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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 September 30, 2021

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.)
B900, Babraham Research Campus Cambridge, United Kingdom	**CB22 3AT**
(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 November 1, 2021, the registrant had 29,399,709 ordinary shares, nominal value £0.01 per share, outstanding.

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Forward-looking Information

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

- statements regarding the impact of the ongoing COVID-19 pandemic and its effects on our operations, research and development and clinical trials and potential disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- our ability to advance our product candidates into, and successfully complete, clinical trials;
- our reliance on the success of our product candidates in our *Bicycle*® Toxin Conjugate, or BTC™, 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, under the laws and regulations of England and Wales, and other jurisdictions;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;

- the amount of and our ability to satisfy interest and principal payments under our debt facility with Hercules Capital, Inc., or Hercules;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations or obtain additional grant funding;
- the rate and degree of market acceptance of any approved products;
- developments relating to our competitors and our industry, including competing therapies;
- our ability to effectively manage our anticipated growth;
- our ability to attract and retain qualified employees and key personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the Jumpstart Our Business Startups Act, or the JOBS Act;
- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance; and
- other risks and uncertainties, including those listed under the caption “Risk Factors.”

Although we believe that we have a reasonable basis for each forward-looking statement contained in this 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.

RISK FACTOR SUMMARY

The below summary risk factors provide an overview of certain of the risks we are exposed to in the normal course of our business activities. The below summary does not contain all of the information that may be important to investors, and investors should read the summary together with the more detailed discussion of risks set forth in Part II, Item 1A, "Risk Factors," of this Quarterly Report on Form 10-Q and those contained in our other public filings.

- We have a history of significant operating losses and expect to incur significant and increasing losses for the foreseeable future, and we may never achieve or maintain profitability.
- We may need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.
- Raising additional capital may cause dilution to our existing shareholders or holders of our American Depositary Shares, or ADSs, restrict our operations or cause us to relinquish valuable rights.
- Our failure to comply with the covenants or payment obligations under our existing term loan facility with Hercules Capital, Inc., or Hercules, could result in an event of default, which may result in increased interest charges, acceleration of our repayment obligations or other actions by Hercules, any of which could negatively impact our business, financial condition and results of operations.
- We are at a very early stage in our development efforts, our product candidates and those of our collaborators represent a new category of medicines and may be subject to heightened regulatory scrutiny until they are established as a therapeutic modality.
- We are substantially dependent on the success of our internal development programs and of our product candidates from our *Bicycle* Toxin Conjugates®, or BTCs, *Bicycle* tumor-targeted immune cell agonist™, or *Bicycle* TICA™, programs, which may not successfully complete clinical trials, receive regulatory approval or be successfully commercialized.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.
- Our current or future product candidates may cause undesirable side effects or have other properties when used alone or in combination with other approved products or investigational new drugs, or IND, that could halt their clinical development, prevent their marketing approval, limit their commercial potential or result in significant negative consequences.
- We may be delayed or not be successful in our efforts to identify or discover additional product candidates.
- We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.
- We may seek designations for our product candidates with the U.S. Food and Drug Administration, or FDA, and other comparable regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, but there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.
- Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate.

- The market opportunities for any current or future product candidate we develop, if and when approved may be limited to those patients who are ineligible for established therapies or for whom prior therapies have failed, and may be small.
- We face significant competition and if our competitors develop and market products that are more effective, safer or less expensive than the product candidates we develop, our commercial opportunities will be negatively impacted.
- Even if we receive marketing approval of a product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products, if approved.
- The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, payors and others in the medical community.
- The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our product candidates, could limit our ability to market those products and decrease our ability to generate revenue.
- Healthcare legislative reform measures may have a negative impact on our business and results of operations.
- We rely on third parties, including independent clinical investigators and clinical research organizations, or CROs, to conduct and sponsor some of the clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for our product candidates.
- We intend to rely on third parties to manufacture product candidates, which increases the risk that we will not have sufficient quantities of such product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.
- If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.
- If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.
- As a company based outside of the United States, we are subject to economic, political, regulatory and other risks associated with international operations.
- COVID-19 could impact our business.
- The market price of our ADSs is highly volatile, and holders of our ADSs may not be able to resell their ADSs at or above the price at which they purchased their ADSs.

PART I - FINANCIAL INFORMATION

Item 1. Financial Statements.

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

	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash	$ 259,524	$ 135,990
Accounts receivable	—	5,456
Prepaid expenses and other current assets	5,644	5,100
Research and development incentives receivable	7,704	9,177
Total current assets	272,872	155,723
Property and equipment, net	2,437	2,317
Operating lease right-of-use assets	3,246	1,290
Other assets	2,778	1,822
Total assets	$ 281,333	$ 161,152
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 1,761	$ 1,365
Accrued expenses and other current liabilities	10,953	11,629
Deferred revenue, current portion	17,463	10,135
Total current liabilities	30,177	23,129
Long-term debt, net of discount	29,753	14,505
Operating lease liabilities, net of current portion	2,495	426
Deferred revenue, net of current portion	45,044	25,021
Other long-term liabilities	3,041	2,611
Total liabilities	110,510	65,692
Commitments and contingencies (Note 11)		
Shareholders' equity:		
Ordinary shares, £0.01 nominal value; 55,295,420 and 31,995,653 shares authorized at September 30, 2021 and December 31, 2020, respectively; 25,595,326 and 21,094,557 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively	329	266
Additional paid-in capital	374,029	249,947
Accumulated other comprehensive loss	(3,193)	(3,193)
Accumulated deficit	(200,342)	(151,560)
Total shareholders' equity	170,823	95,460
Total liabilities and shareholders' equity	$ 281,333	$ 161,152

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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Collaboration revenues	$ 4,333	$ 3,842	$ 7,926	$ 6,542
Operating expenses:				
Research and development	10,513	7,363	31,924	23,091
General and administrative	8,114	7,154	23,596	18,351
Total operating expenses	18,627	14,517	55,520	41,442
Loss from operations	(14,294)	(10,675)	(47,594)	(34,900)
Other income (expense):				
Interest income	24	72	61	655
Interest expense	(823)	—	(2,164)	—
Total other income (expense), net	(799)	72	(2,103)	655
Net loss before income tax provision	(15,093)	(10,603)	(49,697)	(34,245)
Benefit from income taxes	(415)	(465)	(915)	(668)
Net loss	$ (14,678)	$ (10,138)	$ (48,782)	$ (33,577)
Net loss per share, basic and diluted	$ (0.59)	$ (0.52)	$ (2.06)	$ (1.81)
Weighted average ordinary shares outstanding, basic and diluted	25,039,990	19,426,833	23,719,124	18,504,013
Comprehensives Loss:				
Net loss	$ (14,678)	$ (10,138)	$ (48,782)	$ (33,577)
Other comprehensive income (loss):				
Foreign currency translation adjustment	313	743	—	(1,442)
Total comprehensive loss	$ (14,365)	$ (9,395)	$ (48,782)	$ (35,019)

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 Loss	Accumulated Deficit	Total Shareholders' Equity
	Shares	Amount				
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
Issuance of ADSs upon exercise of share options	257,389	4	3,045	—	—	3,049
Issuance of ADSs, net of commissions and offering expenses of $0.9 million	930,900	12	29,831	—	—	29,843
Issuance of ordinary shares pursuant to the Ionis share purchase agreement	282,485	4	7,554	—	—	7,558
Share-based compensation expense	—	—	2,688	—	—	2,688
Foreign currency translation adjustment	—	—	—	313	—	313
Net loss	—	—	—	—	(14,678)	(14,678)
Balance at September 30, 2021	25,595,326	$ 329	$ 374,029	$ (3,193)	$ (200,342)	$ 170,823

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 Loss	Accumulated Deficit	Total Shareholders' Equity
	Shares	Amount				
Balance at December 31, 2019	17,993,701	$ 227	$ 195,056	$ (1,535)	$ (100,550)	$ 93,198
Issuance of ADSs upon exercise of share options	1,071	—	2	—	—	2
Issuance of ordinary shares upon exercise of warrants	21,435	—	—	—	—	—
Share-based compensation expense	—	—	2,121	—	—	2,121
Foreign currency translation adjustment	—	—	—	(2,184)	—	(2,184)
Net loss	—	—	—	—	(11,324)	(11,324)
Balance at March 31, 2020	18,016,207	227	197,179	(3,719)	(111,874)	81,813
Issuance of ADSs upon exercise of share options	4,000	—	9	—	—	9
Issuance of ordinary shares upon exercise of warrants	71,450	1	—	—	—	1
Share-based compensation expense	—	—	1,319	—	—	1,319
Foreign currency translation adjustment	—	—	—	(1)	—	(1)
Net loss	—	—	—	—	(12,115)	(12,115)
Balance at June 30, 2020	18,091,657	228	198,507	(3,720)	(123,989)	71,026
Issuance of ADSs upon exercise of share options	13,483	—	87	—	—	87
Issuance of ADSs, net of commissions and offering expenses of $1.8 million	2,830,713	36	46,287	—	—	46,323
Share-based compensation expense	—	—	1,510	—	—	1,510
Foreign currency translation adjustment	—	—	—	743	—	743
Net loss	—	—	—	—	(10,138)	(10,138)
Balance at September 30, 2020	20,935,853	$ 264	$ 246,391	$ (2,977)	$ (134,127)	$ 109,551

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)

	Nine Months Ended Ended September 30,	
	2021	**2020**
Cash flows from operating activities:		
Net loss	$ (48,782)	$ (33,577)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation expense	9,084	4,950
Depreciation and amortization	1,002	944
Non-cash interest	347	—
Changes in operating assets and liabilities:		
Accounts receivable	5,544	(2,685)
Research and development incentives receivable	1,318	937
Prepaid expenses and other current assets	(719)	(773)
Operating lease right-of-use assets	(2,024)	570
Other assets	(955)	(719)
Accounts payable	270	193
Accrued expenses and other current liabilities	(521)	1,030
Operating lease liabilities	2,123	(193)
Deferred revenue	28,473	27,782
Other long-term liabilities	481	369
Net cash used in operating activities	(4,359)	(1,172)
Cash used in investing activities:		
Purchases of property and equipment	(963)	(716)
Net cash used in investing activities	(963)	(716)
Cash flows from financing activities:		
Proceeds from the issuance of ADSs, net of issuance costs	102,595	46,373
Issuance of ordinary shares pursuant to the Ionis share purchase agreement	7,558	—
Proceeds from the exercise of share options	4,908	98
Proceeds from issuance of debt	15,000	15,000
Payments of debt issuance costs	—	(373)
Proceeds from the exercise of warrants	—	1
Net cash provided by financing activities	130,061	61,099
Effect of exchange rate changes on cash	(1,205)	(1,486)
Net increase in cash	123,534	57,725
Cash at beginning of period	135,990	92,117
Cash at end of period	$ 259,524	$ 149,842
Supplemental disclosure of cash flow information		
Cash paid for interest	$ 1,753	$ —
Cash paid for income taxes	$ 87	$ 124
Public offering costs accrued but not paid	$ —	$ 50
Cash paid for amounts included in the measurement of operating lease liabilities	$ 676	$ 823
Purchases of property and equipment included in accounts payable and accrued expenses	$ 298	$ 40
Debt issuance costs accrued but not paid	$ —	$ 200

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

On June 5, 2020, the Company entered into a Sales Agreement (the "Sales Agreement") with Cantor Fitzgerald & Co. and Oppenheimer & Co. Inc. (the "Sales Agents") with respect to an at-the-market offering program ("ATM") pursuant to which the Company may offer and sell through the Sales Agents, from time to time at the Company's sole discretion, American Depositary Shares ("ADSs"), each ADS representing one ordinary share. As of September 30, 2021, the Company had issued and sold 6,700,497 ADSs, representing the same number of ordinary shares for gross proceeds of $155.8 million, resulting in net proceeds of $150.7 million after deducting sales commissions and offering expenses of $5.1 million.

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

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 will be interest-only until the first payment is due on August 1, 2023, which date was extended from November 1, 2022. If the Company achieves certain performance milestones, the interest-only period will be extended, with the first principal payment due on February 1, 2024, which

date was extended from May 1, 2023. On the Amendment Closing Date and pursuant to the terms of the First Amendment to LSA, the Company borrowed the additional term loan of $15.0 million that had been available from September 30, 2020 to March 15, 2021.

The Company is subject to risks common to companies in the biotechnology industry and in light of the ongoing COVID-19 pandemic, including but not limited to, risks of delays in initiating or continuing research programs and clinical trials, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel and collaboration partners, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations, and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval prior to commercialization. Even if the Company's research and development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The accompanying 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 ADSs, convertible preferred shares, proceeds received from its collaboration arrangements (Note 9), and proceeds from the Loan Agreement with Hercules (Note 6). The Company has incurred recurring losses since inception, including net losses of $14.7 million and $48.8 million, for the three and nine months ended September 30, 2021, respectively. As of September 30, 2021, the Company had an accumulated deficit of $200.3 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 its research or drug development programs or any future commercialization efforts. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

2. Summary of significant accounting policies

The Company's significant accounting policies are disclosed in the audited consolidated financial statements for the year ended December 31, 2020 included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020, which was filed with the Securities and Exchange Commission (the "SEC"), on March 11, 2021 (the "2020 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 procedures for 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 extent to which the ongoing COVID-19 pandemic ultimately impacts the Company's business, clinical development and regulatory efforts, corporate development objectives and the value of and market for the Company's ADSs, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the United Kingdom, United States, Europe and other countries, and the effectiveness of actions taken globally to contain and treat the disease. The global economic slowdown, the overall disruption of global healthcare systems and the other risks and uncertainties associated with the pandemic could have a material adverse effect on the Company's business, financial condition, results of operations and growth prospects.

Unaudited Interim Financial Information

Certain information in the footnote disclosures of the financial statements has been condensed or omitted pursuant to the rules and regulations of the SEC. These 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, 2020 included in the Company's 2020 Annual Report.

The accompanying condensed consolidated balance sheet at September 30, 2021, condensed consolidated statements of operations and comprehensive loss, condensed consolidated statements of shareholders' equity for the three and nine months ended September 30, 2021 and 2020, the condensed consolidated statements of cash flows for the nine months ended September 30, 2021 and 2020, 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, 2020, 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 September 30, 2021, the results of its operations for the three and nine months ended September 30, 2021 and 2020, and its cash flows for the nine months ended September 30, 2021 and 2020. The results for the three and nine months ended September 30, 2021 are not necessarily indicative of the results to be expected for the year ending December 31, 2021, any other interim periods, or any future year or period.

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 recognizes government grant funding in the condensed consolidated statements of operations and comprehensive loss as the related expenses being funded are incurred. The Company classifies government grants received under these arrangements as a reduction to the related research and development expense incurred. The Company analyzes each arrangement on a case-by-case basis. For the three and nine months ended September 30, 2021, the Company recognized $1.0 million and $2.9 million, respectively, and for the three and nine months ended September 30, 2020, the Company recognized $0.1 million and $0.3 million, respectively, as a reduction of research and development expense related to government grant arrangements.

Recently adopted accounting pronouncements

In 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"). ASU 2019-12 simplifies the accounting for income taxes and will be effective beginning after December 15, 2020. The adoption of ASU 2019-12 did not have a material impact on the Company's results of operations or cash flows.

Recently issued accounting pronouncements

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

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 September 30, 2021, and December 31, 2020, the carrying value of the long-term debt approximates its fair value, which was determined using unobservable Level 3 inputs, including quoted interest rates from a lender for borrowings with similar terms. As of September 30, 2021, and December 31, 2020, 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 date of purchase to be cash equivalents. The Company had no cash equivalents at September 30, 2021 and December 31, 2020.

4. Property and equipment, net

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

	September 30, 2021	December 31, 2020
Laboratory equipment	$ 6,423	$ 5,583
Leasehold improvements	380	383
Computer equipment and software	143	188
Furniture and office equipment	220	195
	7,166	6,349
Less: Accumulated depreciation and amortization	(4,729)	(4,032)
	$ 2,437	$ 2,317

Depreciation expense was $0.3 million and $1.0 million for the three and nine months ended September 30, 2021, respectively, and $0.3 million and $0.9 million for the three and nine months ended September 30, 2020, respectively.

5. Accrued expenses and other current liabilities

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

	September 30, 2021	December 31, 2020
Accrued employee compensation and benefits	$ 3,990	$ 4,390
Accrued external research and development expenses	3,803	4,428
Accrued professional fees	2,070	1,759
Current portion of operating lease liabilities	826	844
Other	264	208
	$ 10,953	$ 11,629

6. Long-term debt

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

Borrowings under the Loan Agreement bear interest at an annual rate equal to the greater of (i) 8.85% or (ii) 5.60% plus *The Wall Street Journal* prime rate. On the Amendment Closing Date, the Borrowers entered into 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 will be interest-only until the first payment is 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 achieves certain performance milestones, the interest-only period will be extended, with the first principal payment due on February 1, 2024, which date was extended from May 1, 2023.

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 11.27% at September 30, 2021.

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 nine months ended September 30, 2021 was $0.8 million and $2.1 million, respectively.

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

	September 30, 2021
Term loan payable	$ 30,000
End of term charge	294
Unamortized debt issuance costs	(541)
Carrying value of term loan	$ 29,753

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

Year Ending December 31,	
2021	$ —
2022	—
2023	9,614
2024	21,886
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 September 30, 2021, and 2020, the Company has not declared any dividends.

As of September 30, 2021, and December 31, 2020, the Company's authorized share capital consisted of 55,295,420 and 31,995,653, respectively, ordinary shares with a nominal value of £0.01 per share.

On July 9, 2021, the Company entered into a share purchase agreement (the "Ionis Share Purchase Agreement") with Ionis Pharmaceuticals, Inc. ("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. 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 (Note 9).

8. Share-based compensation

Employee incentive pool

2020 Share Option Plan

In June 2020, the Company's shareholders approved the Bicycle Therapeutics plc 2020 Equity Incentive Plan (the "2020 Plan"), under which the Company may grant market value options, market value stock appreciation rights or restricted shares, restricted share units, performance restricted share units and other share-based awards to the Company's employees. The Company's non-employee directors and consultants are eligible to receive awards under the 2020 Non-Employee Sub-Plan to the 2020 Plan. All awards under the 2020 Plan, including the 2020 Non-Employee Sub-Plan, will be set forth in award agreements, which will detail the terms and conditions of awards, including any applicable vesting and payment terms, change of control provisions and post-termination exercise limitations. In the event of a change of control of the Company, as defined in the 2020 Plan, any outstanding awards under the 2020 Plan will vest in full immediately prior to such change of control. Share options issued under the 2020 Share Option Plan have a 10 year contractual life, and generally vest over either a three year service period for non-employee directors, or a four year service period with 25% of the award vesting on the first anniversary of the commencement date and the balance thereafter in 36 equal monthly installments for employees and consultants. Certain options granted to the Company's non-employee directors vest immediately upon grant.

The Company initially reserved up to 4,773,557 ordinary shares for future issuance under the 2020 Plan, representing 574,679 new shares, 544,866 shares that remained available for future issuance under the Company's 2019 Share Option Plan (the "2019 Plan") immediately prior to the effectiveness of the 2020 Plan and up to 3,654,012 shares subject to options that were granted under the 2019 Plan and that were granted pursuant to option contracts granted prior to the Company's IPO, in each case that expire, terminate, are forfeited or otherwise not issued from time to time, if any. Additionally, the number of ordinary shares reserved for issuance pursuant to the 2020 Plan will automatically increase on the first day of January of each year, commencing on January 1, 2021, in an amount equal to 5% of the total number of the Company's ordinary shares outstanding on the last day of the preceding year, or a lesser number of shares determined by the Company's board of directors. The number of shares reserved for issuance under the 2020 Plan was increased by 1,054,727 shares effective January 1, 2021. As of September 30, 2021, there were 5,310,179 shares available for issuance and options to purchase 1,638,712 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 September 30, 2021, there were 2,259,663 options to purchase ordinary shares outstanding under the 2019 Plan. In conjunction with the adoption of the 2020 Plan, all shares available for future issuance under the 2019 Plan as of June 29, 2020 became available for issuance under the 2020 Plan and the Company ceased making awards under the 2019 Plan. The 2020 Plan is the successor of the 2019 Plan.

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

Employee Share Purchase Plan ("ESPP")

In May 2019, the Company adopted the 2019 Employee Stock Purchase Plan (the "ESPP"), which became effective in conjunction with the IPO. The Company initially reserved 215,000 ordinary shares for future issuance under this plan. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2020 and each January 1 thereafter through January 1, 2029, by the least of (i) 1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 430,000 ordinary

shares or (iii) such lesser number of shares as determined by the Compensation Committee. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization. The number of shares reserved for issuance under the ESPP was increased by 210,945 shares effective January 1, 2021. As of September 30, 2021, the total number of shares available for issuance under the ESPP was 605,882 ordinary shares.

