB issued Accounting Standards Update ("ASU") No. 2016-13, *Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). The standard amends the impairment model by requiring entities to use a forward-looking approach based on expected losses to estimate credit losses for most financial assets and certain other instruments that aren't measured at fair value through net income. For trade receivables, loans and held-to-maturity debt securities, companies will be required to recognize an allowance for credit losses rather than reducing the carrying value of the asset. In November 2019, the FASB issued ASU No. 2019-10, *Financial Instruments — Credit Losses (Topic 326), Derivatives and Hedging (Topic 815), and Leases (Topic 842): Effective Dates* to amend the effective date of ASU 2016-13, for entities eligible to be "smaller reporting companies," as defined by the SEC, to be effective for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. The Company adopted ASU 2016-13 as of January 1, 2022, on a prospective basis. The adoption did not have a material impact on the Company's consolidated financial statements.

In November 2021, the FASB issued ASU No. 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance* ("ASU 2021-10"), which requires additional disclosures regarding the nature and terms of government assistance. ASU No. 2021-10 was effective for financial statements issued for annual periods beginning after December 15, 2021. The adoption of ASU 2021-10 did not have a material impact on the Company's condensed consolidated financial statements.

3. Fair value of financial assets and liabilities

Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable: Level 1, Quoted prices in active markets for identical assets or liabilities; Level 2, Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data; Level 3, unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The carrying values of accounts receivable, research and development incentives receivable, other current assets, accounts payable and accrued expenses and other current liabilities approximate their fair values due to the short-term nature of these assets and liabilities. As of June 30, 2022, and December 31, 2021, the carrying value of the long-term debt approximates its fair value, which was determined using unobservable Level 3 inputs, including quoted interest rates from a lender for borrowings with similar terms. As of June 30, 2022, and December 31, 2021, there were no assets or liabilities measured at fair value on a recurring basis.

Cash and cash equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents. The Company had $200.0 million and $100.0 million of cash equivalents as of June 30, 2022, and December 31, 2021, respectively.

4. Property and equipment, net

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

	June 30, 2022	December 31, 2021
Laboratory equipment	$ 10,328	$ 6,746
Leasehold improvements	10,408	809
Computer equipment and software	393	143
Furniture and office equipment	866	225
	21,995	7,923
Less: Accumulated depreciation and amortization	(5,180)	(4,800)
	$ 16,815	$ 3,123

Depreciation expense was $0.6 million and $1.0 million for the three and six months ended June 30, 2022, respectively, and $0.3 million and $0.7 million for the three and six months ended June 30, 2021, respectively.

5. Accrued expenses and other current liabilities

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

	June 30, 2022	December 31, 2021
Accrued employee compensation and benefits	$ 4,554	$ 6,429
Accrued external research and development expenses	7,685	3,980
Accrued professional fees	850	882
Current portion of operating lease liabilities	2,905	2,383
Other	958	570
	$ 16,952	$ 14,244

6. Long-term debt

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

Borrowings under the Loan Agreement bear interest at an annual rate equal to the greater of (i) 8.85% or (ii) 5.60% plus *The Wall Street Journal* prime rate. On March 10, 2021 ("the Amendment Closing Date"), the Borrowers entered into the First Amendment to the Loan and Security Agreement (the "First Amendment to LSA") with Hercules, in its capacity as administrative agent and collateral agent, and the lenders named in the First Amendment to LSA. Pursuant to the First Amendment to LSA, payments on borrowings under the Company's debt facility with Hercules were interest-only until the first payment was due on August 1, 2023, which date was extended from November 1, 2022, followed by equal monthly payments of principal and interest through the scheduled maturity date on October 1, 2024 (the "Maturity Date"). If the Company achieved certain performance milestones, the interest-only period could be extended, with the first principal payment due on February 1, 2024, which date was extended from May 1, 2023. On the Amendment Closing Date and pursuant to the terms of the First Amendment to LSA, the Company borrowed the additional term loan of $15.0 million that had been available from September 30, 2020 to March 15, 2021. In November 2021, the performance milestones were achieved, and the interest only period was extended until February 1, 2024. On March 15, 2022 the additional term loan of $10.0 million expired unexercised.

At the Borrowers' option, the Borrowers may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to (i) 2.0% of the principal amount outstanding if the prepayment occurs during the first year following the Closing Date, (ii) 1.5% of the principal amount outstanding if the prepayment occurs during the second year following the Closing Date, and (iii) 1.0% of the principal amount outstanding if the prepayment occurs thereafter but prior to the Maturity Date. The Loan Agreement also provides for an end of term charge (the "End of Term Charge"), payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. Borrowings under the Loan Agreement are collateralized by substantially all of the Borrower's personal property and other assets, other than their intellectual property. Hercules has a perfected first-priority security interest in certain cash accounts. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control, as defined in the agreement. There are no financial covenants. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, cross acceleration to third-party indebtedness, certain events relating to bankruptcy or insolvency, and the occurrence of certain events that could reasonably be expected to have a material adverse effect. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal and interest payments due, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement. The Company has determined that the risk of subjective acceleration under the material

adverse events clause is not probable and therefore has classified the outstanding principal in long-term liabilities based on scheduled principal payments.

The Company incurred fees and transaction costs totaling $0.6 million associated with the initial term loan, which are recorded as a reduction to the carrying value of the long-term debt in the condensed consolidated balance sheets. The fees, transaction costs, and the End of Term Charge are amortized to interest expense through the Maturity Date using the effective interest method. The Company evaluated the First Amendment to LSA, and concluded that the amendment represented a modification, as such, the fees and transaction costs associated with the initial term loan will continue to be amortized to interest expense through the Maturity Date. The effective interest rate of the Hercules borrowings was 12.8% at June 30, 2022.

The Company assessed all terms and features of the Loan Agreement in order to identify any potential embedded features that would require bifurcation. As part of this analysis, the Company assessed the economic characteristics and risks of the debt. The Company determined that all features of the Loan Agreement are clearly and closely associated with a debt host and, as such, do not require separate accounting as a derivative liability. Interest expense associated with the Loan Agreement for the three and six months ended June 30, 2022, was $0.9 million and $1.7 million, respectively, and for the three and six months ended June 30, 2021, was $0.8 million and $1.3 million, respectively.

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

	June 30, 2022	December 31, 2021
Term loan payable	$ 30,000	$ 30,000
End of term charge	564	376
Unamortized debt issuance costs	(420)	(503)
Carrying value of term loan	$ 30,144	$ 29,873

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

Year Ending December 31,	
2022	$ —
2023	—
2024	31,500
Total	$ 31,500

7. 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 June 30, 2022, and December 31, 2021, the Company had not declared any dividends.

As of June 30, 2022, and December 31, 2021, the Company's authorized share capital consisted of 57,820,181 and 55,295,420 ordinary shares, respectively, with a nominal value of £0.01 per share. Authorized share capital, or shares authorized, comprises (i) the currently issued and outstanding ordinary shares, (ii) the remaining ordinary shares available for allotment under the existing authority granted to the Board at the annual general meeting held on June 28, 2021, (iii) ordinary shares issuable on the exercise of outstanding options and (iv) ordinary shares reserved for issuance under the Bicycle Therapeutics plc 2020 Equity Incentive Plan and/or the Bicycle Therapeutics plc 2019 Employee Share Purchase Plan.

8. Share-based compensation

Employee incentive pool

2020 Equity Incentive Plan

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

The Company initially reserved up to 4,773,557 ordinary shares for future issuance under the 2020 Plan, representing 574,679 new shares, 544,866 shares that remained available for future issuance under the Company's 2019 Share Option Plan (the "2019 Plan") immediately prior to the effectiveness of the 2020 Plan and up to 3,654,012 shares subject to options that were granted under the 2019 Plan and that were granted pursuant to option contracts granted prior to the Company's IPO, in each case that expire, terminate, are forfeited or otherwise not issued from time to time, if any. On June 27, 2022, the Company's shareholders approved an amendment to the 2020 Plan (the "Amendment") which increased the number of ordinary shares reserved for future issuance by 750,000 shares. Additionally, the number of ordinary shares reserved for issuance pursuant to the 2020 Plan will automatically increase on the first day of January of each year, initially commencing on January 1, 2021, in an amount equal to 5% of the total number of the Company's ordinary shares outstanding on the last day of the preceding year, or a lesser number of shares determined by the Company's board of directors. Pursuant to this "evergreen" provision, on January 1, 2022, the number of shares reserved for issuance under the 2020 Plan was increased by 1,478,968 shares. The Amendment extended the final date upon which an "evergreen" increase may occur under this provision from January 1, 2030, to January 1, 2032. As of June 30, 2022, there were 1,373,139 shares available for issuance.

Share options issued under the 2020 Plan have a 10-year contractual life and generally vest over either a three-year service period for non-employee directors, or a four-year service period with 25% of the award vesting on the first anniversary of the vesting commencement date and the balance thereafter in 36 equal monthly installments for employees and consultants. Certain options granted to the Company's non-employee directors vest immediately upon grant.

In 2022, the Company granted RSUs to non-employee directors and certain employees under the 2020 Plan. Each RSU represents the right to receive one of the Company's ordinary shares upon vesting. RSUs granted to employees vest over a four year service period with 25% of the award vesting on the first anniversary of the vesting commencement date and the remaining RSUs vest in 12 equal quarterly installments. Certain RSUs granted to the Company's non-employee directors vest immediately upon grant.

As of June 30, 2022, there were options to purchase 2,888,197 shares and RSUs for 187,725 shares outstanding under the 2020 Plan.

2019 Share Option Plan

In May 2019, the Company adopted the 2019 Plan, which became effective in conjunction with the IPO. As of June 30, 2022, there were 2,146,635 options to purchase ordinary shares outstanding under the 2019 Plan. In conjunction with the adoption of the 2020 Plan, all shares available for future issuance under the 2019 Plan as of June 29, 2020

became available for issuance under the 2020 Plan and the Company ceased making awards under the 2019 Plan. The 2020 Plan is the successor of the 2019 Plan.

Share options previously issued under the 2019 Plan have a 10-year contractual life, and generally either vest monthly over a three year-service period, or over a four-year service period with 25% of the award vesting on the first anniversary of the vesting commencement date and the balance thereafter in 36 equal monthly installments. Certain awards granted to the Company's non-employee directors were fully vested on the date of grant. The exercise price of share options issued under the 2019 Share Option Plan is not less than the fair value of ordinary shares as of the date of grant.

Employee Share Purchase Plan

In May 2019, the Company adopted the 2019 Employee Stock Purchase Plan (the "ESPP"), which became effective in conjunction with the IPO. The Company initially reserved 215,000 ordinary shares for future issuance under this plan. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2020 and each January 1 thereafter through January 1, 2029, by the lower of: (i) 1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 430,000 ordinary shares or (iii) such lesser number of shares as determined by the Compensation Committee. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in the Company's capitalization. The number of shares reserved for issuance under the ESPP was increased by 295,793 shares effective January 1, 2022. As of June 30, 2022, the total number of shares available for issuance under the ESPP was 901,675 ordinary shares. As of June 30, 2022, 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,	
	2022	2021	2022	2021
Research and development expenses	$ 2,642	$ 1,089	$ 5,006	$ 2,299
General and administrative expenses	3,031	1,486	10,865	4,097
	$ 5,673	$ 2,575	$ 15,871	$ 6,396

Share options

The following table summarizes the Company's option activity since December 31, 2021:

	Number of Shares Underlying Share Options	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2021	4,603,486	$ 14.97	8.13	$ 207,009
Granted	1,210,747	50.63	—	—
Exercised	(51,953)	12.42	—	—
Forfeited	(128,136)	23.50	—	—
Outstanding as of June 30, 2022	5,634,144	$ 22.46	8.02	$ 18,511
Vested and expected to vest as of June 30, 2022	5,634,144	$ 22.46	8.02	$ 18,511
Options exercisable as of June 30, 2022	2,982,451	$ 13.07	7.25	$ 15,878

The weighted average grant-date fair value of share options granted during the six months ended June 30, 2022 and 2021 was $35.32 per share and $13.30 per share, respectively.

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 $0.2 million and $1.2 million for the three and six months ended June 30, 2022, respectively, and was $2.2 million and $3.7 million for the three and six months ended June 30, 2021, respectively.

Total share-based compensation expense for share options granted was $5.0 million and $12.4 million for the three and six months ended June 30, 2022, respectively, and was $2.6 million and $6.4 million for the three and six months ended June 30, 2021, respectively. Expense for non-employee consultants for the three and six months ended June 30, 2022 and 2021 was immaterial.

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,	
	2022	2021	2022	2021
Risk-free interest rate	2.8 %	1.0 %	1.8 %	0.5 %
Expected volatility	82.9 %	80.5 %	81.9 %	79.5 %
Expected dividend yield	—	—	—	—
Expected term (in years)	6.1	6.1	6.0	6.0

As of June 30, 2022, total unrecognized compensation expense related to the unvested employee and director share options was $55.0 million, which is expected to be recognized over a weighted average period of 3.2 years.

Restricted share units

The following table summarizes the Company's RSU activity under the 2020 Plan since December 31, 2021:

	Number of Shares Underlying RSUs	Weighted-Average Grant Date Fair Value
Unvested at December 31, 2021	—	$ —
Granted	222,725	60.86
Vested	(35,000)	60.86
Unvested at June 30, 2022	187,725	$ 60.86

The fair value of RSUs that vested during the three and six months ended June 30, 2022, was zero and $2.1 million, respectively.

Total share-based compensation expense for RSUs granted was $0.7 million and $3.5 million for the three and six months ended June 30, 2022, respectively. As of June 30, 2022, the total unrecognized compensation expense related to unvested RSUs was $10.0 million, which is expected to be recognized over a weighted-average period of 3.5 years.

9. Significant agreements

For the three and six months ended June 30, 2022 and 2021, the Company recognized revenue for its collaborations with Ionis Pharmaceuticals, Inc. ("Ionis"), Genentech, the Dementia Discovery Fund ("DDF"), and AstraZeneca AB ("AstraZeneca"). 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,	
	2022	2021	2022	2021
Collaboration revenues				
Ionis	$ 2,255	$ —	$ 4,569	$ —
Genentech	872	1,631	2,346	3,079
Dementia Discovery Fund	86	154	158	237
AstraZeneca	1,165	—	1,165	277
Total collaboration revenues	$ 4,378	$ 1,785	$ 8,238	$ 3,593

Ionis Agreements

Ionis Evaluation and Option Agreement

On December 31, 2020 (the "Effective Date"), the Company entered into an Evaluation and Option Agreement (the "Evaluation and Option Agreement") with Ionis. Under the terms of the Evaluation and Option Agreement, the Company agreed to transfer *Bicycles* (the "Option Materials") to Ionis in order to evaluate a particular application of the Company's technology platform for a period of up to four months (the "Evaluation Period"). Ionis paid the Company a non-refundable $3.0 million option fee in January 2021.

At any point during the term of the agreement and continuing through 30 days after the expiration of the Evaluation Period, Ionis had the option (the "Ionis Option") to obtain an exclusive license to the Company's intellectual property for the purpose of continued research, development, manufacture and commercialization of products within a particular application of the Company's platform technology. The upfront payment of $3.0 million was fully creditable against the upfront payment to be paid upon the execution of a license agreement.

The Company concluded that the only performance obligation was a material right for the option to obtain an exclusive license. All other promises under the Evaluation and Option Agreement were immaterial in the context of the contract. The Company accounted for the $3.0 million payment as deferred revenue as of December 31, 2020. On July 9, 2021, the Ionis Option was exercised upon the parties' entry into a collaboration and license agreement as contemplated by the Evaluation and Option Agreement. The Company determined that the Ionis Option exercise constituted a continuation of the existing arrangement. Therefore, the $3.0 million in deferred revenue under the Evaluation and Option Agreement was included in the transaction price of the collaboration and license agreement.

Ionis Collaboration Agreement

Following the exercise by Ionis of the Ionis Option granted pursuant to the Evaluation and Option Agreement, on July 9, 2021, the Company and Ionis entered into a collaboration and license agreement (the "Ionis Collaboration Agreement"). Pursuant to the Ionis Collaboration Agreement, the Company granted to Ionis a worldwide exclusive license under the Company's relevant technology to research, develop, manufacture and commercialize products incorporating *Bicycle* peptides directed to the protein coded by the gene TFRC1 (transferrin receptor) ("TfR1 Bicycles") intended for the delivery of oligonucleotide compounds directed to targets selected by Ionis for diagnostic, therapeutic, prophylactic and preventative uses in humans. Ionis will maintain exclusivity to all available targets unless it fails to achieve specified development diligence milestone deadlines. If Ionis fails to achieve one or more development diligence milestone deadlines, the Company has the right to limit exclusivity to certain specific collaboration targets, subject to the payment by Ionis of a low-single-digit million dollar amount per target as specified in the Ionis

Collaboration Agreement. Each party will be responsible for optimization of such TfR1 *Bicycles* and other research and discovery activities related to TfR1 *Bicycles*, as specified by a research plan, and thereafter Ionis will be responsible for all future research, development, manufacture and commercialization activities. The Company will perform research and discovery activities including a baseline level of effort for a period of three years for no additional consideration. The parties will negotiate a commercially reasonable rate if additional research activities are agreed to be performed. For certain research and discovery activities that the Company is responsible for performing, the Company may use the assistance of a contract research organization ("CRO"). The Company has retained certain rights, including the right to use TfR1 *Bicycles* for all non-oligonucleotide therapeutic purposes.

The activities under the Ionis Collaboration Agreement are governed by a joint steering committee ("JSC") with an equal number of representatives from the Company and Ionis. The JSC will oversee the performance of the research and development activities. Upon first commercial sales of a licensed product, the JSC will have no further responsibilities or authority under the Ionis Collaboration Agreement.