Once the Company commences offerings under the ESPP, each offering to the employees to purchase shares under the ESPP will begin on each June 1 and December 1 and will end on the following November 30 and May 31, respectively. On each purchase date, which will fall on the last date of each offering period, ESPP participants will purchase ordinary shares at a price per share equal to 85% of the lesser of (1) the fair market value of the shares on the offering date or (2) the fair market value of the shares on the purchase date. The occurrence and duration of offering periods under the ESPP are subject to the determinations of the Company's compensation committee. As of September 30, 2021, 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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Research and development expenses	$ 1,238	$ 668	$ 3,535	$ 1,863
General and administrative expenses	1,450	842	5,549	3,087
	$ 2,688	$ 1,510	$ 9,084	$ 4,950

Share options

The following table summarizes the Company's option activity since December 31, 2020:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2020	3,736,663	$ 10.51	8.54	$ 27,553
Granted	1,509,205	20.48	—	—
Exercised	(446,600)	10.99	—	—
Forfeited	(82,102)	18.08	—	—
Outstanding as of September 30, 2021	4,717,166	$ 13.53	8.29	$ 127,324
Vested and expected to vest as of September 30, 2021	4,717,166	$ 13.53	8.29	$ 127,324
Options exercisable as of September 30, 2021	2,181,492	$ 10.00	7.73	$ 68,059

The weighted average grant-date fair value of share options granted during the nine months ended September 30, 2021 and 2020 was $13.83 per share and $7.57 per share, respectively.

Total share-based compensation expense for share options granted was $2.7 million and $9.1 million for the three and nine months ended September 30, 2021, respectively, and $1.5 million and $5.0 million for the three and nine months ended September 30, 2020, respectively. Expense for non-employee consultants for the three and nine months ended September 30, 2021 and 2020 was immaterial.

The aggregate intrinsic value of share options is calculated as the difference between the exercise price of the share options and the fair value of the Company's ordinary shares. The aggregate intrinsic value of share options exercised was $5.7 million and $9.4 million for the three and nine months ended September 30, 2021, respectively, and was $0.2 million for each of the three and nine months ended September 30, 2020, respectively.

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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Risk-free interest rate	0.9 %	0.3 %	0.6 %	1.4 %
Expected volatility	80.2 %	74.1 %	79.6 %	74.1 %
Expected dividend yield	—	—	—	—
Expected term (in years)	6.1	6.1	6.0	6.0

As of September 30, 2021, total unrecognized compensation expense related to the unvested employee and director share-based awards was $24.5 million, which is expected to be recognized over a weighted average period of 2.9 years.

9. Significant agreements

For the three and nine months ended September 30, 2021 and 2020, the Company recognized revenue for its collaborations with Ionis, Genentech Inc. (“Genentech”), the Dementia Discovery Fund (“DDF”), AstraZeneca AB (“AstraZeneca”), and Oxurion NV (formerly ThromboGenics NV (“Oxurion”)). 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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Collaboration revenues				
Ionis	$ 2,066	$ —	$ 2,066	$ —
Genentech	1,063	1,209	4,142	3,066
Dementia Discovery Fund	77	58	314	170
AstraZeneca	1,127	213	1,404	944
Oxurion	—	2,362	—	2,362
Total collaboration revenues	$ 4,333	$ 3,842	$ 7,926	$ 6,542

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 agreed to pay a non-refundable $3.0 million option fee within five business days after the Effective Date.

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.

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 the Ionis Share Purchase Agreement with Ionis, pursuant to which Ionis purchased 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 provides that, subject to limited exceptions, Ionis will hold and not sell any of the Ionis Shares until the earlier of (i) the first anniversary of the closing of the sale of the shares under the Ionis Share Purchase Agreement (the "Closing Date") and (ii) the termination of the Ionis Collaboration Agreement pursuant to its terms (provided, however, that in the event the termination of the Ionis Collaboration Agreement occurs less than six months after the Closing Date, Ionis shall hold and will not sell or otherwise enter into a transaction regarding the Ionis Shares until at least the date that is six months after the Closing Date).

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. 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. 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 September 30, 2021 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 recognized revenue of $2.1 million, for each of the three and nine months ended September 30, 2021, respectively. As of September 30, 2021 and December 31, 2020, the Company recorded $34.6 million and $3.0 million, respectively, of deferred revenue in connection with the Ionis Collaboration Agreement and Ionis Evaluation and Option Agreement.

Genentech Collaboration Agreement

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

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

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

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

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

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

Accounting Analysis

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

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

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

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

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

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

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

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

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

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

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

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 allocation of the transaction price as of September 30, 2021 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 time and external expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material rights is recorded as deferred revenue and the Company commences revenue recognition upon exercise of or upon expiry of the respective option. The Company anticipates that the Genentech Collaboration Performance Program #1 and #2 obligations will be performed over a period of approximately two years, and the material rights will be exercised or expire within approximately four years from contract execution.

During the three and nine months ended September 30, 2021, the Company recognized revenue of $1.1 million and $4.1 million, respectively, and during the three and nine months ended September 30, 2020, the Company recognized revenue of $1.2 million and $3.1 million, respectively. As of September 30, 2021 and December 31, 2020, the Company recorded $25.1 million and $27.6 million, respectively, of deferred revenue in connection with the Genentech Collaboration Agreement.

Dementia Discovery Fund Agreement

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

The Company received an upfront payment of $1.1 million in May 2019. The DDF arrangement provided the Company could receive up to an additional $0.7 million, of which $0.6 million has been received as of September 30, 2021, upon achievement of certain milestones such as the identification of lead *Bicycle* candidates with a certain affinity, which would be used to fund additional research and development services including lead optimization.

Intellectual property created by the collaboration shall be owned by the Company, and background intellectual property improvements shall be owned by the party from whose background intellectual property they exclusively relate. If promising lead compounds are identified, the Company, ODDI and DDF have the option (the “DDF Option”) to establish a jointly owned new company (“NewCo”) to advance the compounds through further development towards commercialization. NewCo will receive a royalty and milestone-bearing assignment and license of intellectual property

from the Company for this purpose. The DDF Option is exercisable at any time until 90 days following the completion of the Research Plan and delivery of a final report. If DDF does not elect to exercise the DDF Option during the Option period, then DDF shall have no right in the collaboration intellectual property. NewCo will initially be owned 66% by the Company and 34% by DDF; however, the Company shall not be entitled to exercise more than 50% of the total voting rights related to its ownership interests. After completion of the DDF Option exercise, for a period of two years following the option exercise, NewCo shall have the right to initiate a new research program to develop up to three additional dementia targets, on a target by target basis, and the Company will be entitled to charge NewCo an agreed upon FTE rate for peptide screening and optimization for the active targets.

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

Accounting Analysis

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

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

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

The transaction price was allocated to the single performance obligation of research and development services. The Company is recognizing revenue as the underlying services are performed using a proportional performance model, over the period of service using input-based measurements of total costs, including total full-time equivalent effort incurred to date as a percentage of total costs expected, which best reflects the progress towards satisfaction of the performance obligation. In December 2020, the Company received a payment of $0.5 million upon the achievement of specified scientific criteria. The Company concluded that the payment represents consideration for a single performance obligation to perform lead optimization activities, and will recognize revenue as the underlying services are performed using a proportional performance model, over the period of service using input based measurements of total costs, including total full time equivalent effort incurred to date as a percentage of total costs expected, which best reflects the progress towards satisfaction of the performance obligation.

For the three and nine months ended September 30, 2021, the Company recognized $0.1 million and $0.3 million of revenue, respectively, and for the three and nine months ended September 30, 2020, the Company recognized $0.1 million and $0.2 million, respectively, of revenue, related to its collaboration with DDF. As of September 30, 2021 and December 31, 2020, the Company recorded deferred revenue of $0.5 million and $0.8 million, respectively, related to its collaboration with DDF.

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 made an irrevocable election to exercise an option to nominate up to 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 twelve months (or fifteen 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 had certain target substitution rights should a screening failure or futility determination be reached, but was obligated to fund these additional efforts related to substitution. 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 are options. Upon exercise, AstraZeneca will obtain a research license and the related research and development services and an option to a development and exploitation license. The Company has concluded that the research services option, including the underlying development and exploitation license options related to each respective target results in a material right as the option exercise fee related to the development and exploitation license contains a discount that AstraZeneca would not have otherwise received.

The research license and the related research and development services related to the fourth, fifth and sixth targets were not performance obligations at the inception of the arrangement, as they are optional services that will be performed if AstraZeneca selects additional targets and they reflect their standalone selling prices and do not provide the customer with material rights. The Company's participation in the joint steering committee was assessed as immaterial in the context of the contract.

The total transaction price was initially determined to be $5.7 million, consisting of the $5.0 million option exercise fee and research and development funding of an estimated $0.7 million. The research and development funding is being provided based on the costs that are incurred to conduct the research and development services. The Company utilizes the most likely amount method to determine the amount of research and development funding to be received. Additional consideration to be paid to the Company upon the exercise of the license options by AstraZeneca or upon reaching certain milestones are excluded from the transaction price as they relate to option fees and milestones that can only be achieved subsequent to the license option exercise or are outside of the initial contact term.

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

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

The Company 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 three and nine months ended September 30, 2021. As of September 30, 2021, two research programs were in the AZ Research Term, and the research and development services associated with the Bicycle Research Term the fourth and fifth targets have been completed.

For the three and nine months ended September 30, 2021, the Company recognized $1.1 million and $1.4 million, respectively, of revenue related to the research and development services and termination of the sixth target, and for the three and nine months ended September 30, 2020 the Company recognized $0.2 million and $0.9 million, respectively, of revenue for the Target Three Research License and Related Service, and research and development services for the fourth and fifth targets. As of September 30, 2021 and December 31, 2020, the Company recorded $2.4 million and $3.8 million, respectively, of deferred revenue in connection with the Additional Four Target Option and related contracts.

Oxurion Collaboration Agreement

Summary of Agreement

In August 2013, as amended in November 2017, the Company entered into a Research Collaboration and License Agreement (the "Oxurion Collaboration Agreement") with Oxurion. Under the Oxurion Collaboration Agreement, the Company was responsible for identifying Bicycle peptides related to the collaboration target, plasma kallikrein, for use in various ophthalmic indications. Oxurion is responsible for further development and product commercialization after the defined research screening is performed by the Company. Under the Oxurion Collaboration Agreement, the Company granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Company is eligible to receive up to €8.3 million upon the achievement of specified research, development, regulatory and commercial events of which €3.8 million has been received as of September 30, 2021. In addition, the Company is eligible to receive up to €16.5 million upon achievement of certain regulatory milestone payments (e.g. €5 million for granting first regulatory approval in either the United States or the European Union for the first indication). In addition, to the extent any of the collaboration products covered by the licenses granted to Oxurion are commercialized, the Company would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales.

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

The Company achieved a milestone related to the initiation of a Phase II clinical trial and $2.4 million was recognized in revenue during each of the three and nine months ended September 30, 2020, as there are no remaining performance obligations associated with the Oxurion Collaboration Agreement. No other unpaid development or regulatory milestones have been included in the transaction price, as all milestones are not considered probable at September 30, 2021 and December 31, 2020. The Company recognized no collaboration revenue during each of the three and nine months ended September 30, 2021. As of September 30, 2021, and December 31, 2020 the Company recorded zero deferred revenue related to its collaboration with Oxurion.

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

	Beginning Balance January 1, 2021	Additions	Deductions	Impact of Exchange Rates	Ending Balance September 30, 2021
Contract liabilities:					
Deferred revenue					
Ionis collaboration deferred revenue	$ 3,000	$ 34,442	$ (2,066)	$ (816)	$ 34,560
Genentech collaboration deferred revenue	27,579	2,000	(4,142)	(347)	25,090
DDF collaboration deferred revenue	821	—	(314)	(4)	503
AstraZeneca collaboration deferred revenue	3,756	54	(1,404)	(52)	2,354
Total deferred revenue	$ 35,156	$ 36,496	$ (7,926)	$ (1,219)	$ 62,507

	Beginning Balance January 1, 2020	Additions	Deductions	Impact of Exchange Rates	Ending Balance December 30, 2020
Contract liabilities:					
Deferred revenue					
Ionis evaluation and option agreement deferred revenue	$ —	$ 3,000	$ —	$ —	$ 3,000
Genentech collaboration deferred revenue	—	31,000	(4,896)	1,475	27,579
DDF collaboration deferred revenue	744	500	(436)	13	821
AstraZeneca collaboration deferred revenue	4,913	585	(2,696)	954	3,756
Total deferred revenue	$ 5,657	$ 35,085	$ (8,028)	$ 2,442	$ 35,156

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 September 30, 2021 or December 31, 2020.

The Ionis deferred revenue balance at September 30, 2021 includes $3.9 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 September 30, 2021 includes $21.8 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 September 30, 2021 includes $2.4 million allocated to the Target 4 and Target 5 Material Rights, which will commence revenue recognition when the respective option is exercised at the end of AZ Research Term or when the option expires.

During the three and nine months ended September 30, 2021 and 2020, 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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Revenue recognized in the period from:				
Revenue recognized based on proportional performance	$ 3,206	$ 1,267	$ 6,263	$ 3,496
Revenue recognized based on expiration of material rights	1,127	—	1,507	—
Revenue recognized based on changes in transaction price	—	—	156	—
Total	$ 4,333	$ 1,267	$ 7,926	$ 3,496

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 Development*, 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 $3.0 million and $2.6 million at September 30, 2021 and at December 31, 2020, respectively, which is recorded in other long-term liabilities in the

condensed consolidated balance sheets. The liability is recorded as incremental research and development expense in the 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 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 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 as of September 30, 2021.

10. Income Taxes

During the three and nine months ended September 30, 2021, the Company recorded an income tax benefit of $0.4 million and $0.9 million, respectively, and during the three and nine months ended September 30, 2020, the Company recorded an income tax benefit of $0.5 million and $0.7 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 United Kingdom, and the Company 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 United Kingdom. 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 September 30, 2021 and December 31, 2020.

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

In September 2017, Bicycle Therapeutics Inc. entered into a lease agreement for office and laboratory space in Lexington, Massachusetts, which commenced on January 1, 2018 and expires on December 31, 2022. Bicycle Therapeutics Inc. has the option to extend for a successive period which is not included in the lease term as it is not reasonably certain that the option will be exercised. In conjunction with the lease agreement, Bicycle Therapeutics Inc. paid a security deposit of $0.2 million as well as prepaid rent of $0.1 million for the first month of the third, fourth, and fifth year of the lease. The deposit is recorded in other assets in the condensed consolidated balance sheets. The Company has recorded a right-of-use asset (inclusive of the impact of prepaid rent) and corresponding lease liability, by calculating the present value of lease payments, discounted at 9%, the incremental borrowing rate, over the lease term.

In October 2017, BicycleRD Limited entered into a lease agreement for office and laboratory space in Building 900, Babraham Research Campus, Cambridge, U.K. which expires on December 11, 2021. The annual rent is approximately $0.5 million. The lease agreement provides that the Company has 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 incremental borrowing rate, over the new lease term. The payments for the modified lease are approximately $0.5 million through December 31, 2021, and $0.8 million annually thereafter. Service charges are also payable based on floor area and are estimated to be approximately $0.1 million per year. In conjunction with the October 2017 lease agreement, the Company paid a security deposit of $0.6 million, which

is recorded in other current assets in the condensed consolidated balance sheets. In June 2021, the Company exercised its option to renew the Cambridge, U.K. lease for five years commencing December 12, 2021.

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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Operating lease cost	$ 273	$ 226	$ 773	$ 669
Variable lease cost	222	153	444	456
Total lease cost	$ 495	$ 379	$ 1,217	$ 1,125

The weighted average remaining operating lease term was 4.6 years and 1.9 years for the period ended September 30, 2021 and 2020, respectively, and the weighted average discount rate was 7.89% and 8.61% for the period ended September 30, 2021, and 2020, respectively.

The following table summarizes the maturities of the Company's operating leases as of September 30, 2021, including the payments for the U.K. lease renewal which is reasonably certain of being extended (in thousands):

Year Ending December 31,	
2021	$ 235
2022	1,087
2023	646
2024	646
2025	646
2026	646
Present value adjustment	(585)
Total lease liabilities	3,321
Less: current lease liabilities	(826)
Long term lease liabilities	$ 2,495

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.

In September 2016, BicycleRD Limited, filed a complaint in the District Court of the Hague against Pepscan Systems B.V. and its affiliates ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement entered into with Pepscan in 2009. On November 20, 2020, the Company entered into a settlement and license agreement with Pepscan regarding Bicycle's use of Pepscan's CLIPS peptide technology. The companies agreed to settle all intellectual property disputes worldwide. Under the terms of the settlement, Bicycle has been granted a license to use CLIPS peptide technology in the development of its product candidates BT1718 and THR-149. Bicycle paid €3.0 million in November 2020, will pay €1.0 million on the first anniversary of the date of settlement, and will make additional future milestone payments upon the achievement of development, regulatory and commercial

milestones, with an aggregate total value of $92.4 million. The Company recorded $4.7 million of expense related to the settlement and license agreement with Pepscan during the year ended December 31, 2020, and a liability of $1.2 million related to the Pepscan litigation as of December 31, 2020 and September 30, 2021, which is included in current liabilities in the condensed consolidated balance sheet.

Founder royalty arrangements

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

Indemnification obligations

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has indemnification obligations towards members of its board of directors and officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification arrangements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnification obligations. The Company is not aware of any claims under indemnification arrangements, and therefore it has not accrued any liabilities related to such obligations in its condensed consolidated financial statements as of September 30, 2021 and December 31, 2020.

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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Numerator:				
Net loss	$ (14,678)	$ (10,138)	$ (48,782)	$ (33,577)
Denominator:				
Weighted average ordinary shares outstanding, basic and diluted	25,039,990	19,426,833	23,719,124	18,504,013
Net loss per share, basic and diluted	$ (0.59)	$ (0.52)	$ (2.06)	$ (1.81)

The Company's potentially dilutive securities, which are options to purchase ordinary shares, has 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:

	Nine Months Ended September 30,	
	2021	2020
Options to purchase ordinary shares	4,717,166	3,779,785

13. Benefit plans

The Company established a defined-contribution savings plan under Section 401(k) of the Code (the "401(k) Plan"). The 401(k) Plan covers all U.S. employees and allows participants to defer a portion of their annual compensation on a pre-tax basis. Matching contributions to the 401(k) Plan may be made at the discretion of the Company's board of directors. During the three and nine months ended September 30, 2021, the Company made contributions totaling $0.1 million and $0.2 million, respectively, and during the three and nine months ended September 30, 2020, the Company made contributions totaling $34,000 and $0.1 million, respectively, to the 401(k) Plan.

The Company provides a pension contribution plan for its employees in the United Kingdom, pursuant to which the Company may make contributions each year ("U.K Plan"). During the three and nine months ended September 30, 2021, the Company made contributions totaling $0.2 million, and $0.5 million, respectively, and during the three and nine months ended September 30, 2020, the Company made contributions totaling $0.1 million and $0.3 million, respectively, to the U.K. Plan.

14. Related party transactions

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

The Chairman of the Company's board of directors is associated with Stone Sunny Isles Inc., which provided consultancy services to the Company totaling $43,000 and $0.1 million during the three and nine months ended September 30, 2021, respectively, and $40,000 and $0.1 million during the three and nine months ended September 30, 2020, respectively.

15. 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):

	September 30, 2021	December 31, 2020
United States	$ 1,275	$ 1,708
United Kingdom	4,408	1,899
	$ 5,683	$ 3,607

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

16. Subsequent events

Underwritten Public Offering

On October 15, 2021, the Company issued and sold 3,726,852 ADSs, representing the same number of ordinary shares, at a price to the public of $54.00 per ADS, resulting in gross proceeds of $201.3 million before deducting underwriting discounts, commissions and offering expenses.

Genentech Expansion Option

In October 2021, pursuant to Genentech exercising an option, an additional program has been agreed to be added to the collaboration, which triggers a $10 million payment to the Company under the Genentech Collaboration Agreement.

UK Lease

On November 1, 2021, BicycleTx Limited entered into an agreement for lease for office and laboratory space, in Cambridge, United Kingdom. The lease will commence upon the completion of the landlord’s work. The lease has a contractual period of 10 years, but may be cancelled by BicycleTx Limited on the 5th anniversary of the lease commencement date subject to certain conditions being met. In addition, BicycleTx Limited has a contractual right to renew for a further ten years. The annual rent will be settled once the landlord's work is completed and the premises is measured, subject to a maximum of approximately £2.2 million per year.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our unaudited condensed consolidated financial statements and the related notes appearing elsewhere in this Quarterly Report on Form 10-Q and our audited financial statements and related notes for the year ended December 31, 2020 included in our Annual Report on Form 10-K for the year ended December 31, 2020, or the 2020 Annual Report, which was filed with the Securities and Exchange Commission, or SEC, on March 11, 2021. Some of the information contained in this discussion and analysis or set forth elsewhere in this report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks, uncertainties and assumptions. Factors that might cause future results to differ materially from those projected in the forward-looking statements include, but are not limited to, those set forth under the heading "Risk Factors" in Part II, Item 1A of this report. Such factors may be amplified by the ongoing COVID-19 pandemic and its potential impact on our business and the global economy.