Under the Ionis Collaboration Agreement, Ionis made a non-refundable upfront payment of $31.0 million in addition to the $3.0 million already paid under the Option and Evaluation Agreement. Additionally, Ionis is obligated to reimburse the Company on a pass-through basis for expenses incurred in connection with research and discovery activities performed by a CRO. If Ionis is at risk of failing to achieve a specified development diligence milestone deadline, it can make up to three separate payments of a mid-single-digit million dollar amount to extend the development diligence milestone deadlines. On a collaboration target-by-collaboration target basis, Ionis will be required to make a low-single-digit million dollar payment upon acceptance of an investigational new drug application ("IND") for the first product directed to such collaboration target (provided that Ionis will have a high single-digit million dollar credit to be applied towards the IND acceptance fee for four collaboration targets, or for exclusivity payments for certain targets if specified development diligence milestones deadlines are not achieved), and Ionis will be required to make milestone payments upon the achievement of specified development and regulatory milestones of up to a low double-digit million dollar amount per collaboration target. In addition, the Company is eligible to receive up to a low double-digit million dollar amount in cumulative sales milestone payments. The Company is also entitled to receive tiered royalty payments on net sales at percentages in the low single digits, subject to certain standard reductions and offsets. Royalties will be payable, on a product-by-product and country-by-country basis, until the latest of the expiration of specified licensed patents covering such product in such country, ten years from first commercial sale of such product in such country, or expiration of marketing exclusivity for such product in such country.

In December 2021, the Company and Ionis entered into an amendment to the Ionis Collaboration Agreement (the "Ionis Amendment"). Ionis paid the Company $1.6 million and the Company agreed to perform additional research services utilizing its proprietary phage screening technology to identify and optimize new product candidates that target the TfR1 receptor. The Company will perform the additional research services for an initial six-month period, which was extended in August 2022 for an additional three months, in exchange for consideration of $0.8 million. Ionis has an option for the Company to perform additional research services for an additional six months if specified criteria are mutually agreed to and achieved, in exchange for the remaining consideration of $0.8 million. If the option is not exercised, the Company will refund $0.8 million to Ionis.

Either party may terminate the Ionis Collaboration Agreement for the uncured material breach of the other party or in the case of insolvency. Ionis may terminate the Ionis Collaboration Agreement for convenience on specified notice periods depending on the development stage of the applicable target, either in its entirety or on a target-by-target basis.

Ionis Share Purchase Agreement

Concurrently with the execution of the Ionis Collaboration Agreement on July 9, 2021, the Company entered into a share purchase agreement (the "Ionis Share Purchase Agreement") with Ionis, pursuant to which Ionis purchased 282,485 of the Company's ordinary shares (the "Ionis Shares") at a price per share of $38.94, for an aggregate purchase price of approximately $11.0 million.

Pursuant to the terms of the Ionis Share Purchase Agreement, Ionis has agreed not to, without the Company's prior written consent and subject to certain conditions and exceptions, among other things, directly or indirectly acquire

additional shares of the Company's outstanding equity securities, seek or propose a tender or exchange offer, merger or other business combination involving the Company, solicit proxies or consents with respect to any matter, or undertake other specified actions related to the potential acquisition of additional equity interests in the Company (collectively, the "Standstill Restrictions"). The Standstill Restrictions will expire on the 18-month anniversary of the Ionis Share Purchase Agreement. The Share Purchase Agreement also provided that, subject to limited exceptions, Ionis could not sell any of the Ionis Shares until July 2022.

The Company determined the fair value of the Ionis Shares to be $7.6 million, based on the closing price of the Company's ADSs of $31.11 per ADS on the date of the Ionis Share Purchase Agreement, less a discount for lack of marketability associated with resale restrictions applicable to the Ionis Shares, which was recorded as a component of shareholders' equity. The Company concluded that the premium paid by Ionis under the Ionis Share Purchase Agreement represents additional consideration for the goods and services to be provided under the Ionis Collaboration Agreement. As such, the total premium of $3.4 million was included in the transaction price under the Ionis Collaboration Agreement.

Accounting analysis

Upon execution of the Ionis Collaboration Agreement, the Company identified the following promises in the arrangement: i) a worldwide exclusive license to research, develop, manufacture and commercialize products incorporating TfR1 *Bicycles* intended for the delivery of oligonucleotide compounds directed to targets selected by Ionis for diagnostic, therapeutic, prophylactic and preventative uses in humans; ii) research and discovery activities to customize and optimize such TfR1 *Bicycles*; iii) four material rights associated with options to obtain credits to be applied towards the IND acceptance fee for four collaboration targets.

The Company's participation in the JSC was deemed immaterial in the context of the contract. The Company has concluded that the exclusive license to research, develop, manufacture and commercialize products is not distinct from the research and development services as Ionis cannot obtain the intended benefit of the license without the Company performing the agreed upon research and discovery services, including the optimization of such TfR1 *Bicycles*. The services incorporate proprietary technology, unique skills and specialized expertise to optimize *Bicycles* that are not available in the marketplace. As a result, the exclusive license to research, develop, manufacture and commercialize products has been combined with the research and discovery activities into a single performance obligation. The Company concluded that the low-single-digit million dollar payments upon acceptance of an IND (and payment to extend the exclusive license to research, develop, manufacture and commercialize a product candidate for certain specific collaboration targets if Ionis fails to achieve specified development diligence milestone deadlines) is a customer option, as Ionis has the contractual right to choose to make the payment in exchange for the continued exclusive right to research, develop, manufacture and commercialize the product candidate, and the Company is not presently obligated to provide, and does not have a right to consideration, for the additional goods or services prior to Ionis's exercise of the option. In assessing whether the options under the Ionis Collaboration Agreement represent material rights, the Company considered the additional consideration the Company would be entitled to upon the option exercise and the standalone selling price of the underlying goods and services. For the material rights identified above, the Company concluded that each of the options to obtain credits provided Ionis with a discount that it otherwise would not have received without entering into the Ionis Collaboration Agreement.

The total transaction price was initially determined to be $38.0 million, consisting of the $31.0 million up front payment, the $3.0 million payment under the Option and Evaluation Agreement, that was credited against the total upfront payment payable pursuant to the Ionis Collaboration Agreement, the $3.4 million premium paid under the Ionis Share Purchase Agreement, and an estimated $0.6 million for the reimbursement of CRO costs. Additional variable consideration including development diligence milestone deadline extension payments, development and regulatory milestone payments, sales milestone payments and royalty payments was fully constrained as a result of the uncertainty regarding whether any of the milestones will be achieved.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling price of the Ionis combined licenses and research and discovery performance obligation was based on the nature of the licenses to be delivered, as well as the

services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin for what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the estimated value of the underlying goods and services, and the probability that Ionis would exercise the option. Based on the relative standalone selling price, the allocation of the transaction price as of June 30, 2022, to the separate performance obligations is as follows (in thousands):

Performance Obligations	Allocation of Transaction Price
Combined licenses and research and discovery performance obligation	$ 34,100
Four material rights associated with credits for IND Acceptance fees	3,900
	$ 38,000

The Company is recognizing revenue related to amounts allocated to the combined licenses and research and discovery performance obligation using a proportional performance model over the period of service using input-based measurements including total full-time equivalent effort and CRO costs incurred to date as a percentage of total full-time equivalent effort and CRO costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company commences revenue recognition upon exercise of or upon expiry of the respective option. The Company anticipates that the combined licenses and research and discovery performance obligation will be satisfied over a period of three years and anticipates the material rights may be exercisable or may expire after approximately four years from contract execution.

The Company concluded that the Ionis Amendment will be accounted for as a separate contract, as the services are distinct from the Ionis Collaboration Agreement, and the price of the contract increased by an amount of consideration that reflects the Company's standalone selling price. The Company concluded that the option does not contain a material right. The Company will recognize the $0.8 million as revenue as the underlying services are performed using a proportional performance model over the period of service using input based measurements of total full time equivalent efforts and external costs incurred to date as a percentage of total expected full time equivalent efforts and expected external costs, which best reflects the progress towards satisfaction of the performance obligation. For the three and six months ended June 30, 2022, the Company recognized revenue of $2.3 million and $4.6 million, respectively, and the Company recognized no revenue for the three and six months ended June 30, 2021. As of June 30, 2022, and December 31, 2021, the Company recorded deferred revenue of $26.4 million and $34.1 million, respectively, in connection with the Ionis Collaboration Agreement, Ionis Amendment, and Ionis Evaluation and Option Agreement.

Genentech Collaboration Agreement

On February 21, 2020, the Company entered into a Discovery Collaboration and License Agreement with Genentech, which was amended in November 2021 and June 2022 (as amended, the "Genentech Collaboration Agreement"). The collaboration is focused on the discovery and development of *Bicycle* peptides directed to biological targets selected by Genentech and aimed at developing up to four potential development candidates against multiple immuno-oncology targets suitable for Genentech to advance into further development and commercialization.

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

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

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

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

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

Accounting analysis

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

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

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

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

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

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

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

The Company concluded that certain substitution rights that require the payment of additional consideration, which approximate the standalone selling price of the underlying services to be provided, do not provide the customer with a material right and therefore, are not considered as performance obligations and are accounted for as separate contracts upon exercise, if ever. The Company's participation in the JRC was assessed as immaterial in the context of the contract.

The Company has concluded that the research license is not distinct from the research and development services as Genentech cannot obtain the benefit of the research license without the Company performing the research and development services. The services incorporate proprietary technology and unique skills and specialized expertise, particularly as it relates to constrained peptide technology that is not available in the marketplace. As a result, for each research program, the research license has been combined with the research and development services into a single performance obligation. In addition, the Company concluded that the Dev Go Option is not distinct or separately exercisable from the LSR Go Option, as the customer cannot benefit from the Dev Go Option unless and until the LSR Go Option is exercised.

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

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

In March 2021, the Company achieved specified criteria in accordance with the research plan under the Genentech Collaboration agreement and therefore updated its estimate of the variable consideration to include an additional $2.0 million, that is no longer constrained. The arrangement consideration was increased to $33.0 million.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for the Genentech Collaboration Programs was based on the nature of the services to be performed and estimates of the associated effort and costs of the services, adjusted for a reasonable profit margin for what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees Genentech would pay to exercise the options, the estimated value of the underlying goods and services, and the probability that Genentech would

exercise the option and any underlying options. Based on the relative standalone selling price, the initial allocation of the transaction price to the separate performance obligations is as follows (in thousands):

Performance Obligations	Allocation of Transaction Price
Genentech Collaboration Program #1 Performance Obligation	$ 4,019
Genentech Collaboration Program #2 Performance Obligation	8,037
Specified Targeting Arm Material Right Arm for Genentech Collaboration Program #1	352
Two material rights associated with the LSR Go Option for Collaboration Programs #1 and #2	12,400
Material rights associated with limited substitution rights	1,187
Two material rights for Expansion Options	7,005
	$ 33,000

The Company is recognizing revenue related to amounts allocated to the Genentech Collaboration Program #1 and #2 Performance Obligations as the underlying services are performed using a proportional performance model over the period of service using input-based measurements of total full-time equivalent efforts and external costs incurred to date as a percentage of total full-time equivalent efforts and external costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company will commence revenue recognition upon exercise of or upon expiry of the respective option. The Company anticipates that the Genentech Collaboration Performance Program #1 and #2 obligations will be performed over a period of approximately two to three years, and the material rights will be exercised or expire within approximately four years from contract execution.

In October 2021, Genentech exercised the first Expansion Option to add an additional Genentech Collaboration Program (Genentech Collaboration Program #3) and paid to the Company an expansion fee of $10.0 million during the year ended December 31, 2021. Genentech also elected for the Company to perform discovery and optimization services for a Targeting Arm, and the Company received an additional payment of $1.0 million for additional research services. The Company concluded that the exercise of the Expansion Option and Targeting Arm option is accounted for as a continuation of an existing contract as the customer decided to purchase additional goods and services contemplated in the original contract, and as such, the additional arrangement consideration of $11.0 million received upon the option exercises together with the amount originally allocated to the Expansion Option material right of $3.5 million is allocated to the underlying goods and services associated with the Expansion Option. The arrangement consideration was allocated to the separate performance obligations on the same basis as the initial allocation of the Genentech Collaboration Agreement. The Company will recognize $6.4 million allocated to the Genentech Collaboration Program #3 and Targeting Arm services as the underlying services are performed using a proportional performance model over the period of service of approximately two to three years using input-based measurements of total full-time equivalent efforts and external costs incurred to date as a percentage of total full-time equivalent efforts and external costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material right associated with an LSR Go Option for Genentech Collaboration Program #3 of $7.4 million, and limited substitution material rights of $0.7 million, are recorded as deferred revenue and the Company will commence revenue recognition upon exercise or expiry of the respective option. Other variable consideration for development milestones not subject to option exercises was fully constrained as a result of the uncertainty regarding whether any of the milestones will be achieved.

In June 2022, Genentech exercised the second Expansion Option to add an additional Genentech Collaboration Program (“Genentech Collaboration Program #4”), which triggered a $10.0 million payment to the Company under the Genentech Collaboration Agreement. The Company concluded that the exercise of the Expansion Option is accounted for as a continuation of an existing contract as the customer decided to purchase additional goods and services contemplated in the original contract, and as such, the additional arrangement consideration of $10.0 million received pursuant to the option exercise together with the amount originally allocated to the Expansion Option material right of $3.5 million is allocated to underlying goods and services associated with the Expansion Option. The arrangement consideration was allocated to the separate performance obligations on the same basis as the initial allocation of the Genentech Collaboration Agreement. The Company will recognize $5.3 million allocated to the Genentech

Collaboration Program #4 services as the underlying services are performed using a proportional performance model over the period of service of approximately two to three years using input-based measurements of total full-time equivalent efforts and external costs incurred to date as a percentage of total full-time equivalent efforts and external costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amounts allocated to the material right associated with an LSR Go Option for Genentech Collaboration Target #4 of $7.4 million, limited substitution material rights of $0.7 million, and the material right associated with the option to select a Targeting Arm for Genentech Collaboration Program #4 of $0.1 million, were recorded as deferred revenue and the Company will commence revenue recognition upon exercise or expiry of the respective option. Other variable consideration for development milestones not subject to option exercises was fully constrained as a result of the uncertainty regarding whether any of the milestones will be achieved.

During the three and six months ended June 30, 2022, the Company recognized revenue of $0.9 million and $2.3 million, respectively, and during the three and six months ended June 30, 2021, the Company recognized revenue of $1.6 million and $3.1 million, respectively. As of June 30, 2022, and December 31, 2021, the Company recorded $38.7 million and $34.4 million, respectively, of deferred revenue in connection with the Genentech Collaboration Agreement.

AstraZeneca Collaboration Agreement

In November 2016, the Company entered into a Research Collaboration Agreement (the "AstraZeneca Collaboration Agreement") with AstraZeneca. The collaboration activities initially focused on two targets within respiratory, cardiovascular and metabolic disease, for which collaboration activities were terminated by AstraZeneca in October 2020 and March 2021, respectively. In May 2018, AstraZeneca exercised an option to nominate four additional targets ("Additional Four Target Option"). As a result, AstraZeneca was entitled to obtain research and development services from the Company 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. After discovery and initial optimization of such *Bicycle* peptides, AstraZeneca is 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. Each research program is to continue for an initial period of three years, referred to as the research term, including one year for the Bicycle Research Term and two years for the AZ Research Term. AstraZeneca may extend the research term for each research program by 12 months (or 15 months, if needed to complete certain toxicology studies) or may shorten the research term for a research program if it is ceased due to a screening failure, a futility determination, or abandonment by AstraZeneca. AstraZeneca was obligated to fund two FTEs during the Bicycle Research Term, for each research program, based on an agreed upon FTE reimbursement rate. 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. 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. In addition, to the extent any of the drug 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, subject to certain reductions, including in certain countries where the licensed product faces generic competition. 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

Upon the execution of the Additional Four Target Option, the Company identified the following five performance obligations associated with the May 2018 AstraZeneca 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 were options. Upon exercise, AstraZeneca obtained a research license and the related research and development services and an option to a development and exploitation license. The Company has concluded that the research services option, including the underlying development and exploitation license options related to each respective target resulted in a material right as the option exercise fee related to the development and exploitation license contained a discount that AstraZeneca would not have otherwise received. The research license and the related research and development services related to the fourth, fifth and sixth targets were not performance obligations at the inception of the arrangement, as they were optional services that would be performed if AstraZeneca selected additional targets and they reflected their standalone selling prices and did not provide the customer with material rights. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract.

The total transaction price was initially determined to be $5.7 million, consisting of the $5.0 million option exercise fee and research and development funding of an estimated $0.7 million. The research and development funding was provided based on the costs incurred to conduct the research and development services. The Company utilized 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 was excluded from the transaction price as they related to option fees and milestones that can only be achieved subsequent to the license option exercise or are outside of the initial contact term.

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

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

The Company recognized 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 reflected the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company commences revenue recognition upon exercise of or upon expiry of the option. The optional future research license and the related research and development services related to the fourth, fifth and sixth targets reflect their standalone selling prices and do not provide the customer with a material right and, therefore, are not considered performance obligations and are accounted for as separate contracts. In June 2019, AstraZeneca selected a replacement target for the third target, and as such a new Research Term was started related to the Target Three Research License and Related Services. The total transaction price under the arrangement increased to $6.3 million for the additional research and development funding to be

received. In October 2020, AstraZeneca terminated the collaboration activities related to the third target. As a result, deferred revenue related to the amount allocated to the Target 3 Material Right of $1.5 million was recognized during the year ended December 31, 2020. In August 2021, AstraZeneca terminated the collaboration activities related to the sixth target. As a result, deferred revenue related to the amount allocated to the Target 6 Material Right of $1.1 million was recognized during the year ended December 31, 2021. In June 2022, AstraZeneca terminated the collaboration activities related to the fifth target. As a result, deferred revenue related to the amount allocated to the Target 5 Material Right of $1.2 million was recognized during the three months ended June 30, 2022. As of June 30, 2022, one research program was in the AZ Research Term, and the research and development services associated with the Bicycle Research Term for the fourth target have been completed. In January 2022, AstraZeneca elected to extend the AZ Research Term for the fourth target by 12 months.

For the three and six months ended June 30, 2022, the Company recognized revenue of $1.2 million and $1.2 million, respectively, related to the Additional Four Target Option and related contracts, and for the three and six months ended June 30, 2021, the Company recognized revenue of zero and $0.3 million, respectively, related to the research and development services for the sixth target related to the exercise of the Additional Four Target Option. As of June 30, 2022, and December 31, 2021, the Company recorded $1.1 million and $2.4 million, respectively, of deferred revenue in connection with the Additional Four Target Option and related contracts.

Summary of Contract Assets and Liabilities

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

	Beginning Balance January 1, 2022	Additions	Deductions	Impact of Exchange Rates	Ending Balance June 30, 2022
Contract liabilities:					
Deferred revenue					
Ionis collaboration deferred revenue	$ 34,115	$ —	$ (4,569)	$ (3,159)	$ 26,387
Genentech collaboration deferred revenue	34,436	10,000	(2,346)	(3,412)	38,678
DDF collaboration deferred revenue	428	—	(158)	(35)	235
AstraZeneca collaboration deferred revenue	2,361	—	(1,165)	(117)	1,079
Total deferred revenue	$ 71,340	$ 10,000	$ (8,238)	$ (6,723)	$ 66,379

	Beginning Balance January 1, 2021	Additions	Deductions	Impact of Exchange Rates	Ending Balance December 31, 2021
Contract liabilities:					
Deferred revenue					
Ionis collaboration deferred revenue	$ 3,000	$ 36,002	$ (4,242)	$ (645)	$ 34,115
Genentech collaboration deferred revenue	27,579	13,000	(5,660)	(483)	34,436
DDF collaboration deferred revenue	821	—	(391)	(2)	428
AstraZeneca collaboration deferred revenue	3,756	54	(1,404)	(45)	2,361
Total deferred revenue	$ 35,156	$ 49,056	$ (11,697)	$ (1,175)	$ 71,340

Contract assets represent research and development services which have been performed but have not yet been billed, and are reduced when they are subsequently billed. There were no contract assets at June 30, 2022 or December 31, 2021.

The Ionis deferred revenue balance at June 30, 2022 includes $3.4 million allocated to material rights that will commence revenue recognition when the respective option is exercised or when the option expires. The Genentech deferred revenue balance at June 30, 2022 includes $26.9 million allocated to material rights that will commence revenue recognition when the respective option is exercised or when the option expires. The AstraZeneca deferred revenue balance as of June 30, 2022 includes $1.1 million allocated to the Target 4 Material Right, which will commence revenue recognition when the option is exercised at the end of AZ Research Term or when the option expires.

During the three and six months ended June 30, 2022 and 2021, 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,	
	2022	2021	2022	2021
Revenue recognized in the period from:				
Revenue recognized based on proportional performance	$ 3,213	$ 1,405	$ 7,032	$ 3,057
Revenue recognized based on expiration of material rights	1,165	380	1,206	380
Revenue recognized based on changes in transaction price	—	—	—	156
Total	$ 4,378	$ 1,785	$ 8,238	$ 3,593

Cancer Research UK

BT1718

On December 13, 2016, the Company entered into a Clinical Trial and License Agreement with Cancer Research Technology Limited (“CRTL”), a wholly owned subsidiary of Cancer Research UK that Cancer Research UK’s commercial activities operate through, and Cancer Research UK (the “Cancer Research UK Agreement”). Pursuant to the Cancer Research UK Agreement, as amended in March 2017 and June 2018, Cancer Research UK’s Centre for Drug Development will sponsor and fund a Phase I/IIa clinical trial for BT1718, a *Bicycle* Toxin Conjugate, in patients with advanced solid tumors.

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

The Company granted Cancer Research UK a license to its intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial. The Company retains the right to continue the development of BT1718 during the clinical trial. Upon the completion of the Phase I/IIa clinical trial, the Company has the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and the Company decides to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, the Company will assign or grant to CRTL an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case the Company will receive tiered royalties of 70% to 90% of the net revenue depending on the stage of development when the license is granted). The Cancer Research UK Agreement contains additional future milestone payments upon the achievement of development and regulatory milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a single digit percentage on net sales of products developed.

The Cancer Research UK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such

party). Cancer Research UK may also terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met. The Company was obligated to reimburse Cancer Research UK for certain costs if the Cancer Research UK agreement was terminated by Cancer Research UK prior to the completion of the dose escalation (Phase I) part of the clinical trial for an insolvency event of, or material breach by, the Company or upon termination for safety reasons or if Cancer Research UK determined that the objectives of the clinical trial would not be met, however, these reimbursement obligations expired unexercised upon the completion of the Phase I portion of the clinical trial in 2020. If the Company is subject to a change in control and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party prior to the last cycle of treatment under the Phase IIa clinical trial, the Company will reimburse Cancer Research UK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case, Cancer Research UK will not be obliged to grant a license to the Company in respect of the results of the clinical trial and the Company will assign or grant to CRTL an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company.

The Company concluded that the costs incurred by Cancer Research UK is a liability in accordance with ASC 730, *Research and Developmen*t, as certain payments are not based solely on the results of the research and development having future economic benefit. As such, the Company recorded a liability of $3.3 million at both June 30, 2022 and December 31, 2021, 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 condensed consolidated statements of operations and comprehensive loss.

BT7401

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

The Company granted to Cancer Research UK a license to the Company's intellectual property in order to design, prepare for, sponsor, and carry out the clinical trial and all necessary preclinical activities to support the trial. The Company retains the right to continue the development of BT7401 during the clinical trial. Upon the completion of the Phase I/IIa clinical trial, the Company has the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and the Company decides to abandon development of all products that contain BT7401 or all the pharmaceutically active parts of BT7401, CRTL may elect to receive an exclusive license to develop and commercialize the product on a revenue sharing basis (in which case the Company will receive tiered royalties of 55% to 80% of the net revenue depending on the stage of development when the license is granted) less certain costs, as defined by the agreement. The BT7401 Cancer Research UK agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash, with an aggregate total value of up to $60.3 million for each licensed product, as well as royalty payments based on a single digit percentage on net sales of products developed, and sublicense royalties to the Cancer Research UK in the low double digit percentage of sublicense income depending on the stage of development when the license is granted.

The BT7401 Cancer Research UK agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party), or upon written notice by Cancer Research UK prior to the last cycle of treatment has been completed under the clinical trial. If the trial is terminated by the Company prior to the filing of a clinical trial authorization, or by Cancer Research UK for an insolvency event or a material breach by the Company prior to the start of a clinical trial, the Company will reimburse Cancer Research UK for certain costs paid or committed prior to the start of the clinical trial. In such case where the Company is subject to a change of control and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party, Cancer Research UK will not be obliged to grant a license to the Company in respect of the results of the clinical

trial and CRTL may elect to receive an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company. The Company concluded that the BT7401 Cancer Research UK arrangement does not represent a liability in accordance with ASC 730, *Research and Development*, as the payments are based solely on the results of the research and development having future economic benefit and risk of repayment is substantive and genuine, and as such there was no accounting impact for the three and six months ended June 30, 2022.

10. Income taxes

During the three and six months ended June 30, 2022, the Company recorded an income tax benefit of $0.4 million and $0.9 million, respectively, and during the three and six months ended June 30, 2021, the Company recorded an income tax benefit of $0.2 million and $0.5 million, respectively. The Company is subject to United Kingdom corporate taxation. Due to the nature of its business, the Company has generated losses since inception and has therefore not paid United Kingdom corporation tax. The Company's income tax benefit is mainly the result of deferred tax assets benefitted in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement. 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, 2022, and December 31, 2021.

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 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.

11. Commitments and contingencies

Leases

On December 6, 2021 the Company entered into a lease of new office and laboratory space, in Cambridge, United Kingdom. The lease has a contractual period of 10 years, but may be cancelled by the Company on the fifth anniversary of the lease commencement date. The lease term is five years, representing the non-cancelable lease period, as it is not reasonably certain that the lease will not be cancelled. The Company has a contractual right to renew the lease for a further ten-year period, which also may be cancelled after five years. The annual rent is approximately $3.0 million, payable quarterly in advance beginning in June 2022, following a six month period of free rent. There was no deposit paid in conjunction with the lease. The Company recorded a right of use asset of approximately $11.6 million and a lease liability of approximately $11.1 million at the lease commencement date, based on the present value of future lease payments, discounted at a 6.9%, the Company's estimated incremental borrowing rate at the commencement of the

lease, over the lease term. Rent expense is recognized on a straight-line basis over the five year lease term, including the six month rent-free period.

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 expired on December 11, 2021. The annual rent was approximately $0.5 million. The Company had the right to renew the lease for five years commencing December 12, 2021. The renewal period was not included in the original lease term as it was not reasonably certain that the right would be exercised. In March 2021, the Company concluded that it was reasonably certain that it would exercise the lease renewal option, and accounted for the lease extension as a modification of the existing lease. The Company remeasured the right of use asset and lease liability by calculating the present value of expected lease payments, discounted at 7.70%, the Company's estimated incremental borrowing rate at the date of the modification of the lease, over the new lease term. In December 2021, the lease was renewed. The annual rent for the new lease is approximately $0.6 million. Service charges are also payable based on floor area and are estimated to be approximately $0.2 million per year.

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. In March 2022, Bicycle Therapeutics Inc. notified the landlord of its intent to exercise its option to extend the lease, originally set to expire on December 31, 2022, for a successive period through December 31, 2027. The successive period was not included in the original lease term as it was not reasonably certain that the option would be exercised. In March 2022, the Company accounted for the lease extension as a modification of the existing lease and remeasured the right of use asset and lease liability by calculating the present value of lease payments, discounted at 7.0%, the Company's incremental borrowing rate, over the new lease term. In May 2022, the lease was extended. The payments for the modified lease are approximately $0.2 million remaining through December 31, 2022, $0.7 million in 2023, and increases annually pursuant to an escalation clause with the last year of the lease term having a per annum fixed rent obligation of $0.8 million.

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 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, periods covered by an option to extend the lease when it is reasonably certain that the Company will exercise the extension option, or cancelable option periods when it is reasonably certain that the Company would not exercise such cancelation option.

- *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,		Six Months Ended June 30,	
	2022	2021	2022	2021
Operating lease cost	$ 1,036	$ 273	$ 1,942	$ 505
Variable lease cost	328	143	595	222
Total lease cost	$ 1,364	$ 416	$ 2,537	$ 727

The weighted average remaining operating lease term was 4.7 years and 4.8 years as of June 30, 2022 and 2021, respectively, and the weighted average discount rate was 7.04% and 7.92% as of June 30, 2022 and 2021, respectively.

The following table summarizes the maturities of the Company's operating leases as of June 30, 2022 (in thousands):

Year Ending December 31,	
2022	$ 1,867
2023	3,981
2024	4,003
2025	4,025
2026	3,243
2027	821
Present value adjustment	(2,539)
Total lease liabilities	15,401
Less: current lease liabilities	(2,905)
Long term lease liabilities	$ 12,496

The Company has entered into various agreements with contract research organizations to provide clinical trial services, 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. In some cases, we are contractually obligated to make certain minimum payments to the vendors, based on the timing of the termination notification and the exact terms of the agreement.

Legal proceedings

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

Founder royalty arrangements

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

Indemnification obligations

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has indemnification obligations towards members of its board of directors and officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification arrangements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnification obligations. The Company is not aware of any claims under indemnification arrangements, and therefore it has not accrued any liabilities related to such obligations in its condensed consolidated financial statements as of June 30, 2022, and December 31, 2021.

12. Net loss per share

Basic and diluted net loss per share was calculated as follows (in thousands, except share and per share amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Numerator:				
Net loss	$ (26,828)	$ (17,913)	$ (54,392)	$ (34,104)
Denominator:				
Weighted average ordinary shares outstanding, basic and diluted	29,648,564	24,052,168	29,626,974	23,047,745
Net loss per share, basic and diluted	$ (0.90)	$ (0.74)	$ (1.84)	$ (1.48)

The Company's potentially dilutive securities, which are options to purchase ordinary shares and restricted share units for ordinary 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 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 for the periods indicated because including them would have had an anti-dilutive effect:

	June 30,	
	2022	2021
Restricted ordinary shares	187,725	—
Options to purchase ordinary shares	5,634,144	4,920,831
	5,821,869	4,920,831

13. Related party transactions

The Company has entered into the Founder Royalty Agreement, as amended, with its founders and initial investors (Note 11). No royalties have been earned or paid under the Founder Royalty Agreement, as amended, to date.

The Chairman of the Company's board of directors is associated with Stone Sunny Isles Inc., and Stone Atlanta Estates LLC, the successor-in-interest to Stone Sunny Isles, which provided consultancy services to the Company totaling $0.1 million and $0.1 million during the three and six months ended June 30, 2022, respectively, and $44,000 and $0.1 million during the three and six months ended June 30, 2021, respectively.

14. 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, 2022	December 31, 2021
United States	$ 4,163	$ 1,095
United Kingdom	27,728	16,694
	$ 31,891	$ 17,789

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

15. Subsequent events

On July 15, 2022, the Borrowers entered into the second amendment (the "Second Amendment to LSA") to the Loan and Security Agreement with Hercules (as amended by the First Amendment to LSA). Pursuant to the Second Amendment to LSA, among other amendments, (a) the rate at which the borrowings under the Loan Agreement bear interest was decreased and capped to be an annual rate equal to the lesser of (x) the greater of either (i) 8.05% and (ii) the *Wall Street Journal* prime rate plus 4.55% and (y) 9.05%, (b) the interest-only period was extended to April 1, 2025, (c) the Maturity Date was extended to July 1, 2025, and (d) the Borrowers may request additional term loans, subject to satisfaction of customary conditions, in an aggregate principal amount, including amounts already borrowed pursuant to the Loan Agreement and First Amendment to LSA, of up to $75.0 million on or before December 31, 2024.

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

You should read this discussion and analysis of our financial condition and consolidated results of operations together with 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, 2021, included in our Annual Report on Form 10-K for the year ended December 31, 2021, or the 2021 Annual Report, which was filed with the Securities and Exchange Commission, or SEC, on March 1, 2022. Some of the information contained in this discussion and analysis or set forth elsewhere in this report, including statements of our plans, objectives, expectations and intentions, contain forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this report, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Please also see the section titled "Forward-Looking Statements."

Overview

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

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

Our product candidates, BT5528, BT8009, and BT1718, are each a *Bicycle*® Toxin Conjugate, or BTC™. These *Bicycles* are chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. We are evaluating BT5528, a second-generation BTC targeting Ephrin type A receptor 2, or EphA2, in a company-sponsored Phase I/II clinical trial and BT8009, a second-generation BTC targeting Nectin-4, in a company-sponsored Phase I/II clinical trial. In addition, BT1718 is being developed to target tumors that express Membrane Type 1 matrix metalloproteinase, or MT1 MMP, and is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial sponsored and fully funded by the Cancer Research UK Centre for Drug Development, or Cancer Research UK. In addition, our other product candidates, BT7480 and BT7455, are each a *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™. A *Bicycle* TICA links immune cell receptor binding *Bicycles* to tumor antigen binding *Bicycles*. We are evaluating BT7480, a *Bicycle* TICA targeting Nectin-4 and agonizing CD137, in a company-sponsored Phase I/II clinical trial, and we are conducting IND-enabling studies for BT7455, an EphA2/CD137 *Bicycle* TICA. Our discovery pipeline in oncology includes *Bicycle*-based systemic immune cell agonists and *Bicycle* TICAs.

On October 7, 2021, we announced interim results from our Phase I clinical trial of BT5528 and preliminary results from our ongoing Phase 1 clinical trial of BT8009. We observed signs of anti-tumor activity in our clinical trial of BT5528 in patients with urothelial and ovarian cancer and established a recommended Phase II dose range. On June 8, 2022, we announced that the first patient had been dosed in the expansion portion of the Phase I/II study of BT5528 in urothelial and ovarian cancers, as well as in a basket cohort of other solid tumors, including non-small cell lung cancer,

triple-negative breast cancer, head and neck cancer, and esophageal cancer. Enrollment in these cohorts remains ongoing.

In our ongoing Phase I clinical trial of BT8009, we observed signs of anti-tumor activity in urothelial cancer patients and presented updated results on April 11, 2022. The Phase I clinical trial remains ongoing. Enrollment in the ongoing Phase IIa portion of a Phase I/IIa clinical trial of BT1718 sponsored and fully funded by Cancer Research UK has been ongoing. Enrollment in the BT7480 Phase I trial is ongoing and is progressing on schedule during the dose escalation portion of the clinical trial.

Beyond our wholly owned oncology portfolio, we are collaborating with biopharmaceutical companies and organizations in therapeutic areas in which we believe our proprietary *Bicycle* screening platform can identify therapies to treat diseases with significant unmet medical need. Our partnered programs include collaborations in immuno-oncology, anti-infective, cardiovascular, ophthalmology, dementia, central nervous system, neuromuscular and respiratory indications.

COVID-19 Business Update

We continue to closely monitor the ongoing COVID-19 situation. We have allowed our non-laboratory-based employees to return to the office, however, many non-laboratory-based employees continue to work remotely. In light of continually changing circumstances regarding infection rates and local government recommendations, or if additional restrictions emerge as a result of COVID-19 variants, we may be required to suspend or reverse efforts to return to the office in the future.

With respect to clinical development, our CROs have taken measures to utilize remote and virtual approaches, as necessary, including remote patient monitoring where possible, to maintain patient safety and trial continuity and to preserve trial integrity. Changes in circumstances related to the ongoing COVID-19 pandemic could result in pauses in or other impacts on enrollment. We could also see an impact on the ability to report trial results, or interact with regulators, ethics committees or other important agencies due to limitations in regulatory authority employee resources or otherwise. In addition, we cannot guarantee that our CROs or other third parties will continue to perform their contractual duties in a timely and satisfactory manner. If additional new variants of COVID-19 emerge, we could experience significant disruptions to our clinical development timelines, which would adversely affect our business, financial condition, results of operations and growth prospects.