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.

Each of our product candidates, BT5528, BT8009, and BT1718, is 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 product candidate BT7480 is 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. 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 preliminary 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. We announced that we plan to initiate expansion cohorts in this clinical trial in urothelial and ovarian cancers, as well as in a basket cohort that includes head and neck, non-small cell lung, gastroesophageal and triple negative breast cancers. In our ongoing Phase I clinical trial of BT8009, we observed preliminary signs of anti-tumor activity in urothelial cancer patients, and the dose escalation remains ongoing. In addition, enrollment in the ongoing Phase IIa

portion of a Phase I/IIa clinical trial sponsored and fully funded by Cancer Research UK has been slower than expected and remains below projections, although there has been an acceleration in the second half of the year.

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

COVID-19 Business Update

In 2020, with the global spread of the ongoing COVID-19 pandemic, we 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 our employees, customers and our business. While we are experiencing limited financial and operational impacts at this time, given the global economic slowdown, the overall disruption of global healthcare systems and the other risks and uncertainties associated with the pandemic, our business, financial condition, results of operations and growth prospects could be materially adversely affected. We continue to closely monitor the ongoing COVID-19 situation as we evolve our business continuity plans and response strategy. Our laboratories in the United Kingdom and the United States remain operational. We have implemented plans that allow non-laboratory based employees to return to the office in a phased approach that is principles-based and local in design, with a focus on employee safety and optimal work environment. 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.

Clinical Development

With respect to clinical development, our CROs have taken measures to implement remote and virtual approaches, including remote patient monitoring where possible, to maintain patient safety and trial continuity and to preserve trial integrity. While we have not experienced a material impact to our business, during the first half of 2020, all clinical sites for the Phase I/IIa trial of BT1718 being conducted by CRUK in the United Kingdom temporarily paused enrollment of new patients due to the COVID-19 pandemic. The pause in enrollment was lifted during the second quarter of 2020 and patient enrollment in the Phase IIa portion of the clinical trial remains underway. We are also currently enrolling patients in ongoing Phase I/II clinical trials for BT5528, BT8009 and BT7480. Clinical trial sites have remained open and activities are ongoing. However, changes in circumstances related to the ongoing COVID-19 pandemic could result in future pauses in or other impacts on enrollment. We could also see an impact on the ability to supply study drug, 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 rely on contract research organizations or other third parties to assist us with clinical trials, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the ongoing COVID-19 pandemic. If the COVID-19 pandemic is exacerbated or persists for an extended period of time, or 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.

Supply Chain

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. If the COVID-19 pandemic persists for an extended period of time or begins to impact essential distribution systems such as FedEx and postal delivery, 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.

Other Financial and Corporate Impacts

The impact of the ongoing COVID-19 pandemic on our business operations and financial results, clinical development and regulatory efforts, corporate development objectives and the value of and market for our ADSs, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the United Kingdom, United States, Europe and other countries, and the effectiveness of actions taken globally to contain and treat the disease. If remote work policies for certain portions of our business, or that of our business partners, are extended longer than we currently expect or are reimposed due to increased incidence or infection rates, we may need to reassess our priorities and our corporate objectives. Additionally, our operations, ability to timely and accurately report financial results, the operating effectiveness of our internal controls, and the security of our informational technology and systems could be impacted.

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 (formerly ThromboGenics NV), or Oxurion; and borrowings pursuant to our debt facility with Hercules Capital, Inc., or Hercules. From our inception in 2009 through September 30, 2021, we have received gross proceeds of $354.0 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering and at-the-market, or ATM, offering program; $112.6 million of cash payments under our collaboration revenue arrangements, including $45.0 million from Ionis, $33.0 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 $14.7 million and $48.8 million for the three and nine months ended September 30, 2021, respectively. As of September 30, 2021, we had an accumulated deficit of $200.3 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, BT1718 and BT7480;
- 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, any future commercialization efforts, and our operations as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain marketing approval for one or more of our product candidates, which we expect will take many years and is subject to significant uncertainty. We have no commercial-scale manufacturing facilities of our own, and all of our manufacturing activities have been and are planned to be contracted out to third parties. Additionally, we currently utilize third-party contract research organizations, or CROs, to carry out many of 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. The ongoing COVID-19 pandemic has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, whether as a result of the ongoing COVID-19 pandemic or otherwise, we could experience an inability to access additional capital.

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

As of September 30, 2021, we had cash of $259.5 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.”

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 are recorded as an offset to research and development expense. See "—Benefit from Income Taxes." In addition, we may enter into arrangements with governmental entities for the purpose of obtaining funding for research and development activities. We recognize government grant funding in the condensed consolidated statements of operations and comprehensive loss as a reduction to the related research and development expenses as the related expenses being funded are incurred.

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, BT1718 and BT7480; (ii) initiate clinical trials for our product candidates, including BT7455 and BT7401; and (iii) build our in-house process development and analytical capabilities and continue to discover and develop additional product candidates.

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

- whether our business will be adversely affected by the ongoing COVID-19 pandemic, which could materially affect our operations, delay our research efforts and clinical trials and cause significant disruption in the operations and business of third-party manufacturers, contract research organizations, or CROs, other service providers, and collaborators with whom we conduct business; and

- completing research and preclinical development of our product candidates, including conducting future clinical trials of BT5528, BT8009, BT1718 and BT7480;

- 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. For instance, all clinical sites for the Phase I/IIa trial of BT1718 being conducted by Cancer Research UK in the United Kingdom, temporarily paused enrollment of new patients due to the ongoing COVID-19 pandemic during the first half of 2020. The pause in enrollment was lifted in the second quarter of 2020, and patient enrollment in the Phase IIa portion of the clinical trial remains underway. However, changes in circumstances related to the ongoing COVID-19 pandemic could result in future pauses in or other impacts on enrollment. In addition, we may obtain unexpected results from our clinical trials, and we may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success.

General and Administrative Expenses

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

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

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

Other Income (Expense)

Interest Income

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

Interest Expense

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

Benefit From Income Taxes

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

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

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

Based on criteria established by U.K. law, a portion of expenditures being carried out in relation to our pipeline research and development, clinical trials management and manufacturing development activities were eligible for the SME Program for the year ended December 31, 2020.

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 September 30, 2021 and 2020

The following table summarizes our results of operations for the three months ended September 30, 2021 and 2020:

	Three Months Ended September 30,		
	2021	2020	Change
	(in thousands)		
Collaboration revenues	$ 4,333	$ 3,842	$ 491
Operating expenses:			
Research and development	10,513	7,363	3,150
General and administrative	8,114	7,154	960
Total operating expenses	18,627	14,517	4,110
Loss from operations	(14,294)	(10,675)	(3,619)
Other income (expense):			
Interest income	24	72	(48)
Interest expense	(823)	—	(823)
Total other income (expense), net	(799)	72	(871)
Net loss before income tax provision	(15,093)	(10,603)	(4,490)
Benefit from income taxes	(415)	(465)	50
Net loss	$ (14,678)	$ (10,138)	$ (4,540)

Collaboration Revenues

Collaboration revenues increased by $0.5 million in the three months ended September 30, 2021, compared to the three months ended September 30, 2020, primarily due to an increase of $2.1 million from our collaboration with Ionis entered into in July 2021 and an increase of $0.9 million from our collaboration with AstraZeneca for the termination of the collaboration activities related to the sixth target, offset by a $2.4 million decrease related to our collaboration with Oxurion due to a milestone achieved for the initiation of a Phase II trial of THR-149 in 2020.

Research and Development Expenses

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

	Three Months Ended September 30,		
	2021	2020	Change
	(in thousands)		
BT1718 (MT1)	$ 171	$ 133	$ 38
BT5528 (EphA2)	1,320	1,124	196
BT8009 (Nectin-4)	2,355	1,108	1,247
Bicycle tumor-targeted immune cell agonists	968	378	590
Other discovery and platform related expense	3,797	2,414	1,383
Employee and contractor related expenses	4,085	2,887	1,198
Share-based compensation	1,238	668	570
Facility expenses	389	325	64
Research and development incentives	(3,810)	(1,674)	(2,136)
Total research and development expenses	$ 10,513	$ 7,363	$ 3,150

Research and development expenses increased by $3.2 million in the three months ended September 30, 2021 compared to the three months ended September 30, 2020, due primarily to an increase of $3.5 million in direct program spend, primarily associated with increased clinical program development expenses for BT8009 and other discovery and platform related expenses, including costs of our collaboration agreements and U.K. government grant activities, as well as an increase of $1.2 million in employee and contractor related expenses attributable to increased headcount and $0.6 million of incremental share-based compensation expense. These increases were offset by a $2.1 million increase in research and development incentives, including U.K. research and development tax credit reimbursement due to the corresponding increase in research and development spending in the United Kingdom and $0.9 million associated with U.K. government grants.

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 September 30, 2021, we have incurred approximately $18.5 million, $16.9 million, $14.0 million, and $9.7 million of direct external expenses for the development of the BT5528, BT8009, BT1718, and *Bicycle* tumor-targeted immune cell agonist 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 September 30,		
	2021	2020	Change
	(in thousands)		
Personnel related costs	$ 2,433	$ 1,456	$ 977
Professional and consulting fees	2,732	2,859	(127)
Other general and administration costs	1,653	1,249	404
Share-based compensation	1,450	842	608
Effect of foreign exchange rates	(154)	748	(902)
Total general and administrative expenses	$ 8,114	$ 7,154	$ 960

General and administrative expenses increased by $1.0 million in the three months ended September 30, 2021 compared to the three months ended September 30, 2020. This increase is primarily due to an increase of $1.0 million in personnel related costs, a $0.6 million increase in share-based compensation, an increase of $0.4 million in other general and administrative costs, including insurance expense, to support operations as a public company. These amounts were offset primarily by a $0.9 million favorable impact of foreign exchange rates during the three months ended September 30, 2021 as compared to the three months ended September 30, 2020.

Other Income (Expense), net

Other income (expense), net decreased by $0.9 million in the three months ended September 30, 2021 compared to the three months ended September 30, 2020, primarily due to interest expense related to our Loan Agreement entered into in September 2020.

Comparison of the Nine Months Ended September 30, 2021 and 2020

The following table summarizes our results of operations for the nine months ended September 30, 2021 and 2020:

	Nine Months Ended September 30,		
	2021	2020	Change
	(in thousands)		
Collaboration revenues	$ 7,926	$ 6,542	$ 1,384
Operating expenses:			
Research and development	31,924	23,091	8,833
General and administrative	23,596	18,351	5,245
Total operating expenses	55,520	41,442	14,078
Loss from operations	(47,594)	(34,900)	(12,694)
Other income (expense):			
Interest income	61	655	(594)
Interest expense	(2,164)	—	(2,164)
Total other income (expense), net	(2,103)	655	(2,758)
Net loss before income tax provision	(49,697)	(34,245)	(15,452)
Benefit from income taxes	(915)	(668)	(247)
Net loss	$ (48,782)	$ (33,577)	$ (15,205)

Collaboration Revenues

Collaboration revenues increased by $1.4 million in the nine months ended September 30, 2021, compared to the nine months ended September 30, 2020, primarily due to an increase of $2.1 million from our collaboration with Ionis entered into in July 2021 and $1.1 million from our collaboration with Genentech entered into in February 2020, offset by $2.4 million decrease related to our collaboration with Oxurion due to a milestone achieved for the initiation of a Phase II trial of THR-149 in 2020.

Research and Development Expenses

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

	Nine Months Ended September 30,		
	2021	2020	Change
	(in thousands)		
BT1718 (MT1)	$ 524	$ 547	$ (23)
BT5528 (EphA2)	4,144	3,924	220
BT8009 (Nectin-4)	5,851	2,763	3,088
Bicycle tumor-targeted immune cell agonists	4,434	3,979	455
Other discovery and platform related expense	11,420	6,842	4,578
Employee and contractor related expenses	11,779	8,291	3,488
Share-based compensation	3,535	1,863	1,672
Facility expenses	942	969	(27)
Research and development incentives	(10,705)	(6,087)	(4,618)
Total research and development expenses	$ 31,924	$ 23,091	$ 8,833

Research and development expenses increased by $8.8 million in the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020, primarily due to an increase of $8.3 million in direct program spend, primarily associated with increased clinical program development expenses for BT8009 and other discovery and platform related expenses, including costs of our collaboration agreements and U.K. government grant activities, an increase of $3.5 million in employee and contractor related expenses attributable to increased headcount and an increase of $1.7 million of incremental share-based compensation expense. These increases were offset by a $4.6 million increase in research and development incentives, including U.K. research and development tax credit reimbursement due to the corresponding increase in research and development spending in the United Kingdom and $2.6 million associated with U.K. government grants.

General and Administrative Expenses

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

	Nine Months Ended September 30,		
	2021	2020	Change
		(in thousands)	
Personnel related costs	$ 6,615	$ 4,453	$ 2,162
Professional and consulting fees	7,050	7,953	(903)
Other general and administration costs	4,499	3,551	948
Share-based compensation	5,549	3,087	2,462
Effect of foreign exchange rates	(117)	(693)	576
Total general and administrative expenses	$ 23,596	$ 18,351	$ 5,245

General and administrative expenses increased by $5.2 million in the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020. This increase is primarily due to an increase of $2.2 million in personnel related costs, an increase of $2.5 million in share-based compensation, and an unfavorable impact of foreign exchange rates in the amount of $0.6 million, as well as an increase of $0.9 million in other general and administrative costs, including insurance expense, to support operations as a public company, offset by a decrease of $0.9 million in professional and consulting fees, primarily associated with a decrease in external legal costs.

Other Income (Expense), net

Other income (expense), net decreased by $2.8 million in the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020 primarily due to interest expense related to our Loan Agreement, entered into in September 2020.

Liquidity and Capital Resources

From our inception through September 30, 2021, 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, as well as proceeds received from upfront payments, payments for research and development services, and development milestone payments from our collaboration agreements with Ionis, Genentech, DDF, AstraZeneca, Sanofi and Oxurion and borrowings pursuant to our debt facility.

From our inception in 2009 through September 30, 2021, we have received gross proceeds of $354.0 million from the sale of ADSs, ordinary shares, and convertible preferred shares, including the proceeds from our IPO and our at-the-market, or ATM, offering program; $112.6 million of cash payments under our collaboration revenue arrangements including, $45.0 million from Ionis, $33.0 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.

Ionis Agreements

Ionis Evaluation and Option Agreement

On December 31, 2020, or the Effective Date, we entered into an Evaluation and Option Agreement, or the Evaluation and Option Agreement, with Ionis. Under the terms of the Evaluation and Option Agreement, we agreed to transfer *Bicycles*, or the Option Materials, to Ionis in order to evaluate a particular application of our technology platform for a period of up to four months, the Evaluation Period. Ionis agreed to pay a non-refundable $3.0 million option fee within five business days after the Effective Date.

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, or the Ionis Option, to obtain an exclusive license to our intellectual property for the purpose of continued research, development, manufacture and commercialization of products within a particular application of our 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.

Ionis Collaboration Agreement

On July 9, 2021, we and Ionis entered into a collaboration and license agreement, or the Ionis Collaboration Agreement, following the exercise on July 9, 2021 by Ionis of the Ionis Option granted pursuant to the Evaluation and Option Agreement. Pursuant to the Ionis Collaboration Agreement, we granted to Ionis a worldwide exclusive license under our relevant technology to research, develop, manufacture and commercialize products incorporating *Bicycle* peptides directed to the protein coded by the gene TFRC1 (transferrin receptor), or TfR1 *Bicycles*, intended for the delivery of oligonucleotide compounds directed to targets selected by Ionis for diagnostic, therapeutic, prophylactic and preventative uses in humans.

Under the Ionis Collaboration Agreement, Ionis made an 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 us 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 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 payment of a low-single-digit million dollar amount upon acceptance of an investigational new drug application, or IND, for the first product directed to such collaboration target (provided that Ionis will have a credit of a high single-digit million dollar amount 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, we are also eligible to receive up to a low double-digit million dollar amount in cumulative sales milestone payments. We are 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.

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, we entered into the Ionis Share Purchase Agreement with Ionis, pursuant to which Ionis purchased 282,485 of our ordinary shares at a price per share of $38.94, for an aggregate purchase price of approximately $11.0 million.

Loan Agreement

On September 30, 2020, the Closing Date, we entered into the Loan Agreement with Hercules as agent, which provided for aggregate maximum borrowings of up to $40.0 million, consisting of (i) a term loan of $15.0 million, which was funded on the Closing Date, (ii) subject to customary conditions, an additional term loan of up to $15.0 million available from the Closing Date through March 15, 2021, and (iii) subject to our achievement of certain performance milestones and satisfaction of customary conditions and available until March 15, 2022, an additional term loan of $10.0 million. Borrowings under the Loan Agreement bear interest at an annual rate equal to the greater of (i) 8.85% and (ii) the prime rate of interest plus 5.60%. On March 10, 2021, or the Amendment Closing Date, we entered into the First Amendment to the Loan and Security Agreement, or 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 our debt facility with Hercules will be interest-only until the first payment is due on August 1, 2023, followed by equal monthly payments of principal and interest through October 1, 2024, or the Maturity Date. If we achieve certain performance milestones, the interest-only period will be extended, with the first principal payment due on February 1, 2024. On the Amendment Closing Date and pursuant to the terms of the First Amendment to LSA, we borrowed the additional term loan of $15.0 million that had been available from September 30, 2020 to March 15, 2021. We may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to 2.0% of the principal amount outstanding if the prepayment occurs during the first year following the Closing Date, 1.5% of the principal amount outstanding if the prepayment occurs during the second year following the Closing Date; and 1.0% thereafter but prior to the Maturity Date. The Loan Agreement also provides for an end of term charge, payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. If we fail to make payments when due, or breach any operational covenant or have any event of default, this could have a material adverse effect on our business and financial condition.

On June 5, 2020, we entered into a sales agreement, or the Sales Agreement, with Cantor Fitzgerald & Co. and Oppenheimer & Co. Inc., or the Sales Agents, with respect to an ATM offering program pursuant to which we may offer and sell through the Sales Agents, from time to time at our sole discretion, ADSs. As of September 30, 2021, we had issued and sold 6,700,497 ADSs, representing the same number of ordinary shares, for gross proceeds of $155.8 million, resulting in net proceeds of $150.7 million after deducting sales commissions and offering expenses of $5.1 million.

Cash Flows

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

	Nine Months Ended September 30,	
	2021	2020
Net cash used in operating activities	$ (4,359)	$ (1,172)
Net cash used in investing activities	(963)	(716)
Net cash provided by financing activities	130,061	61,099
Effect of exchange rate changes on cash	(1,205)	(1,486)
Net increase in cash	$ 123,534	$ 57,725

Operating Activities

Net cash used in operating activities for the nine months ended September 30, 2021 included our net loss of $48.8 million, net cash used by changes in our operating assets and liabilities of $34.0 million and non-cash charges of $10.4 million, which primarily included share-based compensation expense of $9.1 million, and depreciation and

amortization of $1.0 million. Net changes in our operating assets and liabilities for the nine months ended September 30, 2021 consisted primarily of an increase of $28.5 million in deferred revenue primarily from the upfront payment received from the Ionis arrangement, a decrease of $5.5 million in accounts receivable, and a decrease of $1.3 million in research and development incentives receivable, offset by an increase of $1.7 million in prepaid expenses and other current assets.

Net cash used in operating activities for the nine months ended September 30, 2020 included our net loss of $33.6 million, net cash generated by changes in our operating assets and liabilities of $26.5 million and non-cash charges of $5.9 million, which included share-based compensation expense of $5.0 million, and depreciation and amortization of $0.9 million. Net changes in our operating assets and liabilities for the nine months ended September 30, 2020 consisted primarily of an increase of $27.8 million in deferred revenue primarily from the upfront payment received from the Genentech arrangement, an increase of $1.0 million in accrued expenses and other current liabilities, a decrease of $0.9 million in research and development incentives receivable, and an increase of $0.4 million in other long-term liabilities, offset by an increase of $2.7 million in accounts receivable.

Investing Activities

During the nine months ended September 30, 2021 and 2020, we used $1.0 million and $0.7 million, respectively, of cash in investing activities for purchases of property and equipment, consisting primarily of laboratory equipment.

Financing Activities

During the nine months ended September 30, 2021, net cash provided by financing activities was $130.1 million, primarily consisting of net proceeds from our ATM of $102.6 million, $15.0 million under our Loan Agreement with Hercules, as well as proceeds of $7.6 million from the issuance of ordinary shares under the share purchase agreement with Ionis, and $4.9 million from the exercise of share options.

During the nine months ended September 30, 2020, net cash provided by financing activities was $61.1 million, primarily consisting of net proceeds from our ATM of $46.4 million and $15.0 million under our Loan Agreement with Hercules, offset by $0.4 million in debt issuance costs.