As for our third-party manufacturers, distributors and other partners, we are working closely with them to manage our supply chain activities and mitigate potential disruptions to our clinical trial materials and supplies as a result of the ongoing COVID-19 pandemic. We currently expect to have adequate global supply of clinical trial materials and supplies to support our current clinical trial activities. However, we could experience disruptions to our supply chain and operations, and associated delays in the manufacturing and supply of our products, which would adversely impact our ability to provide investigational product to our clinical trial sites and to generate sales of and revenues from our approved products, if approved. Our laboratories in the United Kingdom and the United States remain operational.

Financial Overview

Since our inception, we have devoted substantially all of our resources to developing our *Bicycle* platform and our product candidates, BT5528, BT8009, BT1718, BT7480, BT7455 and BT7401, conducting research and development of our product candidates and preclinical programs, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of our American Depositary Shares, or ADSs, ordinary shares, and convertible preferred shares, proceeds received from upfront payments, research and development payments, and development milestone payments from our collaboration agreements with Ionis Pharmaceuticals, Inc., or Ionis, Genentech Inc., or Genentech, the Dementia Discovery Fund, or DDF, Sanofi (formerly Bioverativ Inc.), AstraZeneca AB, or AstraZeneca and Oxurion NV, or Oxurion; and borrowings pursuant to our debt facility with Hercules Capital, Inc., or Hercules. From our inception in 2009 through June 30, 2022, we have received gross proceeds of $558.2 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering, follow-on offering and at-the-

market, or ATM, offering program; and $125.2 million of cash payments under our collaboration revenue arrangements, including $46.6 million from Ionis, $44.0 million from Genentech, $1.7 million from DDF, $10.3 million from AstraZeneca, $15.0 million from Sanofi, and $6.6 million from Oxurion; and borrowings of $30.0 million pursuant to our Loan and Security Agreement, or Loan Agreement, with Hercules. 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 $26.8 million and $54.4 million for the three and six months ended June 30, 2022, respectively. As of June 30, 2022, we had an accumulated deficit of $272.8 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 BT5528, BT8009, BT7480 and BT1718;
- progress the preclinical and clinical development of BT7455 and BT7401;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, commercial and scientific personnel;
- acquire or in-license other products and technologies;
- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and
- add operational, financial and management information systems and personnel, including personnel to support our research and development programs and any future commercialization efforts.

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 and governmental 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. Both the ongoing COVID-19 pandemic and the Russia-Ukraine war have resulted in a significant disruption of global financial markets. If the disruption persists and deepens, whether as a result of these events or otherwise, we could experience an inability to access additional capital.

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

As of June 30, 2022, we had cash and cash equivalents of $372.8 million. We believe that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Quarterly Report on Form 10-Q. We have based this estimate on assumptions that may prove to be wrong, and we could deplete our available capital resources sooner than we expect. See "— Liquidity and Capital Resources" and "Capital Resources and Funding Requirements."

Components of Our Results of Operations

Collaboration Revenues

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

Expenses

Research and Development Expenses

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

- employee-related expenses including salaries, benefits, and share-based compensation expense;
- expenses incurred under agreements with third parties that conduct research and development, preclinical activities, clinical activities and manufacturing on our behalf;
- the cost of consultants;

- the cost of lab supplies and acquiring, developing and manufacturing preclinical study materials and clinical trial materials;
- costs related to compliance with regulatory requirements; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, and other operating costs.

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

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

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

In December 2016, we entered into a Clinical Trial and License Agreement with Cancer Research Technology Limited, or CRTL and Cancer Research UK, pursuant to which the Cancer Research UK Centre for Drug Development is sponsoring and funding a Phase I/IIa clinical trial for our product candidate, BT1718, in patients with advanced solid tumors. Cancer Research UK has designed and prepared and is carrying out and sponsoring the clinical trial at its own cost. Upon the completion of the Phase I/IIa clinical trial, we have the right to obtain a license to the results of the clinical trial upon the payment of a milestone, in cash and ordinary shares, with a combined value in the mid six digit dollar amount. If such license is not acquired, or if it is acquired and the license is terminated and we decide to abandon development of all products that deliver cytotoxic payloads to the MT1 target antigen, CRTL may elect to receive an assignment and exclusive license to develop and commercialize the product on a revenue sharing basis (in which case we will receive tiered royalties of 70% to 90% of the net revenue depending on the stage of development when the license is granted is less certain costs, as defined in the agreement). The Cancer Research UK Agreement contains additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $50.9 million, as well as royalty payments based on a single digit percentage on net sales of products developed. The Cancer Research UK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, upon a change in control involving a tobacco related entity, and in certain other specified circumstances, and includes provisions that require the repayment of costs to Cancer Research UK upon certain termination events. The costs incurred by Cancer Research UK are recorded as a liability in accordance with ASC 730, *Research and Developmen*t as the payments are not based solely on the results of the research and development having future economic benefit. The accrual of the liability is recorded as incremental research and development expense in the condensed consolidated statements of operations and comprehensive loss. Upon the completion of the Phase IIa part of the clinical trial, we expect research and development expenses to increase significantly as we expect to fund the continued development of BT1718, as well as incur additional development milestone payments.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and

development expenses will continue to increase for the foreseeable future as a result of our expanded portfolio of product candidates and as we: (i) continue the clinical development and seek to obtain marketing approval for our product candidates, including BT5528, BT8009, BT7480 and BT1718; (ii) initiate clinical trials for our product candidates, including BT7455; and (iii) build our in-house process development and analytical capabilities and continue to discover and develop additional product candidates.

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

- whether our business will be adversely affected by the ongoing COVID-19 pandemic, which could materially affect our operations, delay our research efforts and clinical trials and cause significant disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business; and
- completing research and preclinical and clinical development of our product candidates, including conducting future clinical trials of BT5528, BT8009, BT7480 and BT1718;
- progressing the preclinical and clinical development of BT7455 and BT7401;
- establishing an appropriate safety profile with IND-enabling studies to advance our preclinical programs into clinical development;
- identifying new product candidates to add to our development pipeline;
- successful enrollment in, and the initiation and completion of clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with others;
- establishing commercial manufacturing capabilities or making arrangements with third party manufacturers;
- the development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials;
- addressing any competing technological and market developments, as well as any changes in governmental regulations;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how, as well as obtaining and maintaining regulatory exclusivity for our product candidates;
- continued acceptable safety profile of the drugs following approval; and
- attracting, hiring and retaining qualified personnel.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, the FDA, EMA or another regulatory authority may require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or we may experience significant trial delays due to patient enrollment or other reasons, including the impacts of the ongoing COVID-19 pandemic, in which case we would be required to expend significant additional financial resources and time on the completion of clinical development. Changes in circumstances related to the ongoing COVID-19 pandemic could result in pauses in or other impacts on enrollment. In addition, we may obtain unexpected results from our clinical trials and we may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success.

General and Administrative Expenses

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

Foreign currency transactions in currencies different from the functional currency of our U.K. 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 continue to incur increased expenses associated with being a public company including costs of accounting, audit, information systems, legal, intellectual property, regulatory and tax compliance services, director and officer insurance and investor and public relations.

Other Income (Expense), net

Interest Income

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

Interest Expense

Interest expense consists primarily of interest expense for financing arrangements. On September 30, 2020, we entered into the Loan Agreement with Hercules and borrowed $15.0 million. On March 10, 2021, we entered into the First Amendment to the Loan and Security Agreement and borrowed an additional $15.0 million.

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 U.K. corporation tax. The benefit from income taxes presented in our condensed consolidated statements of operations and comprehensive loss is mainly the result of deferred tax assets benefited in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement.

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

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

Based on criteria established by U.K. law, a portion of expenditures being carried out in relation to our pipeline research and development, clinical trials management and manufacturing development activities were eligible for the SME Program for the year ended December 31, 2021. For the year ending December 31, 2022, the payable credit claims under the SME Program in excess of £20,000 will be subject to a limitation of three times the total PAYE and NIC liability paid by the Company, unless an exception applies. That exception requires the Company to be creating, taking steps to create, or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. We expect a portion of qualifying research and development expenditures that are subject to the research and development tax credit will decrease in future periods.

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.

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

Results of Operations

Comparison of the Three Months Ended June 30, 2022 and 2021

The following table summarizes our results of operations for the three months ended June 30, 2022 and 2021:

	Three Months Ended June 30,		
	2022	2021	Change
	(in thousands)		
Collaboration revenues	$ 4,378	$ 1,785	$ 2,593
Operating expenses:			
Research and development	19,854	11,722	8,132
General and administrative	11,824	7,340	4,484
Total operating expenses	31,678	19,062	12,616
Loss from operations	(27,300)	(17,277)	(10,023)
Other income (expense):			
Interest income	908	23	885
Interest expense	(883)	(819)	(64)
Total other income (expense), net	25	(796)	821
Net loss before income tax provision	(27,275)	(18,073)	(9,202)
Benefit from income taxes	(447)	(160)	(287)
Net loss	$ (26,828)	$ (17,913)	$ (8,915)

Collaboration Revenues

Collaboration revenues increased by $2.6 million in the three months ended June 30, 2022, compared to the three months ended June 30, 2021, primarily due to increases of $2.3 million from our collaboration with Ionis entered into in July 2021, and $1.2 million from our collaboration with AstraZeneca as a result of the expiration of a material right upon the termination of the collaboration activities related to the fifth target, offset by a decrease of $0.8 million from our collaboration with Genentech.

Research and Development Expenses

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

	Three Months Ended June 30,		
	2022	2021	Change
	(in thousands)		
BT5528 (EphA2)	$ 2,544	$ 1,486	$ 1,058
BT8009 (Nectin-4)	2,419	1,870	549
BT1718 (MT1)	161	182	(21)
Bicycle tumor-targeted immune cell agonists	3,175	2,225	950
Other discovery and platform related expense	4,655	4,344	311
Employee and contractor related expenses	7,168	3,812	3,356
Share-based compensation	2,642	1,089	1,553
Facility expenses	1,560	383	1,177
Research and development incentives	(4,470)	(3,669)	(801)
Total research and development expenses	$ 19,854	$ 11,722	$ 8,132

Research and development expenses increased by $8.1 million in the three months ended June 30, 2022, compared to the three months ended June 30, 2021, due primarily to an increase of $2.8 million in direct program spend, primarily associated with clinical program expenses for BT5528 and BT8009 and *Bicycle* TICA program development expenses, as well as increases of $3.4 million in employee and contractor related expenses attributable to increased headcount, $1.6 million of incremental share-based compensation expense, and $1.2 million in facilities-related expenses primarily associated with our U.K. lease entered into in December 2021. These increases were offset by $0.8 million of incremental research and development incentives, including U.K. research and development tax credit reimbursements due to the corresponding increase in research and development spending.

We begin to separately track program expenses at candidate nomination, at which point we will accumulate all direct external program costs to support that program to date. Through June 30, 2022, we have incurred approximately $23.7 million, $22.4 million, $14.6 million, and $16.0 million of direct external expenses for the development of the BT5528, BT8009, BT1718, and *Bicycle* TICA programs, respectively, since their candidate nominations.

General and Administrative Expenses

The table below summarizes our general and administrative expenses for the period:

	Three Months Ended June 30,		
	2022	2021	Change
	(in thousands)		
Personnel related costs	$ 3,640	$ 2,306	$ 1,334
Professional and consulting fees	2,314	2,077	237
Other general and administration costs	2,159	1,477	682
Share-based compensation	3,031	1,486	1,545
Effect of foreign exchange rates	680	(6)	686
Total general and administrative expenses	$ 11,824	$ 7,340	$ 4,484

General and administrative expenses increased by $4.5 million in the three months ended June 30, 2022, compared to the three months ended June 30, 2021. This increase is primarily due to a $1.5 million increase in share-based compensation, an increase of $1.3 million in personnel related costs due to higher headcount, an increase of $0.7 million in other general and administrative costs, including insurance expense, to support operations as a public company, and a $0.7 million unfavorable effect of foreign exchange rates.

Other Income (Expense), net

Other income (expense), net increased by $0.8 million in the three months ended June 30, 2022, compared to the three months ended June 30, 2021, primarily due to interest income related interest earned on our cash equivalents held in 30-day deposit accounts.

Comparison of the Six Months Ended June 30, 2022 and 2021

The following table summarizes our results of operations for the six months ended June 30, 2022 and 2021:

	Six Months Ended June 30,		Change
	2022	2021	
	(in thousands)		
Collaboration revenues	$ 8,238	$ 3,593	$ 4,645
Operating expenses:			
Research and development	34,138	21,415	12,723
General and administrative	28,783	15,479	13,304
Total operating expenses	62,921	36,894	26,027
Loss from operations	(54,683)	(33,301)	(21,382)
Other income (expense):			
Interest income	1,126	38	1,088
Interest expense	(1,701)	(1,341)	(360)
Total other income (expense), net	(575)	(1,303)	728
Net loss before income tax provision	(55,258)	(34,604)	(20,654)
Benefit from income taxes	(866)	(500)	(366)
Net loss	$ (54,392)	$ (34,104)	$ (20,288)

Collaboration Revenues

Collaboration revenues increased by $4.6 million in the six months ended June 30, 2022, compared to the six months ended June 30, 2021, primarily due to increases of $4.6 million from our collaboration with Ionis entered into in July 2021 and $0.9 million from our collaboration with AstraZeneca as a result of the expiration of a material right upon the termination of the collaboration activities related to the fifth target, offset by a decrease of $0.7 million from our collaboration with Genentech.

Research and Development Expenses

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

	Six Months Ended June 30,		Change
	2022	2021	
	(in thousands)		
BT5528 (EphA2)	$ 3,946	$ 2,824	$ 1,122
BT8009 (Nectin-4)	3,633	3,496	137
BT1718 (MT1)	348	354	(6)
Bicycle tumor-targeted immune cell agonists	4,698	3,466	1,232
Other discovery and platform related expense	9,094	7,624	1,470
Employee and contractor related expenses	12,750	7,694	5,056
Share-based compensation	5,006	2,299	2,707
Facility expenses	2,350	553	1,797
Research and development incentives	(7,687)	(6,895)	(792)
Total research and development expenses	$ 34,138	$ 21,415	$ 12,723

Research and development expenses increased by $12.7 million in the six months ended June 30, 2022, compared to the six months ended June 30, 2021, due primarily to an increase of $4.0 million in direct program spend, primarily associated with clinical program expenses for BT5528, *Bicycle* TICA program development expenses, and increased other discovery and platform related expenses, as well as increases of $5.1 million in employee and contractor related expenses attributable to increased headcount, $2.7 million of incremental share-based compensation expense, and $1.8 million in facilities-related expenses. These increases were offset by $0.8 million of incremental research and development incentives, including U.K. research and development tax credit reimbursements due to the corresponding increase in research and development spending.

General and Administrative Expenses

The table below summarizes our general and administrative expenses for the period:

	Six Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Personnel related costs	$ 6,892	$ 4,182	$ 2,710
Professional and consulting fees	5,998	4,318	1,680
Other general and administration costs	4,235	2,845	1,390
Share-based compensation	10,865	4,097	6,768
Effect of foreign exchange rates	793	37	756
Total general and administrative expenses	$ 28,783	$ 15,479	$ 13,304

General and administrative expenses increased by $13.3 million in the six months ended June 30, 2022, compared to the six months ended June 30, 2021. This increase is primarily due to a $6.8 million increase in share-based compensation expense primarily associated with our annual employee equity grants in January 2022, an increase of $2.7 million in personnel related costs due to higher headcount, an increase of $1.7 million in professional and consulting fees, an increase of $1.4 million in other general and administrative costs, including insurance expense, to support operations as a public company, and an unfavorable impact of $0.8 million due to the effect of foreign exchange rates.

Other Income (Expense), net

Other income (expense), net increased by $0.7 million in the six months ended June 30, 2022, compared to the six months ended June 30, 2021, primarily due to an increase of $1.1 million in interest income related to interest earned on our cash equivalents held in 30-day deposit accounts offset by an increase of $0.4 million in interest expense related to an incremental borrowing of $15.0 million received in March 2021 under the First Amendment to the Loan and Security Agreement.

Liquidity and Capital Resources

Liquidity

From our inception through June 30, 2022, we have not generated any revenue from product sales and have incurred significant operating losses and negative cash flows from our operations. We do not expect to generate significant revenue from sales of any products for several years, if at all.

To date, we have financed our operations primarily with proceeds from the sale of our ADSs, ordinary shares, and convertible preferred shares; proceeds received from upfront payments, payments for research and development services, and development milestone payments pursuant to collaboration agreements with Ionis, Genentech, DDF, AstraZeneca, Sanofi and Oxurion; and borrowings pursuant to our Loan Agreement.

From our inception in 2009 through June 30, 2022, we have received gross proceeds of $558.2 million from the sale of ADSs, ordinary shares, and convertible preferred shares, including the proceeds from our IPO and our ATM offering program; $125.2 million of cash payments under our collaboration revenue arrangements including, $46.6 million from Ionis, $44.0 million from Genentech, $1.7 million from DDF, $10.3 million from AstraZeneca, $15.0 million from Sanofi and $6.6 million from Oxurion; and $30.0 million in borrowings pursuant to our Loan Agreement. We do not have any products approved for sale and have not generated any revenue from product sales.

Cash Flows

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

	Six Months Ended June 30,	
	2022	2021
Net cash used in operating activities	$ (49,931)	$ (26,077)
Net cash used in investing activities	(14,555)	(794)
Net cash provided by financing activities	645	89,611
Effect of exchange rate changes on cash	(2,070)	8
Net (decrease) increase in cash and cash equivalents	$ (65,911)	$ 62,748

Operating Activities

Net cash used in operating activities for the six months ended June 30, 2022, was $49.9 million as compared to $26.1 million for the six months ended June 30, 2021. The increase in cash used in operations is primarily due to an increase in net loss of $20.3 million as described in the Results of Operations above, offset by an increase in non-cash expenses, including $9.5 million of share-based compensation expense, and an increase in cash used by changes in our operating assets and liabilities. The increase in cash used in operating activities was associated with changes in our operating assets and liabilities, primarily driven by changes in accounts receivable of $14.9 million, including a $10.0 million receivable triggered as a result of the Genentech exercise of an expansion option in June 2022, prepaid expenses and other current assets of $2.7 million based on timing of payments, offset by changes in deferred revenue of $3.6 million and accrued expenses and other current liabilities of $3.8 million.

Investing Activities

During the six months ended June 30, 2022 and 2021, we used $14.6 million and $0.8 million, respectively, of cash in investing activities for purchases of property and equipment, consisting primarily of leasehold improvements and laboratory equipment.

Financing Activities

During the six months ended June 30, 2022, net cash provided by financing activities was $0.6 million, primarily consisting of net proceeds from our exercise of share options.

During the six months ended June 30, 2021, net cash provided by financing activities was $89.6 million, primarily consisting of net proceeds from our ATM of $72.8 million and borrowings of $15.0 million under our Loan Agreement with Hercules.

Loan Agreement

We have an outstanding Loan Agreement, as amended from time to time, with Hercules as agent, consisting of (i) outstanding term loans of $30.0 million and (ii) subject customary conditions, additional term loans of up to an aggregate of $45.0 million, which are available through December 31, 2024, but have not yet been drawn. Borrowings under the Loan Agreement bear interest at an annual rate equal to the lesser of (x) the greater of (i) 8.05% and (ii) the prime rate as reported in the Wall Street Journal plus 4.55% and (y) 9.05%. The interest-only period ends on April 1, 2025. We may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to 1.5% prior to December 31, 2023. The Loan Agreement also provides for an end of term charge, payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. In connection with the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. In addition, the Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, as well as customary events of default. For additional information on the Hercules Loan Agreement, see Note 6. Long-term debt and Note 15. Subsequent events of our condensed consolidated financial statements.

Capital Resources and Funding Requirements

Our material cash requirements include expenses associated 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 continuing current clinical trials and conducting future clinical trials of BT5528, BT8009, BT7480 and BT1718;
- progress the preclinical and clinical development of BT7455 and BT7401;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to seek to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, commercial and scientific personnel;
- acquire or in-license other products and technologies;
- expand our infrastructure and facilities to accommodate our growing employee base, including adding equipment and infrastructure to support our research and development; and
- add operational, financial and management information systems and personnel, including personnel to support our research and development programs, and any future commercialization efforts.

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.

The following table summarizes our material contractual obligations as of June 30, 2022, and the effects that such obligations are expected to have on our liquidity and cash flows in future periods. For additional information, see Note 11. Commitments and continencies of our condensed consolidated financial statements.

	Payments due by period				
	Total	Less than 1 year	1 to 3 years	3 years to 5 years	More than 5 years
			(in thousands)		
Operating lease commitments (1)	$ 17,940	$ 3,858	$ 8,005	$ 5,666	$ 411
Debt obligations (2)	37,562	2,889	34,673	—	—
Total	$ 55,502	$ 6,747	$ 42,678	$ 5,666	$ 411

(1) Amounts reflect minimum payments due for our office and laboratory space leases. We have two office leases in Cambridge, U.K. under operating leases with lease terms through December 2026. We lease laboratory space in Lexington, Massachusetts under an operating lease that expires in December 2027.

(2) Amounts in table reflect the contractually required principal, interest, and the final payment under the Loan Agreement with Hercules as of June 30, 2022.

In the ordinary course of business, we enter into various agreements with contract research organizations to provide clinical trial services, with contract manufacturing organizations to provide clinical trial materials, and with vendors for preclinical research studies, synthetic chemistry and other services for operating purposes. These payments are not included in the table above since the contracts are generally cancelable with advanced written notice, generally with a notice period of 90 days or less. From the time of notice until termination, we are contractually obligated to make certain minimum payments to the vendors, based on the timing of the notification and the exact terms of the agreement.

Our arrangements with CRUK provide for additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $111.2 million, as well as royalty payments based on a single digit percentage on net sales of products developed. In addition, in November 2020, we entered into a settlement and license agreement with Pepscan Systems B.V., and its affiliates, or Pepscan, regarding our use of Pepscan's CLIPS peptide technology, which agreement provides for additional future milestone payments by us upon the achievement of development, regulatory and commercial milestones, with an aggregate total value of $92.4 million. We have not included future payments under this agreement in the table of contractual obligations above since these obligations are contingent upon future events. As of June 30, 2022, we were unable to estimate the timing or likelihood of achieving these milestones.

As of June 30, 2022, we had cash and cash equivalents of $372.8 million. We expect that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Quarterly Report on Form 10-Q.

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

- our ability to raise capital in light of the impacts of the ongoing COVID-19 pandemic, the Russia-Ukraine war, and other adverse global or geo-political events on the global financial markets;
- the scope, progress, results, and costs of drug discovery, preclinical development, laboratory testing, and clinical trials for the product candidates we may develop;

- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs, particularly in light of the ongoing COVID-19 pandemic;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, and distribution, for any product candidates for which we receive marketing approval;
- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.
- the success of our collaborations with Ionis, Genentech, DDF, AstraZeneca, Oxurion 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. Future debt financing, if available, may involve covenants restricting our operations or our ability to incur additional debt. Any debt or equity financing that we raise may contain terms that are not favorable to us or our shareholders. Both the ongoing COVID-19 pandemic and the rapidly evolving conflict between Russia and Ukraine have resulted in significant disruptions to global financial markets. If these disruptions persist or deepen, we could experience an inability to access additional capital, which could in the future negatively affect our 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.

Critical Accounting Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our condensed consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of our condensed consolidated 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. We base our estimates on historical experience, known trends and events and various other factors that we believe are

reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

Our critical accounting policies are described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Estimates" in our 2021 Annual Report, which was filed with the SEC on March 1, 2022. 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. Other than as disclosed in Note 2 to the condensed consolidated financial statements included in this Quarterly Report on Form 10-Q, there have been no significant changes to our critical accounting estimates from those described in our 2021 Annual Report.

Item 3. Quantitative and Qualitative Disclosure About Market Risk

Interest Rate Sensitivity

As of June 30, 2022, we had cash and cash equivalents of $372.8 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 and a 30-day deposit account. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We are subject to interest rate risk in connection with our borrowings under our credit facility with Hercules, which were $30.0 million as of June 30, 2022. Our outstanding indebtedness with Hercules bears interest at the greater of 8.85%, or 5.60% plus *The Wall Street Journal* prime rate. As of June 30, 2022, our outstanding indebtedness with Hercules bears interest at 10.35%. In July 2022, we entered into the second amendment to the loan agreement with Hercules which, among other things, capped the interest rate to a maximum of 9.05%. We currently do not engage in any interest rate hedging activity, and we have no intention to do so in the foreseeable future. Based on the current interest rate of the term loan and the scheduled payments thereunder, we do not believe a 1.0% increase in interest rates would have a material impact on our financial condition or results of operations.

Foreign Currency Exchange Risk

The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. The functional currency of Bicycle Therapeutics plc and Bicycle Therapeutics Inc. is the United States Dollar. The functional currency of Bicycle Therapeutics plc's wholly owned non-U.S. subsidiaries, BicycleTx Limited and BicycleRD Limited, is the British Pound Sterling, and the condensed consolidated financial statements are presented in United States Dollars. 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. We recorded foreign exchange losses of $0.7 million and $0.8 million for the three and six months ended June 30, 2022, respectively, and a foreign exchange gain of $6,000 and foreign exchange loss of $37,000 for the three and six months ended June 30, 2021, respectively.

For financial reporting purposes, our condensed consolidated financial statements have been translated into U.S. dollars. We translate the assets and liabilities of BicycleTx Limited and BicycleRD Limited into U.S. dollars 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 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 condensed consolidated statements of shareholders' equity as a component of accumulated other comprehensive income (loss).

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

Item 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

As required by Rule 13a-15(d) of the Exchange Act, our management, including our principal executive officer and our principal financial officer, conducted an evaluation of the internal control over financial reporting to determine whether any changes occurred during the period covered by this Quarterly Report on Form 10-Q that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting. Based on the evaluation of our disclosure controls and procedures at June 30, 2022, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting.

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended June 30, 2022 that have materially affected, or are 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. Other than as described below and in our 2021 Annual Report, we are not currently subject to any material legal proceedings.

European Patent Opposition Proceedings

In May 2017, we and Oxurion filed a notice of opposition in respect of Dyax Corp's European patent 1 854 477, which contained the following claim 1 (among other claims): "A composition comprising at least one peptide that inhibits plasma kallikrein for the use in the treatment of ophthalmic disorders in a patient in need thereof." Dyax Corp subsequently filed a Main Request to replace the granted claims with a claim scope which was limited to a specific consensus sequence. Oral Proceedings were held on October 15, 2019, and the European Patent Office issued a decision to restrict the claims of European patent 1 854 477 to specific peptides and to two specific ophthalmic disorders (namely macular oedema and retinal vein occlusion). Oxurion filed an appeal against this decision at the EPO Technical Board of Appeal to challenge any action from Dyax Corp to broaden the current claims, and the date for the hearing of this appeal has been scheduled for November 15, 2022.

Item 1A. Risk Factors.

Our operations and financial results are subject to various risks and uncertainties, including those described below. The following information about these risks and uncertainties, together with the other information appearing elsewhere in this Quarterly Report on Form 10-Q, and our 2021 Annual Report, filed with the Securities and Exchange Commission, or SEC, on March 1, 2022, including our consolidated financial statements and related notes thereto, should be carefully considered before a decision to invest in our ADSs. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. Additional risks that are currently unknown to us or that we currently believe to be immaterial may also impair our business. In these circumstances, the market price of our ADSs could decline and holders of our ADSs may lose all or part of their investment. We cannot provide assurance that any of the events discussed below will not occur.

Summary of Selected Risk Factors

Our business is subject to numerous risks and uncertainties, of which you should be aware before making a decision to invest in our ADSs. These risks and uncertainties include, among others, the following:

- We have a history of significant operating losses and expect to incur significant and increasing losses for the foreseeable future, and we may never achieve or maintain profitability.
- 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 one or more of our product discovery and development programs or commercialization efforts, if any.
- Raising additional capital may cause dilution to our existing shareholders or holders of our American Depositary Shares, or ADSs, restrict our operations or cause us to relinquish valuable rights.
- Our failure to comply with the covenants or payment obligations under our existing term loan facility with Hercules Capital, Inc., or Hercules, could result in an event of default, which may result in increased interest charges, acceleration of our repayment obligations or other actions by Hercules, any of which could negatively impact our business, financial condition and results of operations.
- We are substantially dependent on the success of our internal development programs and of our product candidates from our *Bicycle* Toxin Conjugate, or BTC, and *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™, programs, which may not successfully complete clinical trials, receive regulatory approval or be successfully commercialized.
- We are at an early stage in our development efforts, our product candidates and those of our collaborators represent a new category of medicines and may be subject to heightened regulatory scrutiny until they are established as a therapeutic modality.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.
- Our current or future product candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs, or IND, that could halt their clinical development, prevent their marketing approval, limit their commercial potential or result in significant negative consequences.

- We may be delayed or not be successful in our efforts to identify or discover additional product candidates.
- We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.
- We may seek designations for our product candidates with the U.S. Food and Drug Administration, or FDA, and other comparable regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, but there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.
- Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate.
- The market opportunities for any current or future product candidate we develop, if and when approved may be limited to those patients who are ineligible for established therapies or for whom prior therapies have failed, and may be small.
- 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.
- 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 commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, payors and others in the medical community.
- The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our product candidates, could limit our ability to market those products and decrease our ability to generate revenue.
- Healthcare legislative reform measures may have a negative impact on our business and results of operations.
- We rely on third parties, including independent clinical investigators and clinical research organizations, or CROs, to conduct and sponsor some of the clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for our product candidates.
- We intend to rely on third parties to manufacture product candidates, which increases the risk that we will not have sufficient quantities of such product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.
- If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to

ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.

- If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.
- 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 ongoing COVID-19 pandemic could impact our business.
- As a company based outside of the United States, we are subject to economic, political, regulatory and other risks associated with international operations.

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 net losses of $54.4 million and $34.1 million, for the six months ended June 30, 2022 and 2021, respectively. As of June 30, 2022, the Company had an accumulated deficit of $272.8 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 and working capital.

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

- continue to develop and conduct clinical trials with respect to our BTC and *Bicycle* TICA™ programs and our other pipeline programs;
- initiate and continue research, preclinical and clinical development efforts for any future product candidates;
- seek to discover and develop additional product candidates and further expand our clinical product pipeline;
- seek marketing and regulatory approvals for any product candidates that successfully complete clinical trials;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- expand our research and development infrastructure, including hiring and retaining additional personnel, such as clinical, quality control and scientific personnel;

- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize products for which we obtain marketing approval, if any;

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

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

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

Our revenue to date has been primarily generated from our research collaborations with Ionis Pharmaceuticals, Inc., or Ionis, Genentech Inc., or Genentech, Dementia Discovery Fund, or DDF, Sanofi (formerly Bioverativ Inc.), AstraZeneca AB, or AstraZeneca, and Oxurion NV, or Oxurion. There can be no assurance that we will generate revenue from our collaborations in the future.

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

Our limited operating history may make it difficult for holders of our ADSs or ordinary shares to evaluate the success of our business to date and to assess our future viability.

Our business commenced operations in 2009. Our operations to date have been limited to financing and staffing our company, developing our technology, conducting preclinical research and early-stage clinical trials for our product candidates and pursuing strategic collaborations to advance our product candidates. We have not yet demonstrated an ability to successfully conduct late-stage clinical trials, obtain marketing approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, any current or prospective holder of our ADSs or ordinary shares should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical-stage biopharmaceutical companies such as ours. 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 one or more of our product discovery and development programs or commercialization efforts, if any.

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

We will be required to expend significant funds in order to advance the development of the product candidates in our pipeline, as well as other product candidates we may seek to develop. In addition, while we may seek one or more collaborators for future development of our product candidates, we may not be able to enter into a collaboration for any of our product candidates for such indications on suitable terms, on a timely basis or at all. In any event, our existing cash will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of any of our product candidates. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. We do not have any committed external source of funds. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash and cash equivalents of $372.8 million as of June 30, 2022, will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Quarterly Report on Form 10-Q. 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.

While the long-term economic impact of either the COVID-19 pandemic or the conflict between Russia and Ukraine is difficult to assess or predict, each of these events has caused significant disruptions to the global financial markets and may reduce our ability to access capital, which could in the future negatively affect our liquidity.

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

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

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

We are party to a secured term loan facility with Hercules. As of June 30, 2022, our outstanding borrowings under this facility totaled $30.0 million. In connection with the Loan Agreement with Hercules, or the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control (as defined by the Loan Agreement), financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a material adverse effect as set forth in the Loan Agreement, cross acceleration to third-party indebtedness and certain events relating to bankruptcy or insolvency. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal and interest payments due, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement, including proceeding against the collateral securing such indebtedness. Such increased interest charges, accelerated repayment, proceedings against the collateral or other actions may have a negative impact on our business, financial condition and results of operations.

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

As of June 30, 2022, we had $30.0 million of borrowings outstanding under the Loan Agreement with Hercules. We could also in the future incur additional indebtedness pursuant to additional loan agreements.

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

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

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

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

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

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

Within our BTC programs, we are evaluating BT5528, a second-generation BTC that targets Ephrin type-A receptor 2, or EphA2 and carries a monomethyl auristatin E, or MMAE cytotoxin payload, in an ongoing, company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics and preliminary clinical activity in patients with advanced malignancies associated with EphA2 expression, and BT8009, a second-generation BTC targeting Nectin-4 and carries a MMAE cytotoxin payload, in a company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics and preliminary clinical activity in patients with Nectin-4 expressing advanced malignancies. In addition, BT1718, a BTC designed to target tumors that express MT1-MMP, is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial sponsored and fully funded by the Cancer Research UK Centre for Drug Development, or Cancer Research UK. Upon the completion of the Phase I/IIa clinical trial for BT1718, we have the right to obtain a license to the results of the clinical trial from Cancer Research UK upon the payment of a milestone, in cash and ordinary shares with a combined value in a mid-six digit dollar amount. If we do not exercise our right to obtain a license to the results of the clinical trial or we fail to obtain a license, our ability to continue development of BT1718 would be negatively impacted. We are also evaluating BT7480, which is a *Bicycle* TICA targeting Nectin-4 and agonizing CD137, in a Company-sponsored Phase I/II clinical trial to assess the safety and tolerability of BT7480, and to determine a recommended Phase II dose. There can be no assurance our BTCs or *Bicycle* TICAs will ever demonstrate

evidence of safety or effectiveness for any use or receive regulatory approval in the United States, the European Union, or any other country in any indication. Even if clinical trials show positive results, there can be no assurance that the U.S. Food and Drug Administration, or FDA, in the United States, European Commission, whose decision is based on a recommendation from the European Medicines Agency, or EMA, in Europe or similar regulatory authorities will approve our BTCs or any of our other product candidates for any given indication for several potential reasons, including the failure to follow Good Clinical Practice, or GCP, a negative assessment of the risks and benefits, insufficient product quality control and standardization, failure to have Good Manufacturing Practices, or GMP, compliant manufacturing facilities, or the failure to agree with regulatory authorities on clinical endpoints.

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

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

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

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

Bicycles represent a new therapeutic modality of peptide compounds intended to combine targeting abilities of antibodies with performance of small molecules. Our product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess. We have not yet succeeded and may never succeed in

demonstrating efficacy and safety for these or any other product candidates in clinical trials or in obtaining marketing approval thereafter.

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

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

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

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

Preclinical studies and clinical trials are long, expensive and unpredictable processes that can be subject to extensive delays. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. It may take several years and require significant expenditures to complete the preclinical studies and clinical trials necessary to commercialize a product candidate, and delays or failure are inherently unpredictable and can occur at any stage. The ongoing COVID-19 pandemic, including many jurisdictions' shelter-in-place, stay-at-home and similar restrictions, may also impact our and our collaboration partners' abilities to activate trial sites or enroll patients in clinical trials or to otherwise advance those clinical trials. Although some jurisdictions have relaxed such restrictions amid ongoing vaccination against the SARS-CoV-2 virus, previously relaxed restrictions may be re-instituted. COVID-19-related interruptions, or infection of site personnel or trial patients with COVID-19, may also reduce our or our collaboration partners' abilities to administer the investigational product to enrolled patients, present difficulties for enrolled patients to adhere to protocol-mandated visits and laboratory/diagnostic testing, increase the possibility of patient dropouts, or impact our and our suppliers' abilities to provide investigational product to trial sites, all of which could negatively impact the data we are able to obtain from our clinical trials and complicate regulatory review.