Funding Requirements

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

- continue our development of our product candidates, including conducting future clinical trials of BT5528, BT8009, BT1718 and BT7480;
- progress the preclinical and clinical development for BT7455 and BT7401;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to seek to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;

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

- acquire or in-license other products and technologies;

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

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

In addition, if we obtain marketing approval for any product candidate that we identify and develop, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing, and distribution to the extent that such sales, marketing, and distribution are not the responsibility of our collaboration partners. Even if we are able to generate product sales, we may not become profitable. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce, or eliminate our research and development programs or future commercialization efforts. The ongoing COVID-19 pandemic has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, or if infection rates increase in areas where they have previously declined, we could experience an inability to access additional capital.

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

- our ability to raise capital in light of the impacts of the ongoing global COVID-19 pandemic on the global financial markets;

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

- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs, particularly in light of the global COVID-19 pandemic;

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

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

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

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

- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, and distribution, for any product candidates for which we receive marketing approval;
- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.
- the success of our collaborations with 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. The ongoing COVID-19 pandemic continues to rapidly evolve and has already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, or if infection rates increase in areas where they have previously declined, we could experience an inability to access additional capital, which could in the future negatively affect our operations. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of September 30, 2021 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

	Payments due by period			
	Total	Less than 1 year	1 to 3 years	More than 3 years to 5 years
	(in thousands)			
Operating lease commitments (1)	$ 3,906	$ 1,041	$ 2,058	$ 807
Debt obligations (2)	38,264	2,692	35,572	—
Total	$ 42,170	$ 3,733	$ 37,630	$ 807

(1) Amounts reflect minimum payments due for our office and laboratory space leases. We lease space in Lexington, Massachusetts under an operating lease that expires in December 2022. We also lease space in Cambridge, United Kingdom under an operating lease that expires in December 2021. In June 2021, we exercised our option to renew our lease for five years commencing December 12, 2021. The amounts include our expected future minimum payments for a five-year extension of our UK operating lease through December 2026.

(2) Amounts in table reflect the contractually required principal, interest, and the final payment under the Loan Agreement with Hercules as of September 30, 2021.

In the ordinary course of business, we enter into various agreements with contract research organizations to provide clinical trial services, with contract manufacturing organizations to provide clinical trial materials, and with

vendors for preclinical research studies, synthetic chemistry and other services for operating purposes. These payments are not included in the table of contractual obligations above since the contracts are generally cancelable with advanced written notice, with a notice period of 90 days or less. 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.

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 September 30, 2021, we were unable to estimate the timing or likelihood of achieving these milestones.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our 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. Our critical accounting policies are described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Significant Judgments and Estimates" in our 2020 Annual Report, which was filed with the SEC on March 11, 2021. 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 policies from those described in our 2020 Annual Report.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities as defined in the rules and regulations of the SEC.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act. The JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to "opt out" of this provision and, as a result, we will comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies or smaller reporting companies.

In addition, we have historically relied on other exemptions and reduced reporting requirements provided by the JOBS Act and intend to do so until such time as we are no longer an EGC. Subject to certain conditions set forth in the JOBS Act, for so long as we are an EGC, we are entitled to rely on certain exemptions, and we are not required to, among other things, (i) provide an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b), (ii) provide all of the compensation disclosure that may be required of non-emerging growth public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements (auditor discussion and analysis), and (iv) disclose certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer's compensation to median employee compensation.

Based on the market value of our ordinary shares and ADSs held by non-affiliates as of June 30, 2021, we expect to cease being an EGC on December 31, 2021.

We were also a smaller reporting company as defined in the Securities Exchange Act of 1934, as amended, until June 30, 2021. We have historically taken, and may continue through the filing of our Annual Report on Form 10-K for the year ending December 31, 2021 to take, advantage of certain scaled disclosures available to smaller reporting companies.

Item 3. Quantitative and Qualitative Disclosure About Market Risk

Interest Rate Sensitivity

As of September 30, 2021, we had cash of $259.5 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in interest-bearing savings accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

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 September 30, 2021. 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 September 30, 2021, our outstanding indebtedness with Hercules bears interest at 8.85%. If the prime rate increases to over 3.25%, the interest on our loan with Hercules will increase. We currently do not engage in any interest rate hedging activity, and we have no intention to do so in the foreseeable future. Based on the current interest rate of the term loan and the scheduled payments thereunder, we do not believe a 1.0% increase in interest rates would have a material impact on our financial condition or results of operations.

Foreign Currency Exchange Risk

The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. The functional currency of Bicycle Therapeutics plc and Bicycle Therapeutics Inc. is the United States dollar. The functional currency of 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 a foreign exchange gain of $0.2 million and foreign exchange loss of $0.7 million for the three months ended September 30, 2021 and 2020, respectively, and foreign exchange gains of $0.1 million and $0.7 million for the nine months ended September 30, 2021, and 2020, 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 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 convertible preferred shares and 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 as September 30, 2021, 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 September 30, 2021 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, in our 2020 Annual Report and in our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2021 and June 30, 2021, 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.

In January and February 2019, we, Oxurion and a further anonymous party filed a notice of opposition in respect of Dyax Corp's European patent 2 374 472, which is a divisional filing of European patent 1 854 477. Claim 1 of this divisional patent reads as follows: "A composition comprising at least one plasma kallikrein inhibitor for the use in the treatment of an ophthalmic disorder". This patent was revoked by the Opposition Division during Oral Proceedings before the European Patent Office on March 11, 2021 and the written decision was issued on May 3, 2021. The deadline for Dyax to appeal this decision was two months from the date of the written decision. On August 17, 2021, the European Patent Office issued a communication indicating that no appeals were filed within the time limit meaning that the decision to revoke the patent is final.

Item 1A. Risk Factors.

Risk Factors

Our operations and financial results are subject to various risks and uncertainties, including those described below. The following information about these risks and uncertainties, together with the other information appearing elsewhere in this Quarterly Report on Form 10-Q, and our 2020 Annual Report, filed with the Securities and Exchange Commission, or SEC, on March 11, 2021, including our consolidated financial statements and related notes thereto, should be carefully considered before a decision to invest in our ADSs. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. Additional risks that are currently unknown to us or that we currently believe to be immaterial may also impair our business. In these circumstances, the market price of our ADSs could decline and holders of our ADSs may lose all or part of their investment. We cannot provide assurance that any of the events discussed below will not occur.

Risks Related to Our Financial Position and Need for Additional Capital

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

We do not expect to generate revenue or profitability that is necessary to finance our operations in the short term. Since inception, we have incurred recurring losses, including net losses of $48.8 million and $33.6 million, for the nine months ended September 30, 2021 and 2020, respectively. As of September 30, 2021, the Company had an accumulated deficit of $200.3 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, AstraZeneca AB, or AstraZeneca, Oxurion NV (formerly ThromboGenics NV), or Oxurion and Sanofi (formerly Bioverativ Inc.). There can be no assurance that we will generate revenue from our collaborations in the future.

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

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

Our business commenced operations in 2009. Our operations to date have been limited to financing and staffing our company, developing our technology, conducting preclinical research and early-stage clinical trials for our product candidates and pursuing strategic collaborations to advance our product candidates. We have not yet demonstrated an ability to successfully conduct late-stage clinical trials, obtain marketing approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, any current or prospective holder of our ADSs or ordinary shares should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical-stage biopharmaceutical companies such as ours, all of which delays and difficulties may be exacerbated as a result of the ongoing COVID-19 pandemic. Any predictions made about our future success or viability may not be as accurate as they would be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

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

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control and reliance should not be made upon the results of any quarterly or annual periods as indications of future operating performance.

We may need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.

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

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

We believe that our existing cash of $259.5 million as of September 30, 2021, 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, including the unanticipated impacts of the ongoing COVID-19 pandemic, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

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

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

- the costs of operating as a public company.

The COVID-19 pandemic, which continues to cause a broad impact globally, may materially affect us economically. While the long-term economic impact of the pandemic is difficult to assess or predict, it has already significantly disrupted global financial markets 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 September 30, 2021, our outstanding borrowings under this facility totaled $30.0 million. Subject to our achievement of certain performance milestones and satisfaction of customary conditions we may borrow an additional term loan of $10.0 million through March 15, 2022. In connection with the Loan Agreement with Hercules, or the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control (as defined by the Loan Agreement), financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a material adverse effect as set forth in the Loan Agreement, cross acceleration to third-party indebtedness and certain events relating to bankruptcy or insolvency. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal balance, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement, including proceeding against the collateral securing such indebtedness. Such increased interest charges, accelerated repayment, proceedings against the collateral or other actions may have a negative impact on our business, financial condition and results of operations.

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

As of September 30, 2021, we had $30.0 million of borrowings outstanding under the Loan Agreement with Hercules, and we may borrow up to an additional $10.0 million in the aggregate under the Loan Agreement, subject to certain conditions. We could also in the future incur additional indebtedness pursuant to additional loan agreements.

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

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

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

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

We are substantially dependent on the success of our internal development programs and of our product candidates from our BTC and* 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* TICA programs, and our other product candidates will depend on, among other things, our ability to:

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

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

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

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

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

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

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

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

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

We may also be required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we contemplate, which may lead to us incurring additional unplanned costs or result in delays in clinical development. In addition, we may be required to redesign or otherwise modify our plans with respect to an

ongoing or planned clinical trial, and changing the design of a clinical trial can be expensive and time consuming. An unfavorable outcome in one or more trials would be a major setback for our product candidates and for us. An unfavorable outcome in one or more trials may require us to delay, reduce the scope of or eliminate one or more product development programs, which could have a material adverse effect on our business, financial position, results of operations and future growth prospects.

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

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

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

Furthermore, we sometimes estimate for planning purposes the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies, clinical trials, the submission of regulatory filings or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the completion of an ongoing clinical trial, the initiation of other clinical programs, the receipt of marketing approval or a commercial launch of a product. The achievement of many of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions, which may cause the timing of achievement of the milestones to vary considerably from our estimates. If we fail to achieve milestones in the timeframes we expect, including as a result of the ongoing COVID-19 pandemic, the commercialization of our product candidates may be delayed, we may not be entitled to receive certain contractual payments, which could have a material adverse effect on our business, financial position, results of operations and future growth prospects.

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

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

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

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

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

In addition, clinical testing of 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 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 trial 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 in all four of these trials, including specific patient responses we have observed and disclosed, may not be replicated in the completed data sets or in future trials at global clinical trial sites in a later stage clinical trial conducted by us or our collaborators. Additionally, notwithstanding the commencement of vaccination efforts, the ongoing COVID-19 pandemic may negatively impact our ability to enroll participants in future or later stage trials. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval.

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

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

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

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

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

Undesirable or clinically unmanageable side effects could occur and cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. Results of our trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. As of September 21, 2021, the most recent date for which information has been provided by Cancer Research UK, the most common treatment-related adverse events (>15%, n=48) in subjects exposed to BT1718 in the ongoing Phase I/IIa clinical trial were anemia, diarrhea, nausea, vomiting, fatigue, alanine aminotransferase increase, aspartate aminotransferase increase, decreased appetite, peripheral neuropathy, and weight decrease. BT5528, a BTC targeting EphA2, has been dosed up to what we believe, based on pre-clinical studies, is toward the top of the therapeutic range, with treatment-related adverse events that were grade-3 or above of transient neutropenia, anemia, pneumonitis, fatigue, ileus, tumor lysis syndrome, and acute tubular necrosis secondary to dehydration observed in the Phase I portion of the ongoing Phase I/II trial. In addition, in the ongoing Phase I/II trial of BT8009, a second-generation BTC targeting Nectin-4, the following treatment-related adverse events that were grade-3 or above have been observed to date: anemia, neutropenia, hypertension, hypokalemia, and fatigue.

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, BT1718, BT7480 or any other of our product candidates are safe in humans.

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

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

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

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

Although we intend to utilize our *Bicycle* screening platform to explore other therapeutic opportunities in addition to the product candidates that we are currently developing, we may fail to identify other product candidates for clinical development for a number of reasons. For example, our research methodology may not be successful in identifying potential product candidates or those we identify may be shown to have harmful side effects or other characteristics that make them unmarketable or unlikely to receive regulatory approval. A key part of our strategy is to utilize our screening technology to identify product candidates to pursue in clinical development. Such product

candidates will require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development. If we fail to identify and develop additional potential product candidates, we may be unable to grow our business and our results of operations could be materially harmed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA or other regulatory authorities may determine that our product

candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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

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

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

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

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

We currently have no marketing, sales or distribution capabilities and have limited sales or marketing experience within our organization. If one or more of our product candidates is approved, we intend either to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize that

product candidate, or to outsource this function to a third party. There are risks involved with either establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services.

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

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

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

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

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

Cancer therapies are sometimes characterized as first-line, second-line, third-line or later-line therapies, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy, immunotherapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We may initially seek approval of BT5528, BT8009, BT1718, BT7480 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 (“CMS”), as the CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for novel products such as ours, as there is no body of established practices and precedents for these new products. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a product is: (1) a covered benefit under its health plan; (2) safe, effective and medically necessary; (3) appropriate for the specific patient; (4) cost-effective; and (5) neither experimental nor investigational. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Even if we obtain coverage for a

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

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

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

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

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

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

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

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

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

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

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

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

- the Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare

program, such as the Medicare and Medicaid programs. "Remuneration" has been interpreted broadly to include anything of value. A person or entity does not need to have actual knowledge of the Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act, or FCA, or federal civil money penalties. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

- the federal civil and criminal false claims laws, including the FCA, and civil monetary penalty 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 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) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information

regarding payments and transfers of value provided, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse-midwives;

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

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

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the 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. Another Executive Order terminated the cost- sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. On April 27, 2020, the U.S. Supreme Court reversed the Federal Circuit decision that previously upheld Congress' denial of $12 billion in "risk corridor." The full effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Concurrently, Congress 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, which ran from February 15, 2021 to August 15, 2021. 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 2030 unless additional Congressional action is taken. However, pursuant to certain COVID-19 relief legislation these Medicare sequester reductions have been suspended from May 1, 2020 through December 31, 2021. 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 and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the former Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, former President Trump signed several Executive Orders aimed at lowering drug pricing that seek to implement several of the administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all U.S. states and territories for a seven-year period and was scheduled to begin on January 1, 2021 and end on December 31, 2027. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. On January 13, 2021, in a separate lawsuit brought by industry groups in the U.S. District of Maryland, the government defendants entered a joint motion to stay litigation on the condition that the government would not appeal the preliminary injunction granted in the U.S. District Court for the Northern District of California and that performance for any final regulation stemming from the MFN Model interim final rule shall not commence earlier than sixty (60) days after publication of that regulation in the Federal Register. 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. Based on a recent executive order, the Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The

implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

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

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

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

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

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

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

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

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

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

Risks Related to Our Business and Our International Operations

COVID-19 could impact our business.

Our business could be adversely affected by the effects of the ongoing COVID-19 pandemic in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations. The COVID-19 pandemic could materially affect our operations as well as causing significant disruption in the operations and business of third-party manufacturers, CROs, other services providers, and collaborators with whom we conduct business.

In response to the COVID-19 pandemic, many state, local and foreign governments, including the United Kingdom and the United States, put in place quarantines, executive orders, shelter-in-place or stay-at-home orders and similar government orders and restrictions, including social distancing requirements, occupancy limitations and mask mandates, in order to control the spread of the disease. While many restrictions have recently been relaxed, others have been re-imposed following prior relaxation as a result of continually evolving incidence and rates of infection, including in light of new variants of the SARS-CoV-2 virus that causes COVID-19. Such new or reinstated orders or restrictions, or the perception that such orders or restrictions could occur or continue for a protracted period of time, could result in additional business closures, work stoppages, slowdowns and delays, work-from-home policies, travel restrictions and cancellation of events, among other effects that could negatively impact productivity and disrupt our business and those of third-party manufacturers, CROs, other services providers, and collaborators with whom we conduct business. While the rollout of vaccines has begun, the timing of and ultimate efficacy of vaccinations, complete lifting of movement restrictions, and full reinstitution of in-person events is unknown.

We have implemented plans that allow our non-laboratory based employees to return to the office, which are based on a phased approach. 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 any efforts to return to the office in the future. Additionally, we may experience disruptions if our employees become ill, despite the

availability of vaccines, and are unable to perform their duties. The effects of any of current or future work-from-home policies may negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course.

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

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

It is impossible to predict all effects and the ultimate impact of the COVID-19 pandemic, as the situation continues to evolve. The full extent of COVID-19's impact on our clinical development and other operations and financial performance depends on future developments that are uncertain and unpredictable, including the timing of vaccine rollouts and herd immunity, virus mutations and variants and any new information that may emerge concerning the SARS-CoV-2 virus, vaccines and containment, all of which may vary across regions. Any of these factors could have a material adverse impact on our business, financial condition, operating results, and ability to execute and capitalize on our strategies.

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

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

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;

- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, natural disasters, including earthquakes, typhoons, floods and fires, or public health crises, including outbreaks of COVID-19 or H1N1 flu.

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

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

The collection and use of personal data (including health-related personal data) in the EEA, is governed by the provisions of the E.U. General Data Protection Regulation 2016/679, or GDPR, which became effective and enforceable across all then-current member states of the EEA on May 25, 2018. Also, notwithstanding the United Kingdom's withdrawal from the EU, 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 the European Commission or other relevant regulatory body has not issued a so-called "adequacy decision," 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 invalidated the use of the EU-U.S. Privacy Shield as a 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 must 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. The implementation of the new Standard Contractual Clauses will necessitate significant contractual overhaul of our data transfer arrangements with customers, sub-processors and vendors.

Use of both the existing and the new Standard Contractual Clauses 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 the Standard Contractual Clauses and there remains some uncertainty with respect to the nature and efficacy of such supplementary measures in ensuring an adequate level of protection of 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 the Standard Contractual Clauses can and cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate and/or engage providers and/or otherwise transfer personal data, it could affect the manner in which we receive and/or provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results and generally increase compliance risk. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of operating our business.

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 SCCs, to enable transfers of personal data from the EEA to the United Kingdom to continue.

In addition, while the U.K. data protection regime currently permits data transfers from the United Kingdom to the EEA and other third countries covered by a European Commission adequacy decision, and currently includes a framework to permit the continued use of the existing version of the EU Standard Contractual Clauses and binding corporate rules for personal data transfers from the United Kingdom to third countries, this is subject to change in the future, and any such changes could have implications for our transfers of personal data from the United Kingdom to the EEA and other third countries. In particular, the U.K. Information Commissioner's Office has stated that it is working on its own bespoke version of Standard Contractual Clauses and it is not clear whether the new Standard Contractual Clauses published by the European Commission will be accepted as a valid mechanism to permit the transfer of personal data from the United Kingdom to third countries and/or whether any U.K. version of Standard Contractual Clauses will supersede the existing and/or new EU Standard Contractual Clauses. This could necessitate the implementation of both U.K. and EU versions of Standard Contractual Clauses, which would require significant resources and necessitate significant cost, to implement and manage.

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, with effect from January 1, 2021, we are not able to benefit from the GDPR's "one stop shop" mechanism. Amongst other things, this would mean that, in the event of a violation of the GDPR affecting data subjects across the United Kingdom and the EEA, we could be investigated by, and ultimately fined by the United Kingdom Information Commissioner's Office and the supervisory authority in each and every EEA member state where data subjects have been affected by such violation. Other countries have also passed or are considering passing laws

requiring local data residency and/or restricting the international transfer of data.

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

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

Risks Related to Our Dependence on Third Parties

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

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

Under our collaborations with 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 could materially affect our operations as well as causing significant disruption in the operations and business of our collaborators and the third-party manufacturers, CROs and other service providers that we and/or our collaborators conduct business with; and

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

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

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

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

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

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

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

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

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

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

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

We remain responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required

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

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

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

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

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

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

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

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

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

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

Third-party manufacturers may not be able to comply with cGMP requirements or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and/or criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. In addition, some of the product candidates we intend to develop, including 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 September 30, 2021, our patent portfolio included four patent families directed to novel scaffolds, 15 patent families directed to our platform technology, 94 patent families directed to bicyclic peptides and related conjugates, and 14 patent families directed to methods of using certain bicyclic peptide conjugates for treating various indications. As of September 30, 2021 the company's trademark portfolio consisted of 41 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. 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.

For example, our U.K. trademark application for "TICA" has been successfully opposed by Immatics Biotechnologies GmbH, a German company, or Immatics, following a decision of the U.K. Intellectual Property Office on April 1, 2021. The decision was based on Immatics' earlier registered rights for the trademarks "TCER" and "TiCR". As a result of the decision, our U.K. trademark application for TICA will no longer continue to apply to the majority of goods and services for which we originally applied, including pharmaceutical products and pharmaceutical preparations being used in relation to oncology. Our trademark application for TICA in Japan and registration in the European Union were filed via the Madrid system using the U.K. applications, so the decision by the U.K. Intellectual Property Office will have a parallel effect on those respective national rights. Our trademark application for TICA in the United States has been abandoned.

Risks Related to Employee Matters and Managing Growth

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

As of September 30, 2021, we had 109 full-time or part-time employees. Our focus on the development of our product candidates requires us to optimize cash utilization and to manage and operate our business in a highly efficient manner. We cannot provide assurance that we will be able to hire or retain adequate staffing levels to develop our product candidates or run our operations or to accomplish all of the objectives that we otherwise would seek to accomplish.

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

We utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks, the confidentiality and the availability and integrity of our data. In addition, due to the ongoing COVID-19 pandemic, we have enabled our non-laboratory-based employees to work remotely, which may make us more vulnerable to cyberattacks. We have been the target of cyber-attacks in the past. For example, in 2019 we were targeted in a phishing incident, which included email accounts being accessed by unauthorized third parties. Promptly after discovery, we performed third-party investigations and as there was no evidence of access or acquisition of any personal information as a result of the incident, we believe that no further action was required under U.K, E.U. (GDPR) or U.S. federal or state law. There was no material impact to our business or financial condition. While we believe we responded appropriately, including implementing remedial measures to stop the cyber-attacks and with the goal of preventing similar ones in the future, there can be no assurance that we will be successful in these remedial and preventative measures or successfully mitigating the effects of future cyber-attacks. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to respond appropriately to such breaches and to implement further data protection measures. We are aware that some public companies have recently received Civil Investigative Demands from the Federal Trade Commission, or FTC, requesting information and documents following disclosures of privacy or security incidents in SEC filings. The FTC has taken the position that inadequately disclosing privacy and security incidents in SEC filings may be a deceptive business practice, and the FTC has relied on SEC filings as a launching pad for incident investigations even where the

filings were not inadequate. We cannot be certain that the FTC will consider our disclosure adequate or that the FTC will not rely on our disclosure to initiate an incident investigation.

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

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

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

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

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

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

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (1) FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities, (2) manufacturing standards, (3) federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, and (4) laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, bribery and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee or collaborator misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. Further, because of the work-from-home policies we implemented due to COVID-19, information that is normally protected, including company confidential information, may be less secure. In May 2019, we adopted a code of conduct and business ethics, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a

significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations.

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

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

Risks Related to Ownership of Our Securities

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

The market price of our ADSs is highly volatile. Since our initial public offering, or IPO, in May 2019, through November 1, 2021, the trading price of our ADSs has ranged from $6.24 to $60.34. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, holders of our ADSs may not be able to sell their ADSs at or above price at which they purchased their ADSs. The market price for our ADSs may be influenced by many factors, including:

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in products similar or perceived to be similar to those we are developing or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us to identify additional product candidates for our pipeline;

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

In addition, companies trading in the stock market in general, and Nasdaq in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies, including very recently in connection with the ongoing COVID-19 pandemic, which has resulted in decreased stock prices for many companies notwithstanding the lack of a fundamental change in their underlying business models or prospects. Broad market and industry factors, including potentially worsening economic conditions and other adverse effects or developments relating to the ongoing COVID-19 pandemic, may negatively affect the market price of our ADSs, regardless of our actual operating performance.

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

As of September 30, 2021, our executive officers, directors, greater than 5% shareholders and their affiliates beneficially own approximately 55.3% of our ordinary shares and ordinary shares in the form of ADSs. Depending on the level of attendance at our general meetings of shareholders, these shareholders either alone or voting together as a group could be in a position to determine the outcome of decisions taken at any such general meeting. Any shareholder

or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, and the approval of certain significant corporate transactions. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that holders of our ADSs may believe are in their best interest as holders of our ordinary shares or ADSs. Some of these persons or entities may have interests different than current holders of our ordinary shares and ADSs. For example, because certain of these shareholders purchased their ordinary shares at prices substantially below the current trading price of our ADSs or have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

Sales of a substantial number of our ADSs in the public market could occur at any time, subject to certain restrictions described below. If our existing shareholders sell, or indicate an intent to sell, substantial amounts of our securities in the public market, the trading price of the ADSs could decline significantly and could decline below the current trading prices of the ADSs. In addition, ordinary shares subject to outstanding options under our equity incentive plans and the ordinary shares reserved for future issuance under our equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

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

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

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

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

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

We are an emerging growth company, or EGC, and, based on the market value of our ordinary shares and ADSs held by non-affiliates as of June 30, 2021 expect to cease being an EGC as of December 31, 2021. As an EGC, we have been and will until December 31, 2021 be permitted to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;

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

- reduced disclosure obligations regarding executive compensation; and

- an exemption from the requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions for so long as we remain an EGC. We cannot predict whether investors will find our ADSs less attractive if we rely on certain or all of these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and our ADS price may be more volatile.

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

We were also a smaller reporting company, as defined in the Securities Exchange Act of 1934, as amended, or the Exchange Act, until June 30, 2021. We have historically taken, and may continue through the filing of our Annual Report on Form 10-K for the year ending December 31, 2021 to take, advantage of certain scaled disclosures available to smaller reporting companies.

Effective as of December 31, 2021, we will be a large accelerated filer, which will increase our costs and demands on management.

As a result of the market value of our ordinary shares and ADSs held by non-affiliates as of June 30, 2021, we will be a large accelerated filer as of December 31, 2021, and we will therefore no longer qualify as EGC. Additionally, due to our public float as of June 30, 2021, we will no longer qualify as a "smaller reporting company" as defined in the Exchange Act. However, we are not required to reflect the change in our smaller reporting company status, and comply with the associated increased disclosure obligations, until our first quarterly report in our next fiscal year (i.e., the quarterly report for the three-month period ended March 31, 2022).

As a large accelerated filer, we will be subject to certain disclosure and compliance requirements that apply to other public companies but did not previously apply to us due to our status as an emerging growth company. These requirements include, but are not limited to:

- the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act of 2002;
- compliance with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- the requirement that we provide full and more detailed disclosures regarding executive compensation; and
- the requirement that we hold a non-binding advisory vote on executive compensation and obtain shareholder approval of any golden parachute payments not previously approved.

We expect that compliance with the additional requirements of being a large accelerated filer will increase our legal and financial compliance costs and may cause management and other personnel to divert attention from operational and other business matters to devote increased time to public company reporting requirements. In addition, if we are not able to comply with changing requirements in a timely manner, the market price of our ADSs could decline, and we

could be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities, which would require additional financial and management resources.

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 2020 taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. As a result, there can be no assurance regarding if we will be PFIC or will not be a PFIC in the future. In addition, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into and our corporate structure.

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

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

As a group that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, under the SME Program, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carry them forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these SME Program tax credit cash rebate claims. The U.K. Government has released draft legislation to introduce a cap on the amount of the payable credit that a qualifying loss-making SME business can receive through R&D relief in any one year. The cap would be applied to restrict payable credit claims in excess of £20,000 with effect for accounting periods beginning on or after April 2021 by reference to, broadly, three times the total employee payroll tax and social security liabilities of the company. The draft legislation also contains an exemption which prevents the cap from applying. That exemption requires the company to be creating, or taking steps to create, intellectual property as well as having research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. The company does not expect this legislation if adopted to have a material impact on its payable credit claims based on amounts currently claimed. If such cap comes into force, and such exception does not apply, this could restrict the amount of payable credit that we claim.

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

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

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

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

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

that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

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

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

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

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

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

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

a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting, as well as the sanction of the U.K. court;

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

General Risks

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

As a U.S. public company, we are incurring and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel currently devote and will continue to devote a substantial amount of time to these compliance initiatives. In addition, based on the market value of our ADSs held by non-affiliates as of June 30, 2021, we expect we will cease to be an emerging growth company on December 31, 2021. As a large accelerated filer, we will incur additional accounting and other expenses. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition, results of operations, ADS price and prospects. The increased costs will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we were an EGC and a smaller reporting company with less than $100.0 million of annual revenue, we historically were not required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. These exemptions will no longer apply on December 31, 2021 and for our annual report on Form 10-K for the year ending December 31, 2021. To achieve compliance with Section 404, we engaged in a process to document and evaluate our internal control over financial reporting. We will need to continue to dedicate internal resources, and potentially engage outside consultants to continue to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk we, or our independent registered public accounting firm, will not be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

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

Our management is required to assess the effectiveness of these controls annually. However, while we have been EGC, our independent registered public accounting firm has not been required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. This exemption will no longer apply on December 31, 2021 and for our annual report on Form 10-K for the year ending December 31, 2021. An independent assessment of the effectiveness of our internal controls over financial reporting by our independent registered accounting firm could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

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

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

We could be subject to securities class action litigation.

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

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

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

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

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

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

Item 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*†	Collaboration and License Agreement, dated as of July 9, 2021, between BicycleTx Limited and Ionis Pharmaceuticals, Inc.
10.2	Share Purchase Agreement, dated as of July 9, 2021, between Bicycle Therapeutics plc and Ionis Pharmaceuticals, Inc.
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*#	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document – 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

Exhibit Number	Description
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 (marked by [***]) 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: November 4, 2021

By: /s/ Kevin Lee

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

(Principal Executive Officer)

Date: November 4, 2021

By: /s/ Lee Kalowski

Lee Kalowski, MBA
Chief Financial Officer and President

(Principal Financial and Accounting Officer)

Exhibit 10.1

[***] = CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THIS DOCUMENT BECAUSE IT IS BOTH NOT MATERIAL AND IS OF THE TYPE THAT THE REGISTRANT TREATS AS PRIVATE AND CONFIDENTIAL.

COLLABORATION AND LICENSE AGREEMENT

between

BICYCLETX LIMITED

and

IONIS PHARMACEUTICALS, INC.

Dated as of July 9, 2021

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COLLABORATION AND LICENSE AGREEMENT

This **Collaboration and License Agreement** (the "**Agreement**") is made and entered into effective as of July 9, 2021 (the "**Effective Date**") by and between **BicycleTx Limited**, a company incorporated in England and Wales with a place of business at Building 900, Babraham Research Campus, Cambridge CB22 3AT, UK ("**BicycleTx**"), and Ionis Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA ("**Ionis**"). BicycleTx and Ionis are referred to herein individually as a "**Party**" and collectively as the "**Parties**".

RECITALS

WHEREAS, BicycleTx, a biopharmaceutical company, has developed certain proprietary technology relating to the use of Bicycles directed to transferrin receptors;

WHEREAS, Ionis, a biotechnology company, has expertise in the research and development of pharmaceutical products, and is working to create and develop novel pharmaceutical products;

WHEREAS, BicycleTx and Ionis entered into that certain Evaluation and Option Agreement dated as of December 31, 2020 (the "**Option Agreement**") pursuant to which BicycleTx granted to Ionis an exclusive option to obtain an exclusive license under BicycleTx's relevant technology to research, develop, manufacture, and commercialize products incorporating TfR1 Bicycles (as defined below) and Ionis has exercised such option in accordance with the terms of the Option Agreement;

WHEREAS, subject to the terms and conditions of this Agreement, BicycleTx will exclusively partner with Ionis with respect to Compounds in the Field; and

WHEREAS, in connection with this transaction, Bicycle Therapeutics plc, an Affiliate of BicycleTx, and Ionis are entering into a stock purchase agreement on even date herewith (the "**Stock Purchase Agreement**") pursuant to which Ionis is purchasing shares of Bicycle Therapeutics plc in accordance with the terms thereof.

NOW THEREFORE, in consideration of the foregoing premises and the mutual promises, covenants, and conditions set forth herein and other valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, hereby agree as follows:

ARTICLE 1
DEFINITIONS

Unless otherwise specifically provided herein, the following terms shall have the following meanings:

1.1 "**Accounting Standards**" means, with respect to a Party and its Affiliates, either (a) International Financial Reporting Standards ("**IFRS**") or (b) United States generally accepted accounting principles ("**GAAP**"), in either case ((a) or (b)) that are used at the applicable time, and as consistently applied, by such Party or any of its Affiliates.

1.2 "**Adverse Ruling**" has the meaning set forth in Section 11.3.2.

1.3 "**Affiliate**" means, with respect to a Party, any Person that, directly or indirectly, through one (1) or more intermediaries, controls, is controlled by, or is under common control with such Party, for

so long as such control exists. For purposes of this definition, "control" and, with correlative meanings, the terms "controlled by" and "under common control with" means (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract relating to voting rights or corporate governance, or otherwise; or (b) the ownership, directly or indirectly, of more than fifty percent (50%) of the voting securities or other ownership interest of a Person (or, with respect to a limited partnership or other similar entity, its general partner or controlling entity).

1.4 "**Agreement**" has the meaning set forth in the preamble hereto.

1.5 "**Alliance Manager**" has the meaning set forth in Section 3.5.

1.6 "**Applicable Law**" means federal, state, local, national, and supra-national laws, statutes, rules, and regulations, including any rules, regulations, guidelines, or other requirements enacted by a government authority, including Regulatory Authorities, major national securities exchanges or major securities listing organizations, that may be in effect from time to time during the Term and applicable to the performance by a Party of its obligations, or exercise of its rights, under this Agreement.

1.7 "**ASO**" means a compound comprising one or more Oligonucleotides [***]. The Parties acknowledge that [***].

1.8 "**ASO-Related Claim**" has the meaning set forth in Section 7.2.1(b).

1.9 "**ASO-Related Claim Application**" has the meaning set forth in Section 7.2.1(b).

1.10 "**Auditor**" has the meaning set forth in Section 6.11.

1.11 "**Available Target(s)**" means:

(a) with respect to a request by Ionis, any Target that as of the date the Gatekeeper (or BicycleTx, as applicable) receives a Target Nomination Notice from Ionis for such Target, or Ionis initiates a request with the Gatekeeper pursuant to Sections 4.8.2 or 4.8.4, as applicable, is not (i) a BicycleTx Excluded Target, (ii) [***], (A) a Target that was placed on the Gatekeeper List during the BicycleTx Initial Target Designation Period pursuant to Section 4.8.3, or (B) a Target placed on the Gatekeeper List by BicycleTx pursuant to Section 4.8.6; and

(b) with respect to a request by BicycleTx under Section 4.8.3 or Section 4.9 following the termination of Oligo Exclusivity, any Target that as of the date BicycleTx makes a BicycleTx Target Request, is not a Collaboration Target, including, for clarity, any Target placed on the Gatekeeper List by Ionis pursuant to Section 4.8.4 (subject to the limitations set forth therein).

1.12 "**Bankruptcy Code**" has the meaning set forth in Section 11.5.1.

1.13 "**Bicycle**" means a monomeric peptide or peptide derivative crosslinked via a central scaffold to form a conformationally constrained structure with more than one cyclic component.

1.14 "**BicycleTx**" has the meaning set forth in the preamble hereto.

1.15 "**BicycleTx Excluded Targets**" means Targets with respect to which BicycleTx has granted exclusive rights to a Third Party under the BicycleTx Existing Third Party Agreements.

1.16 "**BicycleTx Existing Third Party Agreements**" means (a) that certain agreement between [***], and (b) that certain agreement between [***], in each case as such agreements are in effect on the Effective Date. For clarity, during the Term when Oligo Exclusivity applies, BicycleTx [***].

1.17 "**BicycleTx Indemnitees**" has the meaning set forth in Section 10.1.

1.18 "**BicycleTx Initial Target Designation Period**" has the meaning set forth in Section 4.8.3.

1.19 "**BicycleTx Intellectual Property**" means the BicycleTx Know-How, BicycleTx Patents, and BicycleTx's interest in any Joint Inventions and Joint Patents.

1.20 "**BicycleTx Know-How**" means all Know-How that (a) is Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term and (b) (i) with respect to all Know-How other than the Know-How included in the [***], and (ii) with respect to [***], in each case of (i) and (ii), for the Research and Exploitation of Compounds and Licensed Products in the Field. For clarity, "BicycleTx Know-How" includes any TfR1 BicycleTx Inventions and BicycleTx Product Inventions.

1.21 "**BicycleTx Patents**" means all Patents that (a) are Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term and (b) Cover BicycleTx Know-How. For clarity, "BicycleTx Patents" includes any BicycleTx Product Patents. Without limiting the foregoing, an exemplary list of BicycleTx Patents is attached hereto as Schedule 9.2.1.

1.22 "**BicycleTx Platform IP**" means Know-How and Patents that are Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term solely to the extent such Know-How and Patents Cover or specifically relate to **[***]**. The list of Patents included in the BicycleTx Platform IP (the "**BicycleTx Platform Patents**") is attached hereto as Schedule 1.22.

1.23 "**BicycleTx Product Invention**" means a Product Invention solely invented by employees, agents, or independent contractors of BicycleTx or its Affiliates.

1.24 "**BicycleTx Product Patents**" means all Patents that Cover BicycleTx Product Inventions.

1.25 "**BicycleTx Relevant Patent**" has the meaning set forth in Section 7.2.1(b).

1.26 "**BicycleTx Research Stage Target**" has the meaning set forth in Section 4.8.6(a).

1.27 "**BicycleTx Target**" has the meaning set forth in Section 4.9.

1.28 "**BicycleTx Target Request**" has the meaning set forth in Section 4.9.

1.29 "**Breach Cure Period**" has the meaning set forth in Section 11.3.1.

1.30 "**Breach Notice**" has the meaning set forth in Section 11.3.1.

1.31 "**Breaching Party**" has the meaning set forth in Section 11.3.1.

1.32 "**Business Day**" means a day other than a Saturday or Sunday on which banking institutions in San Diego, California and London, England are open for business.

1.33 "**Calendar Quarter**" means each successive period of three calendar months commencing on January 1, April 1, July 1, and October 1, except that the first Calendar Quarter of the Term shall commence on the Effective Date and end on the day immediately prior to the first to occur of January 1, April 1, July 1 or October 1 after the Effective Date, and the last Calendar Quarter shall end on the last day of the Term.

1.34 "**Calendar Year**" means each successive period of twelve (12) calendar months commencing on January 1 and ending on December 31, except that the first Calendar Year of the Term shall commence on the Effective Date and end on December 31 of the year in which the Effective Date occurs and the last Calendar Year of the Term shall commence on January 1 of the year in which the Term ends and end on the last day of the Term.

1.35 "**Clinical Trial**" means a human clinical study (a) in which a pharmaceutical product is administered to human subjects and (b) that is designed to (i) establish that a pharmaceutical product is reasonably safe for continued testing; (ii) investigate the safety and efficacy of the pharmaceutical product for its intended use, and to define warnings, precautions and adverse reactions that may be associated with the pharmaceutical product in the dosage range to be prescribed; (iii) support Regulatory Approval of such pharmaceutical product or label expansion of such pharmaceutical product; or (iv) obtain or maintain marketing approval and for a purpose other than to obtain, support or maintain Regulatory Approval, including any and all post-marketing commitments.

1.36 "**Collaboration Target**" has the meaning set forth in Section 4.8.1.

1.37 "**Combination Product**" means (a) a single pharmaceutical formulation containing as its active ingredients both (i) a Compound and (ii) one or more other therapeutically or prophylactically active ingredients that are not Compounds (each such other therapeutically or prophylactically active ingredient, a "**Non-Compound Active Agent**") or (b) a combination therapy comprised of (i) a Compound and (ii) one or more other therapeutically or prophylactically active products containing at least one Non-Compound Active Agent, whether priced and sold together in a single package containing such multiple products or packaged separately but sold together for a single price, in each case (a) and (b), including all dosage forms, formulations, presentations, line extensions, and package configurations.

1.38 "**Commercialization**" means any and all activities directed to the preparation for sale of, offering for sale of, or sale of a pharmaceutical product, including activities related to marketing, promoting, selling, distributing, importing, and exporting such product, and interacting with Regulatory Authorities regarding any of the foregoing. When used as a verb, "**to Commercialize**" and "**Commercializing**" means to engage in Commercialization, and "**Commercialized**" has a corresponding meaning.

1.39 "**Commercially Reasonable Efforts**" means, with respect to the performance of Research, Development, Commercialization, or Manufacturing activities with respect to a Compound or a Licensed Product, the carrying out of such activities using efforts and resources comparable to the efforts and resources [***], taking into account issues of safety and efficacy, [***].

1.40 "**Compound**" means a TfR1 Bicycle conjugated to an ASO, where such ASO is directed to a Target that is not a BicycleTx Excluded Target.

1.41 "**Confidential Information**" means any information provided orally, visually, in writing or other form by or on behalf of one (1) Party (or an Affiliate or representative of such Party) to the other Party (or to an Affiliate or representative of such other Party) in connection with this Agreement, whether

prior to, on, or after the Effective Date, including information relating to the terms of this Agreement, the identities of Collaboration Targets and Available Targets, any Research or Exploitation of any Licensed Product, any Know-How with respect thereto developed by or on behalf of the disclosing Party or its Affiliates, or the scientific, regulatory, or business affairs or other activities of either Party. In addition, all information disclosed by a Party to the other under the Option Agreement shall be deemed to be such Party's Confidential Information disclosed under this Agreement.

1.42 "**Control**" means, with respect to any Know-How, Regulatory Documentation, material, Patent, or other property right, the possession of the right, whether directly or indirectly, and whether by ownership, license, covenant not to sue, or otherwise (other than by operation of the license and other grants in Sections 2.1 and 2.2), to grant a license, sublicense, or other right to or under such Know-How, Regulatory Documentation, material, Patent, or other property right, as provided for herein without violating the terms of any agreement or other arrangement with any Third Party; provided that with respect to any Know-How, Regulatory Documentation, material, Patent, or other property right obtained by BicycleTx from a Third Party after the Effective Date, BicycleTx shall be deemed to Control such Know-How, Regulatory Documentation, material, Patent, or other property right, as applicable, only if it possesses the right to grant such license, sublicense, or other right thereto without being obligated to pay any royalties or other consideration therefor, unless Ionis agrees to (a) pay such royalties or other consideration arising as a result of Ionis' or its Affiliate's or Sublicensee's use or practice of such Know-How, Regulatory Documentation, material, Patent, or other property right under this Agreement and (b) comply with the terms and conditions of such agreement as it relates to Ionis and this Agreement.