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

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

trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

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

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

Furthermore, we sometimes estimate for planning purposes the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies, clinical trials, the submission of regulatory filings or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the completion of an ongoing clinical trial, the initiation of other clinical programs, the receipt of marketing approval or a commercial launch of a product. The achievement of many of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions, which may cause the timing of achievement of the milestones to vary considerably from our estimates. If we fail to achieve milestones in the timeframes we expect, 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 BT5528, BT8009 and BT1718 is currently taking place outside of the United States. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of protocols related to our novel approach;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

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

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

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and preliminary or 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, our company-sponsored Phase I/II clinical trials of BT5528, BT8009 and BT7480 and the Phase I/IIa trial of BT1718 being conducted by Cancer Research UK are ongoing, and the interim results of these trials, including specific patient responses we have observed and disclosed, may not be replicated in the completed data sets or in future trials at global clinical trial sites in a later stage clinical trial conducted by us or our collaborators. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval.

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

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, our ability to enroll trial participants, including as a result of the ongoing COVID-19 pandemic and notwithstanding vaccination efforts, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

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

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

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

Undesirable or clinically unmanageable side effects could occur and cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. Results of our trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. If unacceptable side effect profiles arise, or side effects beyond those identified to date develop or worsen, as we continue development of our current or future product candidates, we, the FDA or comparable foreign regulatory authorities, the Institutional Review Boards, or IRBs, or independent ethics committees at the institutions in which our studies are conducted, or Safety Review Committees could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete the trial, cause delays in ongoing clinical trials, or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We may be required to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may prevent us from achieving or maintaining market acceptance of the affected product candidate and may harm our business, financial condition and prospects significantly.

Four of our product candidates are currently undergoing safety testing in the form of Phase I/IIa or Phase I/II clinical trials. None of our products have completed this testing to date. While our current and future product candidates will undergo safety testing to the extent possible and, where applicable, under such conditions discussed with regulatory authorities, not all adverse effects of drugs can be predicted or anticipated. Unforeseen side effects could arise either during clinical development or, if such side effects are rarer, after our products have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. So far, we have not demonstrated, and we cannot predict if ongoing or future clinical trials will demonstrate, that BT5528, BT8009, BT7480, 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 be delayed or may not be successful in our efforts to identify or discover additional product candidates.

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

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

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

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

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

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

- the impairment of our business reputation;

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

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

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

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

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

For example, we may seek a Breakthrough Therapy Designation for one or more of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, if preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control

regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

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

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

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

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

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

Obtaining marketing approvals and compliance with regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries outside of the United States. If we fail to comply with the regulatory requirements in international markets and/or receive applicable

marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

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

Following the result of a referendum in 2016, the United Kingdom left the European Union on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom was subject to a transition period until December 31, 2020, or the Transition Period, during which European Union rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, which outlines the future trading relationship between the United Kingdom and the European Union, was agreed upon in December 2020 and formally entered into force on May 1, 2021.

The potential impact on our results of operations and liquidity resulting from Brexit remains unclear. The actual effects of Brexit will depend upon many factors and significant uncertainty remains.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit has had, and will continue to have, a material impact on the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, Great Britain is no longer covered by the centralized procedures for obtaining European Union-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in Great Britain. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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

Brexit may influence the attractiveness of the United Kingdom as a place to conduct clinical trials. The European Union's regulatory environment for clinical trials has been harmonized as part of the Clinical Trials Regulation, which entered into application on January 31, 2022. The MHRA has opened a consultation on proposed revisions to U.K. clinical trials legislation, but it is currently unclear as to what extent the United Kingdom will seek to align its regulations with the European Union. Failure of the United Kingdom to closely align its regulations with the European Union may have an effect on the cost of conducting clinical trials in the United Kingdom as opposed to other countries and/or make it harder to seek a marketing authorization for our product candidates on the basis of clinical trials conducted in the United Kingdom. Pursuant to the Regulation, clinical trial data arising from a clinical trial site in a country outside of the EEA that is used in applications for clinical trial approval in the European Union must adhere to standards that are equivalent to those found in the Regulation. In the short term, there will be few changes to clinical trials that only have sites in the United Kingdom. The MHRA has confirmed that the sponsor of a clinical trial can be

based in the EEA for an initial period following Brexit. Further investigational medicinal products can be supplied directly from the European Union/EEA to either a trial site or a distribution hub in Great Britain. Such products will require oversight by the holder of a U.K. Manufacturing and Import Authorisation but do not currently require recertification. The United Kingdom is now a "third country" for the purpose of clinical trials that have sites in the EEA. For such trials the sponsor/legal representative must be based in the EEA, and the trial must be registered on the EU Clinical Trials Register (including data on sites outside of the EEA).

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

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

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

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. Varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Due to the ongoing COVID-19 pandemic, it is possible that we could experience delays in the timing of our interactions with regulatory authorities due to absenteeism by governmental employees, inability to conduct planned physical inspections related to regulatory approval, or the diversion of regulatory authority efforts and attention to approval of other therapeutics or other activities related to COVID-19, which could delay anticipated approval decisions and otherwise delay or limit our ability to make planned regulatory submissions or obtain new product approvals. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Any marketing approval we ultimately obtain, if any, may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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

regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

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

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

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

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

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

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

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

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

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

Cancer therapies are sometimes characterized as first-line, second-line, third-line or later-line therapies, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy, immunotherapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We may initially seek approval of BT5528, BT8009, BT7480, 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, submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current Good Manufacturing Practice, or cGMP, and Good Clinical Practice, or GCP, for any clinical trials that we conduct post-approval, and prohibitions on the promotion of an approved product for uses not included in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products.

Later discovery of previously unknown problems with any approved candidate, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

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

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

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

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

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

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

There are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. These treatments consist both of small molecule drug products, such as traditional chemotherapy, as well as novel immunotherapies. For example, a number of multinational companies as well as large biotechnology companies, are developing programs for the targets that we are exploring for our BTC programs, including Seagen, Inc, which has a marketed Nectin-4 antibody-drug conjugate. Furthermore, many companies are developing programs for CD137 or CD137 bi-specific antibodies.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe effects, are more convenient, have a broader label, are marketed more effectively, are reimbursed or are less expensive than any products that we may develop. Our competitors also may obtain FDA, European or other marketing approval for their products more rapidly than we may obtain

approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Even if the product candidates we develop achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

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

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

- the U.S. federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the 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, other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;

- U.S. 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

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

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

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive share options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, significant administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, imprisonment, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and imprisonment, any of which could adversely affect our ability to operate our business and our financial results. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Healthcare legislative reform measures may have a negative impact on our business and results of operations.

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

Among policy makers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, the 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.

There have been executive, judicial and Congressional challenges to certain aspects of ACA. For example, former President Trump signed several Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directed federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices.

Concurrently, Congress considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or the Tax Act, included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." On June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013, and due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2031 unless additional Congressional action is taken. However, pursuant to certain COVID-19 relief legislation these Medicare sequester reductions have been suspended from May 1, 2020 through March 31, 2022. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. 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, Presidential executive orders and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the former Trump administration used several means to propose or implement drug pricing reform, including through

federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, former President Trump signed several Executive Orders aimed at lowering drug pricing that seek to implement several of the administration's proposals. In response, the FDA concurrently released a final rule guidance in September 2020, providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all U.S. states and territories for a seven-year period and was scheduled to begin on January 1, 2021 and end on December 31, 2027. As a result of litigation challenging the Most Favored Nation model, on December 27, 2021, CMS published a final rule that rescinded the MFN model interim final rule. Additionally, on November 20, 2020, the Department of Health and Human Services finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers the implementation of which have also been delayed until January 1, 2023. In July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. Similarly, individual states in the United States have also become increasingly aggressive in passing legislation and implementing 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.

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

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

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

Our operations are subject to anti-corruption laws, including the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us, our employees and our intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties

whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

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

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

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

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

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

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

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

Risks Related to Our Business and Our International Operations

The ongoing COVID-19 pandemic could impact our business.

Uncertainty caused by the ongoing COVID-19 pandemic and related government and private sector responsive actions have impacted and may continue to impact the global economy and financial markets. Such global macroeconomic effects of the COVID-19 pandemic may reduce our ability to access capital and therefore could negatively affect our liquidity in the future. Despite the increased availability of COVID-19 vaccines, due to the continuing and evolving nature of the COVID-19 pandemic and the potential for periods of increases in case numbers and the emergence and spread of virus variants in communities in which we and our customers operate, it is impossible to predict all the effects and the ultimate impact of the COVID-19 pandemic, as the situation continues to evolve.

Our business could be adversely affected by the effects of the ongoing COVID-19 pandemic in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations. The COVID-19 pandemic has also disrupted the global supply chain, and any impacts to clinical supplies of our product candidates could materially adversely affect our operations, financial condition, operating results, and ability to execute and capitalize on our strategies as well as cause significant disruption in the operations and business of third-party manufacturers, CROs, other services providers, and collaborators with whom we conduct business.

In March 2020, our global non-laboratory based workforce transitioned to working remotely. We have since implemented plans that allow our non-laboratory based employees to return to the office, however, many non-laboratory based employees continue to work remotely. We have also cancelled, postponed or limited company-sponsored events, including employee attendance at industry events and non-essential in person work-related meetings. These measures could negatively impact our marketing efforts, challenge our ability to enter into collaboration and partnership agreements in a timely manner, slow down our recruiting efforts, or create operational or other challenges, including decreased productivity, any of which could harm our business. In addition, prolonged remote work could result in employee isolation and burnout, leading to operational disruption and unexpected attrition. The increase in remote working for employees, vendors, or contractors may also result in increased consumer privacy, IT security, and fraud concerns.

Additionally, we may experience disruptions if our employees become ill, despite the availability of vaccines, and are unable to perform their duties. The effects of any of our current or future work-from-home policies may negatively impact productivity, disrupt our business and delay our clinical programs and timelines.

In addition, our ability to conduct clinical trials has been and may continue to be affected by the COVID-19 pandemic. While patient enrollment in our clinical trials remains underway, clinical site initiation and patient enrollment, both internationally and domestically, may be suspended or delayed due to prioritization of hospital resources toward the COVID-19 pandemic, including vaccination efforts, or new or renewed shelter-in-place or stay-at-home orders. Some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may adversely impact our future clinical trial operations.

While it is not possible at this time to estimate the full impact that the COVID-19 pandemic could have on worldwide economic activity and our business in particular, the continued spread of COVID-19 and the measures, and the market participant's perception of and responses to the measures, taken by governments, businesses and other organizations in response to COVID-19 could materially and adversely impact our business, results of operations and financial condition. In addition, to the extent COVID-19 could materially and adversely impact our business, results of operations and financial condition, it may also have the effect of heightening many of the other risks and uncertainties described in this "Risk Factors" section which may materially and adversely affect our business, financial condition, operating results, and ability to execute and capitalize on our strategies.

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

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

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

- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, natural disasters, including earthquakes, typhoons, floods and fires, or public health crises, including outbreaks of COVID-19 or H1N1 flu.

Any or all of these factors could have a material adverse impact on our business, financial condition and results of operations. Moreover, global instability increased after Russia invaded Ukraine in February 2022. In response to the invasion, North Atlantic Treaty Organization, or NATO, has deployed additional military forces to Eastern Europe, including to Lithuania, and the U.K., the European Union and the United States implemented certain sanctions against Russia. The invasion of Ukraine and the retaliatory measures that have been taken, or could be taken in the future, by the United States, NATO, and other countries have created global security concerns that could result in a regional conflict and otherwise have a lasting impact on regional and global economies, any or all of which could disrupt our supply chain and adversely affect our ability to conduct ongoing and future clinical trials of our product candidates. In addition, the conflict has had significant ramifications on global financial markets, which may adversely impact our ability to raise capital in the future on favorable terms or at all.

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

The collection and use of personal data (including health-related personal data) in the EEA, is governed by the provisions of the EU General Data Protection Regulation 2016/679, or GDPR, which became effective and enforceable across all then-current member states of the EEA on May 25, 2018. Also, notwithstanding the United Kingdom's withdrawal from the European Union, the data protection obligations of the GDPR continue to apply to United Kingdom-related processing of personal data in substantially unvaried form under the so-called "UK GDPR" (i.e., the GDPR as it continues to form part of law in the United Kingdom by virtue of section 3 of the European Union (Withdrawal) Act 2018, as amended (including by the various Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations)). Accordingly, references in this section to the GDPR are also deemed to be references to the UK GDPR in the context of the United Kingdom, unless the context requires otherwise.

The GDPR also provides that EEA member states may make their own national laws and regulations to introduce specific requirements related to the processing of "special categories of personal data," including personal data related to health, biometric data used for unique identification purposes and genetic information, as well as personal data related to criminal offenses or convictions. In the United Kingdom, the Data Protection Act 2018 complements the UK GDPR in this regard. This may lead to greater divergence in the application, interpretation and enforcement of the law that applies to the processing of personal data across the EEA and/or United Kingdom, compliance with which, as and where applicable, may increase our costs and could increase our overall compliance risk. Such country-specific regulations could also limit our ability to collect, use and share data in the context of our EEA and/or UK operations, and/or could cause our compliance costs to increase, ultimately having an adverse impact on our business and harming our business and financial condition.

The GDPR sets out a number of requirements that must be complied with when handling personal data (i.e., data relating to an identified or identifiable living individual) including: the obligation to appoint a data protection officer in certain circumstances; increased accountability and record-keeping obligations; increased transparency obligations for data controllers; onerous obligations on service providers who process personal data simply on behalf of others; the obligation to carry out so-called data protection impact assessments in certain circumstances; obligations to comply with data subjects' exercise of an increased set of rights in certain circumstances (such as rights for individuals to be "forgotten," rights to data portability, rights to object, etc., together with express rights to seek legal remedies in the event the individual believes his or her rights have been violated); a heightened and more-codified standard of data subject consent; and the obligation to notify certain significant personal data breaches to the relevant supervisory

authority(ies) and affected individuals. In addition, the GDPR materially expanded the definition of what is expressly provided to constitute personal data (including, for example, by expressly clarifying that the GDPR applies to "pseudonymized" (i.e., key-coded) data, which is often processed by sponsors in the context of clinical trials where identification of underlying subjects is not required).

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

In addition, European data protection laws, such as the GDPR, prohibit the transfer of personal data from the EEA, United Kingdom and Switzerland to the United States and other countries, known as "third countries," in respect of which there is no "adequacy decision" issued under the GDPR unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. One of the primary safeguards used for transfers of personal data to the United States was the EU-U.S. Privacy Shield framework administered by the U.S. Department of Commerce. On July 16, 2020, the Court of Justice of the European Union, or CJEU, in a decision known as "Schrems II," invalidated the EU-U.S. Privacy Shield, under which personal data could be transferred from the EEA and the United Kingdom to U.S. entities that had self-certified under the Privacy Shield. To align with the CJEU's decision in respect of the EU-U.S. Privacy Shield, the U.K. government similarly confirmed that use of the EU-U.S. Privacy Shield was not a valid mechanism for lawful personal data transfers from the United Kingdom to the United States under the UK GDPR, and the Swiss Federal Data Protection and Information Commissioner announced that the Swiss-U.S. Privacy Shield regime was also inadequate for the purposes of personal data transfers from Switzerland to the U.S. entities who had self-certified under the Swiss Privacy Shield.

The Schrems II decision also cast doubt on the ability to use one of the primary alternatives to the EU-U.S. Privacy Shield and Swiss-U.S. Privacy Shield, namely, the European Commission's Standard Contractual Clauses, to lawfully transfer personal data to the United States and other third countries.

On June 4, 2021, the European Commission published new versions of the Standard Contractual Clauses. These had to be used for all new transfers of personal data from the EEA to third countries starting September 27, 2021, and all existing transfers of personal data from the EEA to third countries relying on the existing versions of the Standard Contractual Clauses must be replaced by December 27, 2022. Furthermore, the UK government has published an International Data Transfer Agreement, or IDTA, and an addendum to the European Commission's Standard Contractual Clauses, each of which serve as the approved-form standard protection clauses that can be used as a transfer mechanism for data transfers to third countries under the UK GDPR. These new UK GDPR-specific transfer mechanisms came into force on March 21, 2022, need to be used for all new contracts and transfers from September 21, 2022, and used in all new and existing contracts and transfers from March 21, 2024 onwards. The implementation of these new European Commission's Standard Contractual Clauses and new UK GDPR-specific transfer mechanisms, together, Transfer Mechanisms, will necessitate significant contractual overhaul of our data transfer arrangements with customers, sub-processors and vendors.

Use of both the existing and new forms of these Transfer Mechanisms must, following the Schrems II decision, be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals, and supplementary technical, organizational and/or contractual measures may need to be put in place.

At present, there are few if any viable alternatives to these Transfer Mechanisms for many transfers, and there remains some uncertainty with respect to the nature and efficacy of any supplementary measures to effectively ensure an adequate level of protection of transferred personal data. As such, our transfers of personal data to the United States and other third countries may not comply with European data protection law and may increase our exposure to the GDPR's heightened sanctions for violations of its cross-border data transfer restrictions, including fines of up to 4% of annual global revenue or €20.0 million (and/or in respect of the UK GDPR, £17.5 million), whichever is higher, and injunctions against transfers. As supervisory authorities issue further guidance on personal data export mechanisms, including

circumstances where these Transfer Mechanisms can and cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate and/or engage providers and/or otherwise transfer personal data, it could affect the manner in which we receive and/or provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results and generally increase compliance risk. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of operating our business.