1.43 "**Cover**" means, with respect to a particular subject matter at issue and a relevant Patent, that, in the absence of a license under or ownership of such Patent, the developing, making, using, offering for sale, promoting, selling, exporting, or importing of such subject matter would infringe one or more Valid Claims of such Patent (considering any pending claim included in such Patent as if such pending claim were to issue in an issued Patent).

1.44 "**CRO**" shall have the meaning set forth in Section 4.2.3.

1.45 [***]

1.46 "**Development**" means all activities related to (i) human clinical lead optimization with the goal of identifying a Development Candidate (as defined below), test method development and stability testing, toxicology, formulation, process development, manufacturing scale-up, qualification and validation, quality assurance/quality control, (ii)IND-Enabling Toxicology Studies, (iii) Clinical Trials, including Manufacturing in support thereof, (iv) statistical analysis and report writing, (v) the preparation and submission of Drug Approval Applications, regulatory affairs with respect to the foregoing and all other activities necessary or reasonably useful or otherwise requested or required by a Regulatory Authority as a condition or in support of obtaining or maintaining a Regulatory Approval. When used as a verb, "**Develop**" means to engage in Development. For purposes of clarity, Development shall include any submissions and activities required in support thereof required by Applicable Laws or a Regulatory Authority as a condition or in support of obtaining a pricing or reimbursement approval for a Compound or Licensed Product.

1.47 "**Development Candidate**" with respect to Ionis means a Compound that is [***] for further Development and Commercialization in accordance with Ionis' [***]. With respect to BicycleTx, Development Candidate means an active pharmaceutical ingredient [***] for further Development and Commercialization in accordance with BicycleTx's [***].

1.48 "**Diligence Extension Fee**" has the meaning set forth in Section 4.5.3(b).

1.49 "**Dispute**" has the meaning set forth in Section 12.2.

1.50 "**Dollars**" or "**$**" means United States Dollars.

1.51 "**Drug Approval Application**" means an NDA and any corresponding foreign application in the Territory, including, with respect to the European Union, a Marketing Authorization Application (a "**MAA**") filed with the EMA or with the applicable Regulatory Authority of a country in Europe with respect to the mutual recognition or any other national approval procedure.

1.52 "**Effective Date**" means the effective date as set forth in the preamble hereto.

1.53 "**EMA**" means the European Medicines Agency and any successor agency(ies) or authority having substantially the same function.

1.54 "**European Major Market**" means each of the United Kingdom, France, Germany, Italy, and Spain.

1.55 "**Exclusivity Obligations**" has the meaning set forth in Section 2.7.1.

1.56 "**Existing Collaboration Target**" has the meaning set forth in Section 4.8.2.

1.57 "**Existing Patents**" has the meaning set forth in Section 9.2.1.

1.58 "**Exploit**" or "**Exploitation**" means to Develop, use, make, have made, Manufacture, sell, have sold, offer for sale, import, and Commercialize.

1.59 "**Extension Notice**" has the meaning set forth in Section 4.5.3(c).

1.60 "**FDA**" means the United States Food and Drug Administration and any successor agency(ies) or authority having substantially the same function.

1.61 "**FFDCA**" means the United States Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., as amended from time to time, together with any rules, regulations and requirements promulgated thereunder (including all additions, supplements, extensions, and modifications thereto).

1.62 "**Field**" means all diagnostic, therapeutic, prophylactic, and preventative uses in humans.

1.63 "**First Commercial Sale**" means, with respect to a Licensed Product and a country, the first sale for monetary value for use or consumption by the end user of such Licensed Product in such country after Regulatory Approval for such Licensed Product has been obtained in such country.

1.64 "**FTE**" means a full-time equivalent person-year, based upon a total of no less than [***] working hours per year, pro-rated as necessary, undertaken in connection with the conduct of research in a Research Plan. In no circumstance can the work of any given person exceed one (1) FTE.

1.65 "**Gatekeeper**" has the meaning set forth in Section 2.2.1.

1.66 "**Gatekeeper List**" has the meaning set forth in Section 2.2.1.

1.67 "**Generic Product**" means, with respect to a particular Licensed Product that has received Regulatory Approval in a regulatory jurisdiction in the Territory and is being marketed and sold by Ionis or any of its Affiliates or Sublicensees in such jurisdiction, a pharmaceutical product that (a) is sold in such jurisdiction by a Third Party that is not an Affiliate or Sublicensee of Ionis, and did not purchase or acquire such product in a chain of distribution that included Ionis or any of its Affiliates or Sublicensees, (b) has received Regulatory Approval in such jurisdiction for at least one of the same indications as such Licensed Product as a "generic drug", "generic medicinal product", "bioequivalent", or similar designation of interchangeability by the applicable Regulatory Authority in such jurisdiction pursuant to an expedited, abbreviated, or bibliographic approval process in accordance with the then-current rules and regulations in such jurisdiction, where such approval referred to or relied on (i) the approved Drug Approval Application for such Licensed Product held by Ionis, its Affiliate, or a Sublicensee in such jurisdiction or (ii) the data contained or incorporated by reference in such approved Drug Approval Application for such Licensed Product in such jurisdiction.

1.68 "**GLP**" means current good laboratory practice standards promulgated or endorsed by the FDA, as defined in U.S. 21 C.F.R. Part 58 (or such other comparable regulatory standards in jurisdictions outside the U.S.), as updated from time to time.

1.69 "**IND**" means an application filed with a Regulatory Authority for authorization to commence Clinical Trials, including (a) an Investigational New Drug Application as defined in the FFDCA or any successor application or procedure filed with the FDA, (b) any equivalent thereof in other countries or regulatory jurisdictions, (e.g., a Clinical Trial Application (CTA) in the European Union), and (c) all supplements, amendments, variations, extensions, and renewals thereof that may be filed with respect to the foregoing.

1.70 "**IND Acceptance**" means, with respect to a Licensed Product, the earliest of (a) receipt of notice of acceptance by the FDA or the EMA of the filing of an IND for such Licensed Product, (b) the passage of any period of time determined by Applicable Law by the end of which the FDA or EMA, as applicable, is supposed to comment on such filing, extended if any such comments were made by the period of time necessary to address such comments to the reasonable satisfaction of the FDA or EMA, as applicable, or (c) the first dose of such Licensed Product in a Clinical Trial in the U.S. or in any country in the European Union.

1.71 "**IND Acceptance Credit**" shall have the meaning set forth in Section 6.3.

1.72 "**IND Acceptance Fee**" shall have the meaning set forth in Section 6.3.

1.73 "**IND-Enabling Toxicology Study**" means, with respect to a Licensed Product, an in vivo toxicology study conducted under conditions of GLP that is required for filing an IND for such Licensed Product with the FDA or EMA.

1.74 "**Indemnification Claim Notice**" has the meaning set forth in Section 10.3.

1.75 "**Indemnified Party**" has the meaning set forth in Section 10.3.

1.76 "**Indemnifying Party**" has the meaning set forth in Section 10.3.

1.77 "**Initiation**" means, with respect to a Licensed Product and a Clinical Trial, the first dosing of the first patient with such Licensed Product in such Clinical Trial.

1.78 "**Intellectual Property**" has the meaning set forth in Section 11.5.1.

1.79 "**Interim Gatekeeper**" has the meaning set forth in Section 2.2.2.

1.80 "**Internal Development Program**" means on a Target-by-Target basis, a [***] internal program of BicycleTx, pursuant to which BicycleTx is conducting Research, development and/or commercialization activities in connection with compounds or products directed to such Target [***].

1.81 "**Invention**" means any invention, process, method, utility, formulation, composition of matter, article of manufacture, material, creation, discovery, development, or finding, or any improvement thereto, whether or not patentable, including all intellectual property rights therein.

1.82 "**Ionis**" has the meaning set forth in the preamble hereto.

1.83 "**Ionis Indemnitees**" has the meaning set forth in Section 10.2.

1.84 "**Ionis Initial Target Designation Period**" has the meaning set forth in Section 4.8.2.

1.85 "**Ionis Intellectual Property**" means the Ionis Know-How, Ionis Patents, and Ionis' interest in any Joint Inventions and Joint Patents.

1.86 "**Ionis Know-How**" means all Know-How that (a) is Controlled by Ionis or any of its Affiliates on the Effective Date or during the Term and (b) is necessary or reasonably useful for the Exploitation of Compounds and Licensed Products in the Field. For clarity, "Ionis Know-How" includes any Ionis Product Inventions.

1.87 "**Ionis Patents**" means all Patents that (a) are Controlled by Ionis or any of its Affiliates on the Effective Date or during the Term and (b) Cover Ionis Know-How. For clarity, "Ionis Patents" includes any Ionis Product Patents.

1.88 "**Ionis Product Invention**" means a Product Invention solely invented by employees, agents, or independent contractors of Ionis or its Affiliates.

1.89 "**Ionis Product Patents**" means all Patents that Cover Ionis Product Inventions.

1.90 "**Ionis Research Stage Target**" has the meaning set forth in Section 4.8.4.

1.91 "**Ionis Withholding Tax Action**" has the meaning set forth in Section 6.9.3.

1.92 "**Joint Inventions**" has the meaning set forth in Section 7.1.2(b).

1.93 "**Joint Patents**" means all Patents that Cover Joint Inventions.

1.94 "**Joint Product Patents**" means all Joint Patents that Cover [***] developed jointly by employees, agents, or independent contractors of one Party and its Affiliates together with employees, agents, or independent contractors of the other Party and its Affiliates.

1.95 "**JSC**" has the meaning set forth in Section 3.1.1.

1.96 "**Know-How**" means all commercial, technical, scientific, and other know-how and information, Inventions, discoveries, trade secrets, knowledge, technology, methods, processes, practices, formulae, amino acid sequences, nucleotide sequences, instructions, skills, techniques, procedures, ideas, designs, drawings, computer programs, specifications, data and results (including biological, chemical, pharmacological, toxicological, pharmaceutical, physical and analytical, preclinical, clinical, safety, manufacturing and quality control data (including regulatory data, study designs, and protocols), reagents and materials (including assays and compounds) in all cases, whether or not confidential, proprietary, or patentable, in written, electronic, or any other form now known or hereafter developed, but expressly excluding all Patents.

1.97 "**Licensed Product**" means any product that contains or incorporates a Compound, whether alone or in combination with other active ingredients, in any form, formulation, presentation, or dosage, and for any mode of administration.

1.98 "**Losses**" has the meaning set forth in Section 10.1.

1.99 "**MAA**" has the meaning set forth in Section 1.51.

1.100 "**Major Market**" means each of the United States, the European Major Markets, and Japan.

1.101 "**Manufacture**", "**Manufactured**", and "**Manufacturing**" means all activities related to the synthesis, making, production, processing, analysis, purifying, formulating, filling, finishing, packaging, labeling, shipping, and holding of a pharmaceutical product, or any raw materials, intermediate thereof, including process development, process qualification and validation, scale-up, pre-clinical, clinical and commercial production and analytic development, product characterization, stability testing, quality assurance, and quality control, whether by a Party itself or through a Third Party. For clarity, Manufacture of a Compound or Licensed Product will include activities related to the synthesis, making, production, processing, formulating, analyzing for manufacturing purposes and purifying of the TfR1 Bicycle that is incorporated into the applicable Compound or Licensed Product.

1.102 "**Market Exclusivity**" means any exclusive marketing rights or data exclusivity rights conferred by any Regulatory Authority with respect to a Licensed Product other than Patents, including rights conferred in the U.S. under the Hatch-Waxman Act or the FDA Modernization Act of 1997 (including pediatric exclusivity), or rights similar thereto outside the U.S., such as Directive 2001/83/EC (as amended) in the EU.

1.103 "**MHRA**" means the United Kingdom's Medicines and Healthcare products Regulatory Agency and any successor agency(ies) or authority having substantially the same function.

1.104 "**Mono Product**" has the meaning set forth in Section 1.107.

1.105 "**NDA**" means a "**New Drug Application**", as defined in the FFDCA, as amended, and applicable regulations promulgated thereunder by the FDA and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any Regulatory Authority, including all documents, data, and other information concerning a pharmaceutical product, which are necessary for gaining Regulatory Approval to market and sell such pharmaceutical product in the relevant jurisdiction.

1.106 "**Naked Sublicense**" means a sublicense to a Third Party that [***].

1.107 "**Net Sales**" means, with respect to any Licensed Product, the gross amounts invoiced for sales or other dispositions of such Licensed Product by or on behalf of Ionis or its Affiliates or Sublicensees to Third Parties, less the following deductions to the extent included in the gross invoiced sales price for such Licensed Product and determined in accordance with Accounting Standards or otherwise directly paid or incurred by Ionis or its Affiliates or Sublicensees, as applicable, with respect to the sale or other disposition of such Licensed Product:

1.107.1 [***];

1.107.2 [***];

1.107.3 [***];

1.107.4 [***];

1.107.5 [***]; and

1.107.6 [***].

In no event will any particular amount identified above be deducted more than once in calculating Net Sales. Sales of a Licensed Product between Ionis and its Affiliates or Sublicensees for resale shall be excluded from the computation of Net Sales, but the subsequent resale of such Licensed Product to a Third Party shall be included within the computation of Net Sales.

The supply of Licensed Product for no charge or at cost as samples for charitable or promotional purposes, for use in non-clinical or clinical trials or any test or other studies reasonably necessary to comply with Applicable Laws shall not be included in the computation of Net Sales.

If a Licensed Product is sold as part of a Combination Product in a country, the Net Sales with respect to the Combination Product in such country shall be determined as follows:

(a) If a Licensed Product is a Combination Product, the Net Sales for such Combination Product shall be calculated as follows: [***]

Notwithstanding the foregoing, the definition of net sales that [***]; provided that [***]. Ionis shall promptly notify BicycleTx of any [***], including the details thereof.

1.108 "**Nominated Target**" has the meaning set forth in Section 4.8.5.

1.109 "**Non-Breaching Party**" has the meaning set forth in Section 11.3.1.

1.110 "**Non-Compound Active Agent**" has the meaning set forth in Section 1.37.

1.111 "**Oligo Exclusivity**" has the meaning set forth in Section 2.7.1.

1.112 "**Oligonucleotide**" means [***].

1.113 "**Oxford**" shall have the meaning set forth in Section 8.3.3(g).

1.114 "**Party**" and "**Parties**" has the meaning set forth in the preamble hereto.

1.115 "**Patents**" means (a) all national, regional and international patents and patent applications, including provisional patent applications, (b) all patent applications filed either from such patents, patent applications or provisional applications or from an application claiming priority from either of these, including divisionals, continuations, continuations-in-part, provisionals, converted provisionals and continued prosecution applications, (c) any and all patents that have issued or in the future issue from the foregoing patent applications ((a) and (b)), including utility models, petty patents and design patents and certificates of invention, (d) any and all extensions or restorations by existing or future extension or restoration mechanisms, including revalidations, reissues, re-examinations and extensions (including any pediatric exclusivity and other such exclusivities that are attached to patents, patent term extensions, supplementary protection certificates and the like) of the foregoing patents or patent applications ((a), (b), and (c)), and (e) any similar rights, including so-called pipeline protection or any importation, revalidation, confirmation or introduction patent or registration patent or patent of additions to any of such foregoing patent applications and patents.

1.116 "**Person**" means an individual, sole proprietorship, partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture or other similar entity or organization, including a government or political subdivision, department, or agency of a government.

1.117 "**Pivotal Trial**" means a human clinical trial of a Licensed Product that (a) satisfies the requirements of 21 C.F.R. section 312.21(c), or its foreign equivalent or (b) is a registration trial designed to establish statistically significant efficacy and safety of such Licensed Product for the purpose of enabling the preparation and submission of a Drug Approval Application, as evidenced by (i) an agreement with or statement from the FDA on a Special Protocol Assessment or equivalent in another country, or (ii) other guidance or minutes issued by the FDA for such registration trial or equivalent in another country, in each case ((i) and (ii)) where the results of such clinical trial are intended to be used to establish both safety and efficacy of such Licensed Product in patients that are the subject of such trial and serve as the basis for obtaining initial or supplemental Regulatory Approval of such Licensed Product in such country. For clarity, [***].

1.118 "**PMDA**" means Japan's Pharmaceuticals and Medical Devices Agency and any successor agency(ies) or authority having substantially the same function.

1.119 "**Product Invention**" means, on a Compound-by-Compound and Licensed Product-by-Licensed Product basis, an Invention that (a) is generated in the performance of activities under this Agreement and (b) specifically relates to a Compound or Licensed Product.

1.120 "**Product Patents**" means all Patents that Cover any Product Invention.

1.121 "**Publishing Notice**" has the meaning set forth in Section 8.6.

1.122 "**Publishing Party**" has the meaning set forth in Section 8.6.

1.123 "**Redacted Agreement**" shall have the meaning set forth in Section 8.3.2.

1.124 "**Regulatory Approval**" means, with respect to a country or other jurisdiction in the Territory, all approvals (including Drug Approval Applications), licenses, registrations, or authorizations of any Regulatory Authority necessary to Commercialize a Compound or Licensed Product in such country or other jurisdiction, and including pricing or reimbursement approval in such country or other jurisdiction

where such pricing and reimbursement approval is legally required for the sale of such Compound or Licensed Product.

1.125 "**Regulatory Authority**" means any applicable supra-national, federal, national, regional, state, provincial, or local governmental or regulatory authority, agency, department, bureau, commission, council, or other entities (e.g., the FDA, EMA, MHRA, and PMDA) regulating or otherwise exercising authority with respect to activities contemplated in this Agreement, including the Exploitation of the Licensed Products in the Territory.

1.126 "**Regulatory Documentation**" means all (a) applications (including all INDs and Drug Approval Applications), registrations, licenses, authorizations, and approvals (including Regulatory Approvals), (b) correspondence and reports submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority) and all supporting documents with respect thereto, including all regulatory drug lists, advertising and promotion documents, adverse event files, and complaint files, and (c) data contained or relied upon in any of the foregoing, in each case ((a), (b), and (c)) to the extent relating to a Compound or Licensed Product.

1.127 "**Research**" means preclinical research and other non-clinical testing, including gene function, gene expression, target validation research, and investigating inhibition of a target in therapeutic models, but specifically excludes Development (including, for the avoidance of doubt, all IND-Enabling Toxicology Studies), Exploitation, or Commercialization.

1.128 "**Research Activities**" has the meaning set forth in Section 4.2.

1.129 "**Research Plan**" has the meaning set forth in Section 4.2.

1.130 "**Research Term**" means the period of time commencing on the Effective Date and ending upon the completion of all activities under the Research Plan.

1.131 "**Reserved Target**" has the meaning set forth in Section 2.2.3.

1.132 "**Royalty Floor Country**" means each of the [***].

1.133 "**Royalty Term**" means, with respect to each Licensed Product and each country in the Territory, the period beginning on the date of the First Commercial Sale of such Licensed Product in such country and ending on the latest to occur of (a) the [***] anniversary of the First Commercial Sale of such Licensed Product in such country or other jurisdiction, (b) the expiration date of the last-to-expire Valid Claim of [***] that [***] such Licensed Product in such country, and (c) the expiration of all Market Exclusivity for such Licensed Product in such country.

1.134 "**Senior Officer**" means, with respect to BicycleTx, its [***] or his/her designee, and with respect to Ionis, its [***] or his/her designee.

1.135 "**SOFR**" has the meaning set forth in Section 6.10.

1.136 "**Stock Purchase Agreement**" has the meaning set forth in the Recitals.

1.137 "**Sublicensee**" means a Person, other than an Affiliate, that is granted a sublicense by Ionis under the license grant in Section 2.1 as provided in Section 2.4.

1.138 "**Target**" means (a) [***], or (b) [***]. Such Target shall be deemed to include [***].

1.139 "**Target Acceptance Date**" has the meaning set forth in Section 4.8.5.

1.140 "**Target Availability Notice**" has the meaning set forth in Section 4.8.5.

1.141 "**Target Exclusivity**" has the meaning set forth in Section 4.8.1.

1.142 "**Target Nomination Notice**" has the meaning set forth in Section 4.8.5.

1.143 "**Target Sanction**" means with respect to Ionis, [***], all in accordance with Ionis' standard procedures consistently applied.

1.144 "**Term**" has the meaning set forth in Section 11.1.

1.145 "**Terminated Asset**" means, with respect to a Target that is terminated by either Party under ARTICLE 11, each Compound and Licensed Product directed to such Terminated Target.

1.146 "**Terminated Target**" has the meaning set forth in Section 11.6.

1.147 "**Territory**" means worldwide.