Furthermore, following Brexit, the relationship between the United Kingdom and the EEA in relation to certain aspects of data protection law remains somewhat uncertain. On June 28, 2021, the European Commission issued an adequacy decision under the GDPR which allows transfers (other than those carried out for the purposes of United Kingdom immigration control) of personal data from the EEA to the United Kingdom to continue without restriction for a period of four years ending June 27, 2025. After that period, the adequacy decision may be renewed, however, only if the United Kingdom continues to ensure an adequate level of data protection. During these four years, the European Commission will continue to monitor the legal situation in the United Kingdom and could intervene at any point if the United Kingdom deviates from the level of data protection in place at the time of issuance of the adequacy decision. If the adequacy decision is withdrawn or not renewed, transfers of personal data from the EEA to the United Kingdom will require a valid 'transfer mechanism' and we may be required to implement new processes and put new agreements in place, such as the European Commission's Standard Contractual Clauses, to enable transfers of personal data from the EEA to the United Kingdom to continue.

Additionally, as noted above, the United Kingdom has transposed the GDPR into United Kingdom domestic law by way of the UK GDPR with effect from January 2021, which could expose us to two parallel regimes, each of which potentially authorizes similar fines and other potentially divergent enforcement actions for certain violations (each regime separately having the ability to fine up to the higher of €20.0 million/£17.5 million or 4% of an undertaking's total global annual turnover). Also, following the expiry of the post-Brexit transitional arrangements, the U.K. Information Commissioner's Office is not able to be our "lead supervisory authority" in respect of any "cross border processing" for the purposes of the GDPR. For so long as we are unable to, and/or do not, designate a lead supervisory authority in an EEA member state we are not able to benefit from the GDPR's "one stop shop" mechanism. Amongst other things, this would mean that, in the event of a violation of the GDPR affecting data subjects across the United Kingdom and the EEA, we could be investigated by, and ultimately fined by the United Kingdom Information Commissioner's Office and the supervisory authority in each and every EEA member state where data subjects have been affected by such violation. Other countries have also passed or are considering passing laws requiring local data residency and/or restricting the international transfer of data.

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

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union and Asia that are billed in U.S. dollars. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place. Any fluctuation in the exchange rate of these foreign currencies may negatively impact our business, financial condition and operating results. Global economic events, such as the ongoing COVID-19 pandemic, have and may continue to significantly impact local economies and the foreign exchange markets, which may increase the risks associated with sales denominated in foreign currencies.

Risks Related to Our Dependence on Third Parties

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

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

Under our collaborations with AstraZeneca, DDF, Genentech, Ionis, and Oxurion, we are responsible for identifying and optimizing *Bicycle* peptides related to collaboration targets and our collaborators are responsible for further development and product commercialization after we complete the defined research screening and compound optimization. In addition, Cancer Research UK is sponsoring and funding a Phase I/IIa clinical trial of BT1718, in patients with advanced solid tumors, and will sponsor and fund development of BT7401 from current preclinical studies through the completion of a Phase IIa trial in patients with advanced solid tumors. We depend on these collaborators to develop and, where applicable, commercialize products based on *Bicycle* peptides, and the success of their efforts directly impacts the milestones and royalties we will receive. We cannot provide assurance that our collaborators will be successful in or that they will devote sufficient resources to the development or commercialization of their products. If our current or future collaboration and commercialization partners do not perform in the manner we expect or fail to fulfill their responsibilities in a timely manner, or at all, if our agreements with them terminate or if the quality or accuracy of the clinical data they obtain is compromised, the clinical development, regulatory approval and commercialization efforts related to their and our product candidates and products could be delayed or terminated and it could become necessary for us to assume the responsibility at our own expense for the clinical development of such product candidates.

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

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

- the collaborations may not result in product candidates to develop and/or preclinical studies or clinical trials conducted as part of the collaborations may not be successful;

- product candidates developed with collaborators may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to stop commercialization of our product candidates;

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

- that the ongoing COVID-19 pandemic and other adverse global economic conditions could materially affect our operations as well as causing significant disruption in the operations and business of our collaborators and the third-party manufacturers, CROs and other service providers that we and/or our collaborators conduct business with; and

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

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

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

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

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

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

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

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

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

For example, we were previously involved in litigation with Pepscan Systems B.V., and its affiliates, or Pepscan, related to a non-exclusive patent license agreement that our subsidiary, BicycleRD Limited, or BicycleRD, entered into with Pepscan in 2009.

Conflicts with our development and commercialization collaborators or licensors could materially adversely affect our business, financial condition or results of operations and future growth prospects. If we are unable to prevail against these challenges, our intellectual property estate may be materially harmed, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections.

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

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

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

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

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

able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

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

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

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

In order to conduct clinical trials of product candidates, we will need to have them manufactured in potentially large quantities. Our third-party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities and at any other time. For example, ongoing data on the stability of our product candidates may shorten the expiry of our product candidates and lead to clinical trial material supply shortages, and potentially clinical trial delays. Additionally, our manufacturers may experience delays as a result of impacts due to the ongoing COVID-19 pandemic or the Russia-Ukraine war. If our third-party manufacturers are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed or infeasible, and regulatory approval or commercial launch of that product candidate may be delayed or not obtained, which could significantly harm our business.

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

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

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

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

Third-party manufacturers may not be able to comply with cGMP requirements or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and/or criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. In addition, some of the product candidates we intend to develop, including BT5528, BT8009, and 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, including as a result of the impacts of the ongoing COVID-19 pandemic on the global workforce and manufacturing operations, we likely would experience delays in advancing these tests and trials while we identify and qualify replacement suppliers or manufacturers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our product candidates or the substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively.

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

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

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

proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

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

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

Risks Related to Our Intellectual Property

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on research, manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. As of June 30, 2022, our patent portfolio included four patent families directed to novel scaffolds, 16 patent families directed to our platform technology, 89 patent families directed to bicyclic peptides and related conjugates, and 12 patent families directed to methods of making or using certain bicyclic peptide conjugates for treating various indications. As of June 30, 2022, our trademark portfolio consisted of 59 trademark registrations across 4 territories (the United Kingdom, European Union, United States and Japan) as well as a number of pending applications for new trademarks.

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 United States Patent and Trademark Office (USPTO), or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. An adverse determination in any of the foregoing proceedings could result in the revocation or cancellation of, or amendment to, our patents in such a way that they no longer cover our products or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our products and product candidates. Such a loss of patent protection may materially harm our intellectual property estate, which would impair our ability to establish competitive barriers to entry in the form of intellectual property protections.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology and pharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. While we intend to protect our intellectual property rights in major markets for our products, we cannot

ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

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

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

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we were previously party to protracted litigation with Pepscan, which we settled in 2020. We may become party to, or be threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our products candidates, including interference and post-grant proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the composition, use or manufacture of our product candidates. We cannot guarantee that any of our patent searches or analyses including, but not limited to, the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on intellectual property rights that exist now or arise in the future. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use or manufacture. The scope of protection afforded by a patent is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

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

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

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

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

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

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

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

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

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

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

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

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

Our trademarks or trade names may be challenged, infringed, circumvented or declared invalid, generic or determined to be infringing on other marks. We rely on both registration and common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive objections. Although we would be given an opportunity to respond to those objections, we may be unable to overcome such objections. In addition, in the USPTO and in comparable Intellectual Property Offices in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings have been and may in the future be filed against our trademarks, and our trademarks may not survive such proceedings. For example, our U.K. trademark application for "TICA" was successfully opposed in the U.K., Japan and the European Union for the majority of goods and services for which we originally applied, and we have abandoned our trademark application for "TICA" in the United States as a result. 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

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

We utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks, the confidentiality and the availability and integrity of our data. In addition, due to the ongoing COVID-19 pandemic, we have enabled our non-laboratory-based employees to work remotely, which may make us more vulnerable to cyberattacks. We have been the target of cyber-attacks in the past. For example, in 2019 we were targeted in a phishing incident, which included email accounts being accessed by unauthorized third parties. Promptly after discovery, we performed third-party investigations and as there was no evidence of access or acquisition of any personal information as a result of the incident, we believe that no further action was required under U.K, EU (GDPR) or U.S. federal or state law. There was no material impact to our business or financial condition. While we believe we responded appropriately, including implementing remedial measures to stop the cyber-attacks and with the goal of preventing similar ones in the future, there can be no assurance that we will be successful in these remedial and preventative measures or successfully

mitigating the effects of future cyber-attacks. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to respond appropriately to such breaches and to implement further data protection measures. We are aware that some public companies have recently received Civil Investigative Demands from the Federal Trade Commission, or FTC, requesting information and documents following disclosures of privacy or security incidents in SEC filings. The FTC has taken the position that inadequately disclosing privacy and security incidents in SEC filings may be a deceptive business practice, and the FTC has relied on SEC filings as a launching pad for incident investigations even where the filings were not inadequate. We cannot be certain that the FTC will consider our disclosure adequate or that the FTC will not rely on our disclosure to initiate an incident investigation.

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

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

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

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

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

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

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (1) FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities; (2) manufacturing standards; (3) federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities; and (4) laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, bribery and other abusive practices.

These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee or collaborator misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. Further, because of the work-from-home policies we implemented due to COVID-19, information that is normally protected, including company confidential information, may be less secure. We have adopted a code of conduct and business ethics to which all of our employees must adhere, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations.

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

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

Risks Related to Ownership of Our Securities

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

The market price of our ADSs is highly volatile. Since our initial public offering, or IPO, in May 2019, through August 1, 2022, the trading price of our ADSs has ranged from $6.24 to $62.08. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, holders of our ADSs may not be able to sell their ADSs at or above price at which they purchased their ADSs. The market price for our ADSs may be influenced by many factors, including:

- adverse results or delays in preclinical studies or clinical trials;

- reports of adverse events in products similar or perceived to be similar to those we are developing or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us to identify additional product candidates for our pipeline;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- changes in the structure of healthcare payment systems;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial projections we may provide to the public;
- failure by us to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partners or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- sales of our ADSs or ordinary shares by us or our shareholders in the future; and
- the trading volume of our ADSs.

The global economy, including credit and financial markets, has experienced extreme volatility and disruptions, including, among other things, severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, supply chain shortages, increases in inflation rates, higher interest rates and uncertainty about economic stability. For example, the COVID-19 pandemic resulted in widespread unemployment, economic slowdown and extreme volatility in the capital markets. Similarly, the ongoing

war between Russia and Ukraine has created extreme volatility in the global capital markets and is expected to have further global economic consequences, including disruptions of the global supply chain and energy markets. Any such volatility and disruptions may have adverse consequences on us or the third parties on whom we rely. If the equity and credit markets continue to deteriorate, it may make any necessary debt or equity financings more difficult to obtain in a timely manner or on favorable terms, more costly or more dilutive. Increased inflation rates can adversely affect us by increasing our costs, including labor and employee benefit costs. In addition, higher inflation and macro turmoil and uncertainty could also adversely affect our buyers and sellers, which could reduce demand for our products. These factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

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.

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

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

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

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be declared and paid. Therefore, we must have distributable profits before declaring and paying a dividend. In addition, the terms of our indebtedness with Hercules prohibit us from paying dividends. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs will be a holder's sole source of gains for the foreseeable future, and holders will suffer a loss on their investment if they are unable to sell their ADSs at or above the original purchase price.

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

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

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

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether U.K. courts would entertain original actions brought in the United Kingdom against us or our directors or senior

management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

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

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

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

Each Ten Percent Shareholder should also be aware that because our group includes a U.S. subsidiary, certain of our non-U.S. subsidiaries will be treated as CFCs (regardless of whether or not we are treated as a CFC). We cannot provide any assurances that we will assist shareholders in determining whether we are or any of our non-U.S. subsidiaries is treated as CFC or whether any shareholder is treated as a Ten Percent Shareholder with respect to any such CFC or furnish to any shareholders information that may be necessary to comply with reporting and tax paying obligations. The Internal Revenue Service has provided limited guidance on situations in which investors may rely on publicly available information to comply with their reporting and tax paying obligations with respect to foreign-controlled CFCs.

The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. U.S. Holders (as defined below) should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. A "U.S Holder" is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

- an individual who is a citizen or individual resident of the United States;
- a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

- a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election in effect to be treated as a U.S. person under applicable U.S. Treasury Regulations.

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

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

Based on our analysis of our income, assets, activities and market capitalization, we believe that we were not a PFIC in the 2021 taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. As a result, there can be no assurance regarding if we will be PFIC or will not be a PFIC in the future. In addition, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into and our corporate structure.

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

As an entity incorporated and tax resident in the United Kingdom, we are subject to U.K. corporate taxation. Due to the nature of our business, we have generated losses since inception and therefore have not paid any U.K. corporation tax. Subject to numerous utilization criteria and restrictions (including the Corporate Income Loss Restriction and the Corporate Capital Loss Restriction that, broadly, restrict the amount of carried forward losses that can be utilized to 50% of group profits or gains arising above £5.0 million per tax year, we expect losses to be eligible for carry forward and utilization against future operating profits. In addition, if we were to have a major change in the nature of the conduct or the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a group that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, under the SME Program, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carry them forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these SME Program tax credit cash rebate claims. We may not be able to continue to claim payable research and development tax credits in the future if we cease to qualify as a small or medium-sized enterprise under the SME Program, based on size criteria concerning employee headcount, turnover and gross assets. The U.K. Finance Act 2021 introduced a cap on payable credit claims under the SME Program in excess of £20,000 with effect from April 2021 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception which prevents the cap from applying. That exception requires the company to be creating, taking steps to create or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. If such exception does not apply, this could restrict the amount of payable credit that we claim. Additionally, on October 27, 2021, the U.K. Government announced its intention to introduce (following consultation) further restrictions to the U.K. research and development relief programs,

refocusing such programs towards innovation in the United Kingdom. A subsequent U.K. Government report proposed restrictions which (if enacted) could, in particular, limit our ability to make claims under the existing relief programs in respect of (i) research and development subcontracted to a third party (and, in the case of the RDEC Program, in respect of contributions made to a qualifying body) where such third party (or qualifying body) performs the work outside of the United Kingdom, and (ii) expenditure incurred on externally provided workers that are not paid through U.K. payroll. These and other potential future changes to the U.K. research and development tax relief programs may be made which mean we no longer qualify or may impact on the extent to which we can make claims.

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% by giving an additional tax deduction. 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 eligible for this tax deduction. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term rate of corporation tax lower than the statutory rate to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax relief programs 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. This may impact our ongoing requirement for investment and the timeframes within which additional investment is required.

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

The tax treatment of the company is, and our ADSs and ordinary shares are, subject to changes in tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, as well as tax policy initiatives and reforms related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project (including "BEPS 2.0"), the European Commission's state aid investigations and other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid, or the stamp duty or stamp duty reserve tax treatment of our ADSs or ordinary shares. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

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

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

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

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

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

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

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act 2006, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. The principal differences include the following:

- under English law and our articles of association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings;
- under English law, the number of shares determines the number of votes a holder may cast only on a poll. However, that the voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank;
- under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise;
- under English law and our articles of association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the articles of association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other significant transactions;
- in the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, if we were to be subject to the Takeover Code, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a "squeeze out" to obtain 100% control of us. Accordingly, acceptances of 90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting, as well as the sanction of the U.K. court;

- under English law and our articles of association, shareholders and other persons whom we know or have reasonable cause to believe are, or have been, interested in our shares may be required to disclose information regarding their interests in our shares upon our request, and the failure to provide the required information could result in the loss or restriction of rights attaching to the shares, including prohibitions on certain transfers of the shares, withholding of dividends and loss of voting rights. Comparable provisions generally do not exist under U.S. law; and
- the quorum requirement for a shareholders' meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder that is a corporation, represented by a duly authorized officer. Under U.S. law, a majority of the shares eligible to vote must generally be present (in person or by proxy) at a shareholders' meeting in order to constitute a quorum. The minimum number of shares required for a quorum can be reduced pursuant to a provision in a company's certificate of incorporation or bylaws, but typically not below one-third of the shares entitled to vote at the meeting.

General Risks

As a smaller reporting company, we are subject to scaled disclosure requirements that may make it more challenging for investors to analyze our results of operations and financial prospects.

We were a large accelerated filer for the year ended December 31, 2021. Based on the market value of our ADSs held by non-affiliates as of June 30, 2022, we expect to be a "smaller reporting company" and "non-accelerated filer" on December 31, 2022. A company that determines that it qualifies as a smaller reporting company as of the end of its second fiscal quarter may provide scaled disclosure immediately in its next quarterly report rather than wait until the first quarter of the next year. Specifically, as a "smaller reporting company," we (i) are able to provide simplified executive compensation disclosures in our filings, (ii) are exempt from the provisions of Section 404(b) of the Sarbanes-Oxley Act requiring that independent registered public accounting firms provide an attestation report on the effectiveness of internal control over financial reporting, and (iii) have certain other decreased disclosure obligations in our filings with the SEC, including being required to provide only two years of audited financial statements in our annual reports. Consequently, it may be more challenging for investors to analyze our results of operations and financial prospects. We will remain a smaller reporting company if we have either (i) a public float of less than $250 million held by non-affiliates as of the last business day of the second quarter of our then current fiscal year or (ii) annual revenues of less than $100 million during such recently completed fiscal year with less than $700 million in public float as of the last business day of the second quarter of such fiscal year.

We incur and will continue to incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company we will continue to incur significant legal, accounting, and other expenses that we did not incur as a private company, including costs resulting from public company reporting obligations under the Securities Act, or the Securities Exchange Act of 1934, as amended, or the Exchange Act, and regulations regarding corporate governance practices. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the results of the SEC, the Nasdaq listing requirements, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We have hired, and may continue to hire, additional accounting, finance and other personnel in connection with our becoming, and our efforts to comply with the requirements of being, a public company, and our management and other personnel devote a substantial amount of time towards maintaining compliance with these requirements. These requirements have increased our legal and financial compliance costs and have made and will make some activities more time-consuming and costly. We continuously evaluate the rules and regulations applicable to us as a public company and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These reporting requirements, rules and regulations, coupled with the increase in potential litigation exposure associated with being a public company, could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees or to serve as executive officers, or to obtain certain types of insurance, or including directors' and officers' insurance, on acceptable terms.