1.148 "**TfR1 Bicycle**" means a Bicycle that is directed to a Transferrin Transporter, including any such composition provided by BicycleTx to Ionis under the Option Agreement and any such composition that is synthesized by the Parties under the Evaluation Studies (as defined in the Option Agreement) under the Option Agreement or the Research Plan.

1.149 "**TfR1 BicycleTx Invention**" means an Invention that [***]. For clarity, [***].

1.150 [***]

1.151 "**Third Party**" means any Person other than BicycleTx, Ionis, and their respective Affiliates.

1.152 "**Third Party Claims**" has the meaning set forth in Section 10.1.

1.153 "**Transferrin Transporter**" means the protein coded by the gene TFRC1 (transferrin receptor), a cell surface protein important for the cellular iron uptake through the process of receptor-mediated endocytosis, which has also been proposed as a mechanism for transporting other molecules across the blood-brain barrier by the same process.

1.154 "**Ultra-Rare Disease Product**" means a Licensed Product with an estimated target patient population that is less than [***] patients in the U.S.

1.155 "**United States**" or "**U.S.**" means the United States of America and its territories and possessions (including the District of Columbia and Puerto Rico).

1.156 "**United States – United Kingdom Income Tax Convention**" means the Convention between the government of the United States of America and the government of the United Kingdom of

Great Britain and Northern Ireland for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with Respect to Taxes on Income and Capital Gains.

1.157 "**Valid Claim**" means (a) a claim of any issued and unexpired Patent that has not been revoked or held unenforceable, unpatentable, or invalid by a decision of a court or other governmental agency of competent jurisdiction that is not appealable or has not been appealed within the time allowed for appeal, and that has not been abandoned, disclaimed, denied, or admitted to be invalid or unenforceable through reissue, re-examination, or disclaimer or otherwise and (b) a claim of a pending patent application that has not been cancelled, withdrawn, or abandoned or finally rejected by an administrative agency action from which no appeal can be taken and that has not been pending for more than [***].

ARTICLE 2
GRANT OF RIGHTS

2.1 Grant to Ionis.

2.1.1 Subject to the terms and conditions of this Agreement, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis a license (with the right to grant sublicenses in accordance with Section 2.4), under the BicycleTx Intellectual Property to Research Compounds and Licensed Products in the Field in the Territory. This license under Section 2.1.1 is exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) so long as Ionis maintains Oligo Exclusivity and non-exclusive if Ionis loses Oligo Exclusivity.

2.1.2 Subject to the terms and conditions of this Agreement, including Section 4.5.4, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis an exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) license (with the right to grant sublicenses in accordance with Section 2.4) under the BicycleTx Intellectual Property to Exploit Compounds and Licensed Products in the Field in the Territory for so long as Ionis maintains Oligo Exclusivity. For clarity, upon the termination of Oligo Exclusivity, the license granted in this Section 2.1.2 shall automatically terminate, and the license grant set forth in Section 2.1.3 shall apply.

2.1.3 On a Collaboration Target-by-Collaboration Target basis, and subject to the terms and conditions of this Agreement, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis an exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) license (with the right to grant sublicenses in accordance with Section 2.4), under the BicycleTx Intellectual Property to Exploit Compounds and Licensed Products directed to such Collaboration Target in the Field in the Territory.

2.2 Excluded Targets; Reserved Targets; Gatekeeper. The Parties acknowledge and agree that the BicycleTx Excluded Targets are excluded from Ionis' licenses under Section 2.1. To enable the Parties to effectively manage their respective rights and obligations under this Agreement, the Parties hereby agree as follows:

2.2.1 Gatekeeper. Promptly following the Effective Date, BicycleTx shall engage an independent Third Party mutually agreeable to the Parties (the "**Gatekeeper**") for the purposes of performing the applicable functions set forth in this Section 2.2, including (a) maintaining the list of BicycleTx Excluded Targets, and (b) maintaining the list of Reserved Targets ((a) and (b) together, the "**Gatekeeper List**"). [***] Such engagement shall be on terms consistent with this Agreement and mutually agreeable to the Parties, including provisions relating to confidentiality.

2.2.2 Managing BicycleTx Excluded Targets. In conjunction with or immediately following the appointment of the Gatekeeper, BicycleTx shall provide the Gatekeeper with a current list of BicycleTx Excluded Targets. Until the appointment of the Gatekeeper, the list of BicycleTx Excluded Targets shall be held by an independent Third Party that has been mutually agreed by the Parties (the "**Interim Gatekeeper**"). The identity of the BicycleTx Excluded Targets shall be deemed the Confidential Information of BicycleTx. Following the appointment of a Gatekeeper, BicycleTx shall notify the Gatekeeper promptly of [***].

2.2.3 Reserved Targets. Ionis may designate up to [***] Targets that Ionis wishes to reserve to be potentially the subject of its Research and Development efforts under this Agreement, and that are not BicycleTx Excluded Targets ("**Reserved Targets**") as further described in this Section 2.2.3. The Parties acknowledge and agree that as of the Effective Date, BicycleTx has provided the Interim Gatekeeper with the current list of BicycleTx Excluded Targets, and Ionis has provided the Interim Gatekeeper with its current list of Reserved Targets. During the Term when Oligo Exclusivity applies, [***]. Ionis may not [***] without BicycleTx's prior written consent. Each Reserved Target shall remain on the Gatekeeper List until [***] directed to such Reserved Target and notifies BicycleTx in writing of the applicable Target. Upon the termination of Oligo Exclusivity, if applicable, all Reserved Targets shall be removed from the Gatekeeper List. The identity of the Reserved Targets shall be the Confidential Information of Ionis. BicycleTx agrees that it will not take any action that would cause a Reserved Target to become BicycleTx Excluded Target.

2.2.4 Targets [***]. Ionis acknowledges and agrees that no rights are granted by BicycleTx to Ionis under this Agreement to conduct Research or Development activities in connection with any BicycleTx Excluded Target, or any compound or product directed thereto. [***]. Notwithstanding the foregoing, if such Target later ceases to be a BicycleTx Excluded Target, and [***], and Ionis will have the right to deliver a Target Nomination Notice for such Target in accordance with Section 4.8.5.

2.3 Grants to Bicycle. Subject to the terms and conditions of this Agreement, Ionis hereby grants to BicycleTx, during the Research Term, a non-exclusive, royalty-free license, without the right to grant sublicenses (other than to permitted subcontractors of BicycleTx in accordance with Section 4.10), under the Ionis Intellectual Property solely for purposes of performing BicycleTx's obligations under, and as set forth in, the Research Plan.

2.4 Sublicenses. Ionis shall have the right to grant sublicenses, through multiple tiers of sublicensees, under the licenses granted in Section 2.1, to its Affiliates and Third Parties; provided that (a) any sublicense by Ionis or its Affiliates of the rights granted pursuant to Section 2.1.1 to a Third Party shall only permit such Sublicensee to grant further sublicenses (i) [***], (b) each such sublicense shall be consistent with the terms and conditions of this Agreement, including terms of confidentiality and non-use no less restrictive than those set forth in this Agreement, (c) Ionis may not grant to any Third Party any rights to prosecute or enforce any BicycleTx Patents, (d) Ionis shall remain directly liable to BicycleTx with respect to its obligations under this Agreement and for the performance and acts and omissions of all Sublicensees, and (e) Ionis will [***]. As soon as reasonably practicable (but in any case, within [***]) after the execution of any such sublicense agreement, Ionis shall [***].

2.5 Retained Rights. Notwithstanding the exclusive license granted to Ionis pursuant to Section 2.1 during the Term and without limiting Section 2.7, BicycleTx shall retain all rights under the BicycleTx Intellectual Property (a) to perform, and to subcontract pursuant to Section 4.10, its obligations under this Agreement, (b) [***], and (c) for any purpose outside the scope of the license and rights granted under Section 2.1. For clarity, BicycleTx shall have the right to collaborate with academic institutions and

non-profit organizations with respect to the use of TfR1 Bicycles for the delivery of ASOs for Research purposes, except with respect to [***].

2.6 No Implied Licenses. Except as expressly provided herein, BicycleTx grants no other right or license to Ionis hereunder, including any rights or licenses to the BicycleTx Intellectual Property not expressly granted herein. Except as expressly provided herein, Ionis grants no other right or license to BicycleTx hereunder, including any rights or licenses to the Ionis Intellectual Property not expressly granted herein.

2.7 Exclusivity.

2.7.1 During the Term, except with respect to BicyleTx's conduct of Research Activities under this Agreement, and subject to Section 4.5.4, BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including by the grant of any license, but subject to BicycleTx's rights under Section 2.5), [***] in the Field in the Territory, and during such period, Ionis shall have the exclusive right to perform the foregoing activities ("**Oligo Exclusivity**"). Notwithstanding the foregoing, Oligo Exclusivity shall apply only to Compounds directed to Targets that are not BicycleTx Excluded Targets.

2.7.2 BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including the grant of any license) [***]. To enable BicycleTx to comply with its obligations in the foregoing sentence, Ionis shall [***].

2.7.3 If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, then BicycleTx's obligations under Section 2.7.1 shall terminate, and in lieu of such obligations, BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including the grant of any license, but subject to BicycleTx's rights under Section 2.5) [***].

ARTICLE 3
COLLABORATION MANAGEMENT

3.1 Joint Steering Committee

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3.1.1 Formation. Within [***] days after the Effective Date, the Parties shall establish a joint steering committee (the "**JSC**"). The JSC shall consist of two representatives from each of the Parties (with the number of such representatives at each Party's election, but with each Party collectively having one vote). Each representative shall have the requisite experience and seniority to enable such person to make decisions on behalf of the applicable Party with respect to the issues falling within the decision making authority of the JSC. From time to time, each Party may substitute one or more of its representatives to the JSC on written notice to the other Party. Each Party shall select from its representatives a representative who will chair the JSC jointly with the selected representative from the other Party. Each Party may replace its co-chairperson from time to time by informing the other Party in writing.

3.1.2 Specific Responsibilities. The JSC shall oversee the performance of the Research Plan and serve as a consultative and information-exchange body for the Development of Licensed Products. In particular, the JSC shall:

(a) review and discuss the Research Plan, and review and approve any amendments thereto;

(b) set timelines for implementing the Research Plan and measurables for the conduct and progress of the Research Plan;

(c) oversee the conduct and progress of the Research Plan and serve as a forum for discussion of results generated under the Research Plan;

(d) serve as a forum for discussion of Development activities with respect to Compounds and Licensed Products, including results arising from such activities;

(e) establish secure access methods (such as secure databases) for the exchange of Know-How and other information as contemplated under this Agreement;

(f) monitor and implement the technology transfer to Ionis pursuant to Section 4.7; and

(g) perform such other functions as are set forth herein or as the Parties may mutually agree in writing, except where in conflict with any provision of this Agreement.

3.2 General Provisions Applicable to the JSC.

3.2.1 Meetings and Minutes. The JSC shall meet [***], or at such frequency as otherwise agreed to by the Parties, either in person or by tele-/videoconference with the venue of the in-person meetings alternating between locations designated by BicycleTx and locations designated by Ionis. The Alliance Manager shall be permitted to attend the JSC meetings. The chairperson of the JSC shall be responsible for calling meetings on no less than [***] notice. Each Party shall make all proposals for agenda items and shall provide all appropriate information with respect to such proposed items at least [***] in advance of the applicable meeting; provided that under exigent circumstances requiring input by the JSC, a Party may provide its agenda items to the other Party within a shorter period of time in advance of the meeting, or may propose that there not be a specific agenda for a particular meeting, so long as the other Party consents to such later addition of such agenda items or the absence of a specific agenda for such meeting. The chairpersons of the JSC (or their designee) shall prepare and circulate minutes of each meeting within [***] after the meeting for the Parties' review and approval. The Parties shall agree on the minutes of each meeting promptly, but in no event later than within [***] following circulation of the draft minutes.

3.2.2 Procedural Rules. The JSC shall have the right to adopt such standing rules as necessary for its work, so long as such rules are not inconsistent with this Agreement. A quorum of the JSC shall exist whenever there is present at a meeting at least [***] appointed by each Party. Representation by proxy shall be allowed. The JSC shall take action by consensus of the representatives present at a meeting at which a quorum exists, with each Party having a single vote irrespective of the number of representatives of such Party in attendance, or by a written resolution signed by at least [***] appointed by each Party.

3.2.3 Non-Member Attendance. Each Party may from time to time invite a reasonable number of participants, in addition to its representatives, to attend JSC meetings in a non-voting capacity; provided that if either Party intends to have any Third Party (including any consultant) attend such a meeting, such Party shall provide reasonable prior written notice to the other Party and obtain the other Party's approval for such Third Party to attend such meeting, which approval shall not be unreasonably

withheld, conditioned, or delayed. Such Party shall ensure that such Third Party is bound by written confidentiality and non-use obligations consistent with the terms of ARTICLE 8.

3.3 Decisions.

3.3.1 Decision Making Authority. The JSC shall decide matters within its responsibilities pursuant to Section 3.1.2.

3.3.2 Consensus; Good Faith. The members of the JSC shall in good faith cooperate with one another and shall endeavor to seek agreement with respect to issues to be decided by the JSC.

3.3.3 Final Decision Right; Dispute Resolution. If the JSC cannot, or does not, reach consensus on an issue, then (a) BicycleTx shall have final say on [***]; (b) subject to Section 3.3.3(c), Ionis shall have final say on [***]; and (c) neither Party shall have final say on [***]. Notwithstanding the foregoing, neither Party shall use its final decision-making authority to (i) impose any requirement on the other Party to undertake obligations beyond those for which it is responsible or to forgo any of its rights under this Agreement, (ii) require the other Party to violate any Applicable Law, ethical requirement, or any agreement it may have with any Third Party, or (iii) amend the terms and conditions of this Agreement. Disputes arising between the Parties in connection with or relating to this Agreement or any document or instrument delivered in connection herewith, and that are outside of the decision-making authority of the JSC, shall be finally resolved pursuant to Section 12.2.

3.4 Limitations on Authority. Each Party shall retain the rights, powers, and discretion granted to it under this Agreement and no such rights, powers, or discretion shall be delegated to or vested in the JSC unless such delegation or vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing. The JSC shall not have the power to amend, modify, or waive compliance with this Agreement, which may only be amended or modified as provided in Section 12.3 or compliance with which may only be waived as provided in Section 12.5.

3.5 Alliance Manager. Each Party shall appoint a person who shall oversee contact between the Parties for all matters between meetings of the JSC and shall have such other responsibilities as the Parties may agree in writing after the Effective Date (each, an "**Alliance Manager**"). If not already a member of the JSC, each Alliance Manager shall be permitted to attend JSC meetings as appropriate as a non-voting participant. Each Party may replace its Alliance Manager at any time by notice in writing to the other Party.

3.6 Discontinuation of the JSC. The activities to be performed by the JSC shall solely relate to governance under this Agreement and are not intended to be or involve the delivery of services. Upon the date of First Commercial Sale of a Licensed Product in the Field in the Territory, or such earlier date agreed by the Parties in writing, the JSC shall have no further responsibilities or authority under this Agreement and, unless otherwise agreed by the Parties in writing, will be considered fully dissolved by the Parties. Thereafter, each Party shall designate, to the extent necessary, a contact person for the exchange of information under this Agreement or such exchange of information shall be made through the Alliance Managers, and decisions of the JSC, if any, shall be decisions as between the Parties, subject to the other terms and conditions of this Agreement.

3.7 Expenses. Each Party shall be responsible for all travel and related costs and expenses of its Alliance Manager and of its members and other representatives to attend meetings of, and otherwise participate on, the JSC.

ARTICLE 4
RESEARCH AND DEVELOPMENT

4.1 Collaboration Overview. Subject to the terms and conditions of this Agreement, the Parties shall collaborate in connection with the performance of activities under the Research Plan. Following the completion of the Research Plan, subject to Section 4.5.4, Ionis shall have the sole and exclusive right and responsibility, at its own expense, for the Development of the Compounds and Licensed Products in the Territory.

4.2 Research Plan. BicycleTx and Ionis will conduct certain activities to optimize TfR1 Bicycles for use in Compounds, and such other research and discovery activities relating to TfR1 Bicycles as the Parties may agree through the JSC from time to time as reflected by the written minutes of the JSC (the "**Research Activities**"), which activities will be set forth in a mutually agreed research plan (the "**Research Plan**"). The Parties will work together during the [***] following the Effective Date to prepare and finalize the Research Plan. The Research Plan will include [***], which period may be extended upon mutual agreement of the Parties, the cost of which will be borne by BicycleTx. With respect to the Research Activities:

4.2.1 BicycleTx will conduct the Research Activities at no additional cost to Ionis as set forth in the Research Plan including by way of example and without limitation, X-ray crystallography.

4.2.2 Any work by BicycleTx requested by Ionis over and above the [***] annually will be discussed in good faith by the parties with a view to agreeing upon an allocation of costs to the applicable activities. In the event that internal BicycleTx resources are required, the Parties will agree on a commercially reasonable rate payable to BicycleTx.

4.2.3 BicycleTx may utilize a contract research organization or other subcontractor ("**CRO**") to conduct such activities under the Research Plan, provided that the Parties shall discuss and agree upon the scope of such CRO activities at the JSC, and Ionis shall be responsible for the out of pocket costs incurred in connection with such CRO activities, on a pass-through basis without mark-up. Subject to Section 3.3, the Parties may amend the Research Plan upon the JSC's written agreement. If the Parties (via the JSC) amend the Research Plan to include additional Research or Development work to be conducted by BicycleTx in respect of the TfR1 Bicycles or any Compounds, the Parties will negotiate in good faith to agree upon a commercially reasonable FTE rate payable to BicycleTx for the conduct of such additional activities.

4.2.4 Notwithstanding the extent of what is set forth in the Research Plan at any given time, all Research Activities that the Parties agree to conduct under this Agreement that are reflected in the written minutes of the JSC will be deemed to have been conducted under the Research Plan (whether or not specifically set forth therein).

4.3 Research Activities. BicycleTx shall carry out the Research Activities assigned to it in the Research Plan in good scientific manner, in accordance with this Agreement, and in compliance with all Applicable Law. Through the JSC, Ionis shall provide reasonable assistance requested by BicycleTx in connection with BicycleTx's performance of the Research Activities. Following the completion of the Research Activities, BicycleTx shall deliver to Ionis, through the JSC, the results and data arising from such Research Activities and set forth to be delivered to the JSC in the Research Plan.

4.4 Development of Licensed Products. Following completion of the Research Plan, Ionis shall have the sole right and responsibility to Develop and Manufacture, including seeking Regulatory Approvals for, Compounds and Licensed Products in the Field in the Territory, in each case at Ionis' sole expense. If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, such rights and responsibilities shall be limited to Compounds and Licensed Products directed to Collaboration Targets.

4.5 Diligence.

4.5.1 General.

(a) BicycleTx shall use Commercially Reasonable Efforts to perform the Research Activities assigned to it under the Research Plan.

(b) With respect to [***], Ionis shall use Commercially Reasonable Efforts to Develop and obtain Regulatory Approval for a Licensed Product directed to such Target in at least [***] for use in [***]. Ionis shall have the right to satisfy its diligence obligations under this Section 4.5 through its Affiliates and Sublicensees.

4.5.2 Diligence Milestones. Without limiting the generality of the foregoing Section 4.5.1(b), and subject to Section 4.5.3, Ionis shall:

(a) [***];

(b) [***];

(c) [***]; and

(d) [***].

Notwithstanding anything to the contrary herein, [***].

4.5.3 Diligence Milestone Extensions. The deadlines set forth in Section 4.5.2 may be extended as follows:

(a) to the extent of [***]; or

(b) on a one-time basis [***] the following subsections ((i) – (iv)) by a period of [***] upon payment to BicycleTx of a non-refundable, non-creditable payment of [***] per subsection (the "**Diligence Extension Fee**"):

(i) [***];

(ii) [***];

(iii) [***]; and

(iv) [***].

(c) Ionis will have the right to extend any deadline set forth in Section 4.5.2 pursuant to Section 4.5.3(a) or 4.5.3(b) by (i) providing BicycleTx with a written notice therefor prior to

the date on which such milestone is required to be performed (an "**Extension Notice**") and (ii) if such extension is pursuant to (A) Section 4.5.3(a), [***], or (B) Section 4.5.3(b), paying to BicycleTx the Diligence Extension Fee, in each case ((A) and (B)) concurrently with the delivery of such notice provided that any further extensions pursuant to Section 4.5.3(a) will require the Parties to [***]. For clarity, the maximum amount payable to BicycleTx pursuant to Section 4.5.3(b) is [***] (i.e. the milestones could be extended pursuant to the application of all of subclauses (i), (ii) and (iv), or by the application of all of subclauses (ii), (iii) and (iv)). For example, [***].

4.5.4 Failure to Achieve Milestones; Termination of Oligo Exclusivity.

(a) If Ionis fails to meet one or more of the diligence milestones set forth in Section 4.5.2 (as the dates for achievement of such diligence milestones may be extended pursuant to Section 4.5.3), and does not elect to extend such diligence milestones as provided under Section 4.5.3 (or no further extension is available to Ionis), then subject to Section 4.5.4(b), BicycleTx shall have the right, by written notice to Ionis at any time after such failure, to terminate the Oligo Exclusivity effective as of the date of such written notice.