As a public company and large accelerated filer for the year ended December 31, 2021, we were required to provide management's attestation on internal controls pursuant to Sarbanes-Oxley Act Section 404. To achieve compliance with Sarbanes-Oxley Act Section 404, we engaged in a process to enhance our documentation and evaluate our internal control over financial reporting, which was both costly and challenging. However, as we requalify as a smaller reporting company for the year ended December 31, 2022, we will no longer be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm in our Annual Report on Form 10-K.

If these compliance activities divert the attention of our management and personnel from other business matters, they could have a material adverse effect on our business, financial condition, results of operations, ADS price and prospects. The substantial costs associated with being a public company and complying with applicable rules and regulations will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business. Additionally, being a public company has made it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage.

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. Our management is required to assess the effectiveness of our controls over financial reporting annually. Pursuant to Section 404, we are also 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 at such time when we are no longer a smaller reporting company. 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 disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

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

We could be subject to securities class action litigation.

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

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

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

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

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

The trading market for our ADSs depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. Although we have obtained research coverage from certain analysts, there can be no assurance that analysts will continue to cover us or provide favorable coverage. If one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

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

Not Applicable.

Item 3. Defaults Upon Senior Securities.

Not Applicable.

Item 4. Mine Safety Disclosures.

Not Applicable.

Item 5. Other Information.

Not Applicable.

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).
10.1*†	First Amendment to the Discovery Collaboration and License Agreement, dated November 5, 2021, by and between Genentech, Inc. and BicycleTx Limited
10.2*†	Second Amendment to the Discovery Collaboration and License Agreement, dated June 27, 2022, by and between Genentech, Inc. and BicycleTx Limited
10.3	Second Amendment to Loan and Security Agreement, dated as of July 15, 2022, by and among Bicycle Therapeutics plc and each of its Subsidiaries, the Lenders and Hercules Capital, Inc., as Agent (incorporated by reference to Exhibit 10.1 to the Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on July 15, 2022).
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.

Exhibit Number	Description
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 – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File – the cover page XBRL tags are embedded within the Inline XBRL document (included in Exhibit 101)

* Filed herewith.

† Pursuant to Item 601(b)(10)(iv) of Regulation S-K, certain portions of this exhibit have been omitted because the identified information is not material and is the type that the registrant treats as private or confidential.

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 4, 2022

By: /s/ Kevin Lee

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

(Principal Executive Officer)

Date: August 4, 2022

By: /s/ Lee Kalowski

Lee Kalowski, MBA
Chief Financial Officer and President

(Principal Financial and Accounting Officer)

First Amendment
to the
Discovery Collaboration and License Agreement

between

Genentech, Inc.
1 DNA Way, South San Francisco, California 94080, US
("Genentech")

on the one hand

and

BicycleTx Limited

B900 Babraham Research Campus, Cambridge, England CB22 3AT

("BicycleTx ")

Whereas, Genentech and BicycleTx entered into a certain discovery collaboration and license agreement effective February 21, 2020 (the "**Agreement**"); and

Whereas, Genentech and BicycleTx now desire to amend the Agreement in accordance with this first amendment (the "**First Amendment**").

Now therefore, in consideration of the mutual covenants and promises contained in this First Amendment and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto, intending to be legally bound, do hereby agree as follows:

1. This First Amendment is effective as of February 21, 2020.

2. All capitalised terms not defined in this First Amendment shall have the meanings given to them in the Agreement.

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

3. The following new paragraph shall be added at the end of Section 2.4.1 of the Agreement:

*In order to facilitate the activities contemplated under the Discovery Research Plan, Genentech may provide to BicycleTx certain Genentech materials, assays or chemical compounds (collectively, "**Genentech Materials**"). Except as otherwise expressly set forth in this Agreement, all such Genentech Materials delivered to BicycleTx will remain the sole property of Genentech, will be used only as specified in the Discovery Research Plan, will not be used, modified, or delivered to or for the benefit of any Third Party (including any sublicensee) without the prior written consent of Genentech (except for subcontractors performing any activities under the Discovery Research Plan), will not be reverse engineered, and will be used in compliance with Applicable Law. BicycleTx will use the Genentech Materials supplied under this Agreement with prudence and appropriate caution in any experimental work as not all of their characteristics may be known. Genentech will provide BicycleTx the most current material safety data sheet for the Genentech Materials upon transfer of any Genentech Materials, if available. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, THE GENENTECH MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE GENENTECH MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.*

*Genentech will deliver Genentech Materials to BicycleTx **[*]** (to either Building B900, Babraham Research Campus, Cambridge, CB223AT, UK or 4 Hartwell Place, Lexington, MA, 02421-3122 as nominated by BicycleTx) **[*]**. BicycleTx will provide to Genentech prior to Genentech Material deliveries all the necessary import documentation including but not limited to licenses and other permissions.*

BicycleTx shall return to Genentech or, at Genentech's discretion, destroy, at the end of the applicable Term, any unused amount of Genentech Materials provided by Genentech under this Agreement.

The transfer of Genentech Materials under this Agreement shall be a bailment and shall not constitute a sale of Genentech Materials or grant option or license of any patent or other rights owned or controlled by Genentech."

4. Section 15.8.1 shall be replaced in its entirety by the following new Section 15.8.1

***15.8.1 Notice Requirements**. Any notice, request, demand, waiver, consent, approval, or other communication permitted or required under this Agreement shall be in writing, shall refer specifically to this Agreement and shall be deemed given only if (a) delivered by hand, (b) sent **by e-mail to the then current Alliance Manager of the receiving Party or** facsimile transmission (with transmission confirmed), or (c) by internationally recognized overnight delivery service that maintains records of delivery, addressed to the Parties at their respective addresses specified in Section 15.8.2 or to such other address as the Party to whom notice is to be given may have provided to the other Party in accordance with this Section 15.8.1. Such notice shall be deemed to have been given as of the date delivered by hand, **sent by e-mail** or transmitted by facsimile (with transmission confirmed) or on the second Business Day (at the place of delivery) after*

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

deposit with an internationally recognized overnight delivery service. This Section 15.8.1 is not intended to govern the day-to-day business communications necessary between the Parties in performing their obligations under the terms of this Agreement.

5. A new Section 1.107a shall be inserted into the Agreement:

   ***1.107a "Genentech Materials"** has the meaning set forth in Section 2.4.1.*

6. Except as amended herein, all other terms of the Agreement shall remain in full force and effect.

7. The Parties agree that in order to fulfill the written form requirement of this First Amendment, as alternative to handwritten signatures on a hardcopy, electronic signatures ("eSignature[s]") of duly authorized representatives of the Parties may be used. eSignature shall mean a signature that consists of one or more letters, characters, numbers or other symbols in digital form incorporated in, attached to or associated with the electronic document, that (a) is unique to the person executing the signature; (b) the technology or process used to make the signature is under the sole control of the person making the signature; (c) the technology or process can be used to identify the person using the technology or process; and (d) the electronic signature can be linked with an electronic document in such a way that it can be used to determine whether the electronic document has been changed since the electronic signature was incorporated in, attached to or associated with the electronic document.

[*remainder of page intentionally blank*]

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

IN WITNESS WHEREOF, the Parties have entered into this First Amendment as of the last date set forth below.

BicycleTx Limited

/s/ Michael Skynner
Name: Michael Skynner
Title: Chief Operating Officer (COO)

Genentech, Inc.

/s/ Beth Odeh-Frikert
Name: Beth Odeh-Frikert
Title: Head Alliance & Asset Management, SSF

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

Second Amendment to
the
Discovery Collaboration and License Agreement

between

Genentech, Inc.
1 DNA Way, South San Francisco, California 94080, US
(“Genentech”)

on the one hand

and

BicycleTx Limited
B900 Babraham Research Campus, Cambridge, England CB22 3AT
("BicycleTx ")

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

Whereas, Genentech and BicycleTx entered into a certain discovery collaboration and license agreement effective February 21, 2020, as amended (the "**Agreement**");

Whereas the Agreement was amended by the First Amendment effective 21 February 2020; and

Whereas, Genentech and BicycleTx now desire to amend the Agreement in accordance with this second amendment (the "**Second Amendment**").

Now therefore, in consideration of the mutual covenants and promises contained in this Second Amendment and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto, intending to be legally bound, do hereby agree as follows:

1. This Second Amendment is effective as of February 21, 2020.

2. All capitalised terms not defined in this Second Amendment shall have the meanings given to them in the Agreement.

3. The following sentences in Section 2.4.1 of the Agreement shall be deleted:

   "*BicycleTx may agree from time to time to transfer materials, including any Bicycle Constructs or Discovery Constructs to Genentech, to enable Genentech to perform certain Discovery Research Activities. BicycleTx's agreement for any such transfer shall not be unreasonably withheld, conditioned or delayed and shall be performed under the terms of a material transfer agreement (The "MTA"), which MTA shall provide that (a) such materials may only be used in connection with the Discovery Research Activities Genentech has agreed to perform, during the period set forth in such MTA, and (b) no modification or reverse engineering of any materials by or on behalf of Genentech will be permitted, except to the extent expressly set forth in such MTA. The Parties shall negotiate in good faith and agree upon the form of such MTA* ***[*]***."

4. The deleted sentences mentioned in Article 3 of this Second Amendment shall be replaced by the following:

   *"BicycleTx may agree from time to time to transfer materials, including any Bicycle Constructs or Discovery Constructs, to Genentech to enable Genentech to perform certain Discovery Research Activities (collectively, "****BicycleTx Materials****"). BicycleTx's agreement for any such transfer shall not be unreasonably withheld, conditioned or delayed and, except as outlined in this Agreement, shall be subject to the following conditions:*
   - *except as otherwise expressly set forth in this Agreement, all such BicycleTx Materials delivered to Genentech will remain the sole property of BicycleTx;*
   - *Genentech may only use the BicycleTx Materials as specified in the Discovery Research Plan or as outlined in this Agreement;*
   - *Genentech will ensure that the BicycleTx Materials are not used in human subjects or for primary diagnostic purposes;*
   - *Genentech will ensure that the BicycleTx Materials are not used, modified, or delivered to or for the benefit of any Third Party (including any sublicensee) without the prior written consent of BicycleTx* (such consent not to be unreasonably withheld, conditioned, or delayed)*; and*
   - *Genentech will ensure that the BicycleTx Materials are not reverse engineered, and will be used in compliance with Applicable Law.*

   Genentech will use the BicycleTx Materials supplied under this Agreement with

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

prudence and appropriate caution in any experimental work as not all of their characteristics may be known. BicycleTx will provide Genentech the most current material safety data sheet for the BicycleTx Materials upon transfer of any BicycleTx Materials, if available. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, THE BICYCLETX MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE BICYCLE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

*BicycleTx will deliver BicycleTx Materials to Genentech **[*]** to a location specified by Genentech **[*]**. Genentech will provide to BicycleTx prior to BicycleTx Material deliveries all the necessary import documentation including but not limited to licenses and other permissions.*

Genentech shall return to BicycleTx or, at BicycleTx's discretion, destroy, at the end of the applicable Term, any unused amount of BicycleTx Materials provided by BicycleTx under this Agreement.

The transfer of BicycleTx Materials under this Agreement shall be a bailment and shall not constitute a sale of BicycleTx Materials or grant option or license of any patent or other rights owned or controlled by BicycleTx."

5. The following sentences in Section 2.4.1 of the Agreement shall be deleted:

*"In order to facilitate the activities contemplated under the Discovery Research Plan, Genentech may provide to BicycleTx certain Genentech materials, assays or chemical compounds (collectively, "**Genentech Materials**"). Except as otherwise expressly set forth in this Agreement, all such Genentech Materials delivered to*

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

BicycleTx will remain the sole property of Genentech, will be used only as specified in the Discovery Research Plan, will not be used, modified, or delivered to or for the benefit of any Third Party (including any sublicensee) without the prior written consent of Genentech (except for subcontractors performing any activities under the Discovery Research Plan), will not be reverse engineered, and will be used in compliance with Applicable Law. BicycleTx will use the Genentech Materials supplied under this Agreement with prudence and appropriate caution in any experimental work as not all of their characteristics may be known. Genentech will provide BicycleTx the most current material safety data sheet for the Genentech Materials upon transfer of any Genentech Materials, if available. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, THE GENENTECH MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE GENENTECH MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

*Genentech will deliver Genentech Materials to BicycleTx **[*]** (to either Block A & B, Portway Building, Granta Park, Great Abingdon, Cambridge, CB21 6GP UK or 4 Hartwell Place, Lexington, MA, 02421-3122 as nominated by BicycleTx) **[*]**. BicycleTx will provide to Genentech prior to Genentech Material deliveries all the necessary import documentation including but not limited to licenses and other permissions.*

BicycleTx shall return to Genentech or, at Genentech's discretion, destroy, at the end of the applicable Term, any unused amount of Genentech Materials provided by Genentech under this Agreement.

The transfer of Genentech Materials under this Agreement shall be a bailment and shall not constitute a sale of Genentech Materials or grant option or license of any patent or other rights owned or controlled by Genentech."

6. The deleted sentences mentioned in Article 5 of this Second Amendment shall be replaced by the following:

"*In order to facilitate the activities contemplated under the Discovery Research Plan, Genentech may provide to BicycleTx certain Genentech materials, assays or chemical compounds (collectively, "Genentech Materials"). Genentech's agreement for any such transfer will not be unreasonably withheld, conditioned or delayed and shall be subject to the following conditions:*

- *except as otherwise expressly set forth in this Agreement, all such Genentech Materials delivered to BicycleTx will remain the sole property of Genentech;*

- *BicycleTx will use the Genentech Materials only as specified in the Discovery Research Plan;*

- *BicycleTx will ensure that the Genentech Materials are not used in human subjects or for primary diagnostic purposes;*

- *BicycleTx will ensure that the Genentech Materials are not used, modified, or delivered to or for the benefit of any Third Party (including any sublicensee) without the prior written consent of Genentech (except for subcontractors performing any activities under the Discovery Research Plan); and*

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

- *BicycleTx will ensure that the Genentech Materials are not reverse engineered, and will be used in compliance with Applicable Law.*

BicycleTx will use the Genentech Materials supplied under this Agreement with prudence and appropriate caution in any experimental work as not all of their characteristics may be known. Genentech will provide BicycleTx the most current material safety data sheet for the Genentech Materials upon transfer of any Genentech Materials, if available. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, THE GENENTECH MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE GENENTECH MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

*Genentech will deliver Genentech Materials to BicycleTx **[*]** to a location specified by BicycleTx **[*]**. BicycleTx will provide to Genentech prior to Genentech Material deliveries all the necessary import documentation including but not limited to licenses and other permissions.*

BicycleTx shall return to Genentech or, at Genentech's discretion, destroy, at the end of the applicable Term, any unused amount of Genentech Materials provided by Genentech under this Agreement.

The transfer of Genentech Materials under this Agreement shall be a bailment and shall not constitute a sale of Genentech Materials or grant option or license of any patent or other rights owned or controlled by Genentech."

7. Section 15.8.1 shall be deleted in its entirety and replaced with the following;

*15.8.1 Notice Requirements. Any notice, request, demand, waiver, consent, approval, or other communication permitted or required under this Agreement shall be in writing, shall refer specifically to this Agreement and shall be deemed given only if (a) delivered by hand, (b) sent by e-mail to the then current Alliance Manager of the receiving Party and, in the case of BicycleTx, to **[*]** or facsimile transmission (with transmission confirmed), or (c) by internationally recognized overnight delivery service that maintains records of delivery, addressed to the Parties at their respective addresses specified in Section 15.8.2 or to such other address as the Party to whom notice is to be given may have provided to the other Party in accordance with this Section 15.8.1. Such notice shall be deemed to have been given as of the date delivered by hand, sent by e-mail or transmitted by facsimile (with transmission confirmed) or on the second Business Day (at the place of delivery) after deposit with an internationally recognized overnight delivery service. This Section 15.8.1 is not intended to govern the day-to-day business communications necessary between the Parties in performing their obligations under the terms of this Agreement.*

8. A new Section 1.24a shall be inserted into the Agreement:

***1.24a "BicycleTx Materials"** has the meaning set forth in Section 2.4.1.*

9. Except as amended herein, all other terms of the Agreement shall remain in full force and effect.

10. The Parties agree that in order to fulfill the written form requirement of this Second Amendment, as alternative to handwritten signatures on a hardcopy, electronic

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

signatures (“eSignature[s]”) of duly authorized representatives of the Parties may be used. eSignature shall mean a signature that consists of one or more letters, characters, numbers or other symbols in digital form incorporated in, attached to or associated with the electronic document, that (a) is unique to the person executing the signature; (b) the technology or process used to make the signature is under the sole control of the person making the signature; (c) the technology or process can be used to identify the person using the technology or process; and (d) the electronic signature can be linked with an electronic document in such a way that it can be used to determine whether the electronic document has been changed since the electronic signature was incorporated in, attached to or associated with the electronic document. This Second Amendment may be executed in two counterparts, each of which shall be deemed an original and which together shall constitute one instrument.

[remainder of page intentionally blank]

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

IN WITNESS WHEREOF, the Parties have entered into this Second Amendment as of the last date set forth below.

BicycleTx Limited

/s/ Michael Skynner

Name: Michael Skynner

Title: Chief Technology Officer Date: 27-Jun-2022

Genentech, Inc.

/s/ Beth Odeh-Frikert

Name: Beth Odeh-Frikert

Title: Head Alliance & Asset Management, SSF Date: 25-Jun-2022

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

Exhibit 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

I, Kevin Lee, certify that:

1. I have reviewed this Quarterly Report on 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: August 4, 2022

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

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

I, Lee Kalowski, certify that:

1. I have reviewed this Quarterly Report on 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: August 4, 2022

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

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, 2022, 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 4, 2022

IN WITNESS WHEREOF, the undersigned have set their hands hereto as of the 4th day of August, 2022.

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."