(b) If, before BicycleTx provides written notice to Ionis terminating the Oligo Exclusivity under Section 4.5.4(a), Ionis [***], then BicycleTx shall [***].

(c) Following the termination of Oligo Exclusivity as provided in Section 4.5.4(a), (1) BicycleTx shall continue to be subject to its obligations under Section 2.7, and (2) Ionis' license under Section 2.1.2 shall terminate but Ionis' licenses under Sections 2.1.1 and 2.1.3 shall continue without any further action by either Party.

4.6 Updates.

4.6.1 BicycleTx Updates. At each regularly scheduled JSC meeting during the performance of the Research Plan, BicycleTx shall provide the JSC with a report detailing its activities under the Research Plan, to the extent then-ongoing, and the results of such activities. The Parties shall discuss the status, progress, and results of such activities at such JSC meetings.

4.6.2 Ionis Updates. For each Target for which Ionis reaches Target Sanction, Ionis shall notify BicycleTx or the Gatekeeper of the Target within [***] of the Target Sanction decision by Ionis' RMC. For each Target for which Ionis is Developing a Licensed Product, on an annual basis during the Term until the grant of Regulatory Approval for a Licensed Product directed to such Target in each of [***], Ionis will provide to BicycleTx annual reports, within [***] after the start of each Calendar Year, summarizing, with respect to activities by Ionis, its Affiliates and Sublicensees: (a) the significant Development activities undertaken and the results achieved with respect to the applicable Licensed Products during the preceding 12-month period and (b) the significant Development activities planned for the applicable Licensed Products during the following 12-month period, provided however that such reports need not be specifically generated in compliance with this section and Ionis may rely on existing reports and internal communications to its Research Management Committee or other executive management, as long as such reports reasonably provide the information set forth the foregoing (a) and (b). Following the delivery of each report, Ionis will make appropriate personnel reasonably available to BicycleTx during business hours and on reasonable advanced notice to answer questions regarding the information contained in such report in order for BicycleTx to obtain a reasonable understanding regarding the Development status of the applicable Licensed Products.

4.7 Technology Transfer.

4.7.1 Know-How. As soon as reasonably practicable following the completion of the Research Plan (and in any event not more than [***] after), BicycleTx shall, and shall cause its Affiliates to, [***], disclose and make available to Ionis (which obligation may include granting personnel designated by Ionis controlled access to an electronic data room), in such form as maintained by BicycleTx in the ordinary course of business, a copy of the BicycleTx Know-How and jointly owned Know-How (to the extent such jointly owned Know-How is in BicycleTx's possession). The Parties shall reasonably cooperate to provide a smooth and prompt provision of all such Know-How.

4.7.2 Technical Assistance. BicycleTx shall reasonably assist Ionis and its designee(s) in the use and understanding of the BicycleTx Know-How and jointly owned Know-How provided pursuant to Section 4.7.1 and with respect to such BicycleTx Know-How and jointly owned Know-How, shall provide reasonable technical assistance and make its technical personnel reasonably available to Ionis as necessary for Ionis to Exploit the Compounds and Licensed Products, provided that such technical assistance at BicycleTx's cost shall not be required to exceed, in the aggregate, a total of [***]. For any assistance requested by Ionis and provided by BicycleTx in excess of [***], Ionis shall reimburse BicycleTx for all reasonable internal costs, at an agreed FTE rate, and out-of-pocket costs incurred by BicycleTx in providing such additional assistance.

4.8 Target Exclusivity; Collaboration Targets.

4.8.1 Following termination of Oligo Exclusivity by BicycleTx pursuant to Section 4.5.4, Ionis shall retain exclusivity with respect to TfR1 Bicycles for the delivery of ASOs directed to each Collaboration Target (such residual exclusivity, "**Target Exclusivity**"). A "**Collaboration Target**" is each Target that is (a) an Existing Collaboration Target under Section 4.8.2, or (b) designated by Ionis as a Collaboration Target in accordance with Section 4.8.4, and in each case of (a) and (b), is not a Terminated Target.

4.8.2 Within [***] following termination of Oligo Exclusivity (such period, the "**Ionis Initial Target Designation Period**"), Ionis shall provide to BicycleTx and the Gatekeeper written notice specifying the Targets (that are not BicycleTx Excluded Targets) with respect to which Ionis was conducting (a) Research that has [***], or (b) [***] (each, subject to [***], an "**Existing Collaboration Target**"). The Gatekeeper shall update the list of Collaboration Targets by the end of the Ionis Initial Target Designation Period.

4.8.3 During the [***] period following the expiration of the Ionis Initial Target Designation Period (the "**BicycleTx Initial Target Designation Period**"), BicycleTx may make a BicycleTx Target Request under Section 4.9, and may place on the Gatekeeper List (i.e. in addition to any BicycleTx Excluded Targets already on the Gatekeeper List) any Target (a) for which BicycleTx commences, during the BicycleTx Initial Target Designation Period, an Internal Development Program (meeting the criteria set forth in Section 1.79(a) and (b)), or (b) that is the subject of [***].

4.8.4 At any time after expiration of the BicycleTx Initial Target Designation Period, Ionis may nominate as Collaboration Targets (a) up to [***] additional Targets (in addition to any Targets already designated by Ionis under Section 4.8.2) for which Ionis has [***], (in each case of (i) and (ii) in accordance with the terms of this Agreement and without, for clarity, any requirement that [***]) (each, an "**Ionis Research Stage Target**"), and/or (b) any Target [***] for which Ionis (or any Third Party to whom Ionis has granted rights in such Target) [***], in each case of (a) and/or (b) by following the procedure set

forth in Section 4.8.5. For clarity, there may be no more than [***] Ionis Research Stage Targets nominated or placed on the Gatekeeper List at any given time, provided that upon Ionis designating a Development Candidate directed to an Ionis Research Stage Target, Ionis may notify the Gatekeeper, and such Target shall thereafter remain a Collaboration Target, but shall no longer be an Ionis Research Stage Target, and Ionis may nominate an additional Ionis Research Stage Target to the Gatekeeper List, subject to (A) any such Target being Available, (B) pre-payment of the IND Acceptance Fee, and (C) the foregoing limit of [***] Ionis Research Stage Targets in total at any time.

4.8.5 To nominate an additional Target as a Collaboration Target under Section 4.8.4 subject to Target Exclusivity, Ionis shall provide the Gatekeeper with a confidential written description of the applicable Target (the "**Nominated Target**"), including, to the extent available, [***] for such Target (the "**Target Nomination Notice**"). Within [***] following the Gatekeeper's receipt of the Target Nomination Notice with respect to a Nominated Target, the Gatekeeper shall verify whether such Nominated Target is an Available Target and notify Ionis in writing ("**Target Availability Notice**"). If the Nominated Target is an Available Target on the date that the Gatekeeper receives the applicable Target Nomination Notice, then such Nominated Target shall be designated as a Collaboration Target and shall be subject to Target Exclusivity as of the date of the Gatekeeper's receipt of the Target Nomination Notice for such Target (the "**Target Acceptance Date**") so long as Ionis pre-pays the IND Acceptance Fee for such Target within [***] of receipt of an invoice therefor. Effective as of the Target Acceptance Date for a Collaboration Target nominated pursuant to this Section 4.8.5, the Parties will have all rights and obligations hereunder in connection with such Collaboration Target (including each Party's respective rights and obligations under Sections 2.1, 2.5, and 2.7). For clarity, if Ionis elects, at its discretion, to provide a Target Nomination Notice directly to BicycleTx, rather than to the Gatekeeper, then this Section 4.8.5 shall be deemed to refer to provision of such Target Nomination Notice to BicycleTx, *mutatis mutandis*.

4.8.6 At any time after the expiration of the BicycleTx Initial Target Designation Period, BicycleTx may place on the Gatekeeper List:

(a) up to [***] additional Targets (in addition to the then-current BicycleTx Excluded Targets and any Targets already designated by BicycleTx during the BicycleTx Initial Target Designation Period under Section 4.8.3) for which BicycleTx [***] (each, a "**BicycleTx Research Stage Target**");

(b) any Target (without any cap on number) [***]; and/or

(c) any Target that is the subject of [***].

in each case of (a) through (c), subject to BicycleTx first confirming with the Gatekeeper that any such Target is Available in accordance with Section 4.9. For clarity, (A) any Target placed on the Gatekeeper list pursuant to Section 4.8.6(c) shall not be counted as a BicycleTx Research Stage Target or against the associated limit of [***], regardless of the stage of Research or Development at which rights in such Target are granted to a Third Party, and (B) there may be no more than [***] BicycleTx Research Stage Targets nominated or placed on the Gatekeeper List at any given time, provided that upon BicycleTx designating a Development Candidate directed to an BicycleTx Research Stage Target, BicycleTx may notify the Gatekeeper, and such Target shall remain on the Gatekeeper List but shall no longer be an BicycleTx Research Stage Target, and BicycleTx may nominate an additional BicycleTx Research Stage Target to the Gatekeeper List, subject to (1) any such Target being Available, and (2) the foregoing limit of [***] BicycleTx Research Stage Targets in total at any time.

4.8.7 Expanded Role of Gatekeeper. Promptly following the termination of Oligo Exclusivity, BicycleTx shall expand the engagement of the Gatekeeper for the purposes of performing the applicable functions set forth in this Section 4.8, to include (in addition to the duties set forth in Section 2.2.1): (a) maintaining a list of Targets that are not Available Targets, (b) issuing the Target Availability Notice, (c) maintaining the list of Collaboration Targets, and (d) performing the functions with respect to Bicycle that are set forth in Section 4.9. [***]. Such engagement shall be on terms consistent with this Agreement and mutually agreeable to the Parties, including provisions relating to confidentiality.

4.8.8 Unavailable Targets. Following the termination of Oligo Exclusivity, if applicable, BicycleTx shall notify the Gatekeeper of any Targets that are not Available Targets (i.e. those falling within Section 4.8.6) promptly, but in no event later than [***] after the Gatekeeper notifies BicycleTx that it has received any Target Nomination Notice, to enable the Gatekeeper to comply with its obligations to Ionis under Section 4.8. Upon receipt of such notification, the Gatekeeper shall update the Gatekeeper List accordingly. If any Nominated Target that was not an Available Target at the time of the Target Nomination Notice later becomes an Available Target, the Gatekeeper shall notify Ionis of the Available Target within [***] of the Gatekeeper receiving notice that such Available Target is available and Ionis shall have sole discretion whether such Available Target becomes a Collaboration Target under this Agreement.

4.9 BicycleTx Use of Gatekeeper to Clear Targets. Following the termination of Oligo Exclusivity, if applicable, BicycleTx shall notify the Gatekeeper of any Target(s) that BicycleTx wishes to place on the Gatekeeper List pursuant to Section 4.8.3 or Section 4.8.6 (each, a "**BicycleTx Target**") to enable the Gatekeeper to determine whether such BicycleTx Targets are Collaboration Targets (and therefore not Available for BicycleTx). To screen a BicycleTx Target, BicycleTx shall provide the Gatekeeper with a confidential written description of the applicable Target including, to the extent available, [***] for such Target ("**BicycleTx Target Request**"). Within [***] following the Gatekeeper's receipt of the BicycleTx Target Request with respect to a BicycleTx Target, the Gatekeeper shall verify if such BicycleTx Target is Available and notify BicycleTx in writing.

4.10 Subcontracting. Each Party shall have the right to subcontract any of its Development activities to a Third Party; provided that (a) such Party remains responsible for the work allocated to, and payment to, such subcontractors to the same extent it would if it had done such work itself; (b) each subcontractor undertakes in writing obligations of confidentiality and non-use regarding Confidential Information that are substantially the same as those undertaken by the Parties pursuant to ARTICLE 8; and (c) each subcontractor agrees in writing to assign all intellectual property developed in the course of performing any such work to such Party in accordance with Section 7.1.3(a).

4.11 Regulatory Matters.

4.11.1 Regulatory Activities. As between the Parties, Ionis, at its sole expense, shall have the sole right to prepare, obtain, and maintain the Drug Approval Applications (including the setting of the overall regulatory strategy therefor), Regulatory Approvals, and other Regulatory Documentation, and to conduct communications with Regulatory Authorities, for Compounds and Licensed Products in the Territory, provided that following the termination of Oligo Exclusivity (if applicable), Ionis' right to conduct the foregoing regulatory activities shall apply only to Licensed Products directed to Collaboration Targets (and for clarity, such right with respect to Collaboration Targets shall be a sole right). Upon Ionis' request [***], BicycleTx shall provide Ionis with reasonable assistance in obtaining Regulatory Approvals for the Licensed Products, including providing necessary documents or other materials required by Applicable Law to obtain such Regulatory Approvals, provided that such assistance shall be limited to

assistance that relates directly to the work BicycleTx conducted pursuant to the Research Plan, and provided further that nothing in this Section 4.11.1 shall obligate BicycleTx to generate any additional data or other Know-How.

4.11.2 Recalls. Ionis shall notify BicycleTx promptly following its determination that any event, incident, or circumstance has occurred that may result in the need for a recall, market suspension, or market withdrawal of a Licensed Product in the Territory, and shall include in such notice the reasoning behind such determination and any supporting facts. Ionis (or its Sublicensee) shall have the right to make the final determination whether to voluntarily implement any such recall, market suspension, or market withdrawal in the Territory. If a recall, market suspension, or market withdrawal is mandated by a Regulatory Authority in the Territory, Ionis (or its Sublicensee) shall initiate such a recall, market suspension, or market withdrawal in compliance with Applicable Law. For all recalls, market suspensions, or market withdrawals undertaken pursuant to this Section 4.11.2, Ionis (or its Affiliate or Sublicensee) shall be solely responsible for the execution thereof, and BicycleTx shall reasonably cooperate in all such recall efforts [***].

4.12 Records. Each of BicycleTx and Ionis shall, and shall ensure that its contractors, maintain records in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, and in compliance with Applicable Law, which shall be complete and accurate and shall properly reflect all work done and results achieved in the performance of its Research Activities and Development activities hereunder, which shall record only such activities and shall not include or be commingled with records of activities outside the scope of this Agreement. Such records shall be retained by BicycleTx or Ionis, as the case may be, for at least [***] after the termination of this Agreement, or for such longer period as may be required by Applicable Law.

ARTICLE 5
COMMERCIALIZATION

5.1 In General. Ionis (itself or through its Affiliates or Sublicensees) shall have the sole right and responsibility to Commercialize Licensed Products in the Field in the Territory, at its own expense, provided that following the termination of Oligo Exclusivity (if applicable), Ionis' right to conduct the foregoing Commercialization activities shall apply only to Licensed Products directed to Collaboration Targets (and for clarity, such right with respect to Collaboration Targets shall be a sole right).

5.2 Commercialization Diligence. For each Target for which Ionis has paid (or, for up to four Targets, as applicable, applied a credit toward) the IND Acceptance Fee (including, for clarity, any Collaboration Target), Ionis shall use Commercially Reasonable Efforts to Commercialize at least [***] following receipt of Regulatory Approval therefor in such Major Market. With respect to any such Target, if Ionis decides to discontinue the Development or Commercialization of a Compound and Licensed Product in favor of another Compound and Licensed Product directed to such Target, its obligations under this Section 5.2 shall cease with respect to such initial Compound and Licensed Product in favor of such other Compound and Licensed Product directed to such Target.

5.3 Commercial Updates. Ionis shall update BicycleTx on [***] basis regarding its significant Commercialization activities with respect to Licensed Products corresponding to each Target for which Ionis has paid (or, for [***], as applicable, applied a credit toward) the IND Acceptance Fee in the Territory. Each such update shall summarize Ionis and its Affiliates' and Sublicensees' significant Commercialization activities with respect to each such Licensed Product and Target in the Territory and shall contain information at a level of detail reasonably required by BicycleTx to determine Ionis'

compliance with its diligence obligations set forth herein, provided however that such updates and reports need not be specifically generated in compliance with this section and Ionis may rely on existing reports and internal communications to its Research Management Committee or other executive management, as long as such reports appropriately encompass the information required under this Section 5.3.

5.4 Commercial Supply of Compounds and Licensed Products. As between the Parties, Ionis shall have the sole right and responsibility, at its expense, to Manufacture (or have Manufactured) and supply Compounds and Licensed Products for commercial sale in the Territory by Ionis and its Affiliates and Sublicensees. If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, such rights and responsibilities shall be limited to Compounds and Licensed Products directed to the Collaboration Targets.

ARTICLE 6
PAYMENTS AND RECORDS

6.1 Upfront Payment. Within [***] after the Effective Date, Ionis shall pay to BicycleTx a one-time, non-refundable, non-creditable (except as set forth in Section 6.3) payment in the amount of Thirty-One Million Dollars ($31,000,000). The Parties acknowledge and agree that the Three Million Dollar ($3,000,000) Option Fee (as defined in the Option Agreement) paid to BicycleTx by Ionis pursuant to Section 4.1 of the Option Agreement has been fully credited against the total agreed upfront payment under this Agreement of Thirty-Four Million Dollars ($34,000,000).

6.2 Equity Consideration. In partial consideration for the rights granted by BicycleTx under this Agreement, Bicycle Therapeutics plc and Ionis will enter into a Stock Purchase Agreement in the form set forth as Exhibit 6.2, pursuant to which Bicycle Therapeutics plc will issue to Ionis a number of Ordinary Shares equal to Eleven Million Dollars ($11,000,000) divided by the Share Value in accordance with the terms set forth therein (as the terms Ordinary Shares and Share Value are defined in the Stock Purchase Agreement).

6.3 IND Acceptance Fee. On a Target-by-Target basis, within [***] after IND Acceptance for the first Licensed Product directed to such Target being Developed by Ionis, its Affiliates or Sublicensees, Ionis shall pay to BicycleTx a one-time, non-refundable, non-creditable payment in the amount of [***] (the "**IND Acceptance Fee**"); provided, however, that Ionis will have a credit up to [***] (the "**IND Acceptance Credit**"), which shall be deemed included in (and pre-paid pursuant to) the upfront payment paid to BicycleTx under Section 6.1, and may be applied against the IND Acceptance Fee for the first Licensed Product directed to each of up to [***] Targets. For clarity, Ionis shall not be required to apply the IND Acceptance Credit against the first four Targets (and associated Licensed Products), and shall have sole discretion in determining, on a Licensed Product-by-Licensed Product basis, whether it wishes to pay the IND Acceptance Fee in cash, or apply a portion of the remaining IND Acceptance Credit against such Licensed Product, until the full amount of the IND Acceptance Credit has been exhausted. If Oligo Exclusivity expires, and Ionis has, at such time, not exhausted the IND Acceptance Credit, Ionis may apply any remaining amount against any prepayment of the IND Acceptance Fee for Targets that Ionis designates to be Collaboration Targets pursuant to Section 4.8.2. For clarity, if this Agreement is terminated prior to the exhaustion of the IND Acceptance Credit, BicycleTx will not be required to refund any unused portion of the IND Acceptance Credit to Ionis.

6.4 Development and Regulatory Milestones.

6.4.1 Development and Regulatory Milestone Payments. In partial consideration of the rights granted by BicycleTx to Ionis under this Agreement and subject to the terms and conditions set forth in the remainder of this Section 6.4, on a Target-by-Target basis, Ionis shall pay to BicycleTx the non-refundable, non-creditable milestone payment set forth in the table below upon the first achievement of the corresponding milestone event by a Licensed Product directed to such Target by or on behalf of Ionis or its Affiliates or Sublicensees:

Milestone Event (payable for the first Licensed Product directed to a given Target)		Milestone Payment Amount
1.	[***]	[***]
2.	[***]	[***]
3.	[***]	[***]
4.	[***]	[***]

6.4.2 One-Time Payment per Target; Deemed Achievement. For clarity, the foregoing milestone payments shall be payable one-time only with respect to each Target, regardless of the number of Licensed Products directed to such Target to achieve such milestone event. For further clarity, milestone #1 shall be deemed achieved and payable, if not already achieved, upon achievement of any of milestones #2, #3, or #4 by a Licensed Product directed to the same Target.

6.4.3 Ultra-Rare Disease Product Delay in Payment. Notwithstanding the foregoing, with respect to the achievement of any of the foregoing milestone events by an Ultra-Rare Disease Product, Ionis' payment to BicycleTx of the corresponding milestone payments will be deferred until the first to occur of [***].

6.4.4 Notice and Payment. Ionis shall notify BicycleTx within [***] after achieving any milestone event set forth in the table above. Except as otherwise provided in Section 6.4.3 with respect to an Ultra-Rare Disease Product, Ionis shall pay to BicycleTx the applicable milestone payment within [***] after receipt of an invoice for the achievement of the applicable milestone event.

6.5 Collaboration Milestones.

6.5.1 Collaboration Milestone Payments. In partial consideration of the rights granted by BicycleTx to Ionis hereunder and subject to the terms and conditions set forth in the remainder of this Section 6.5, Ionis shall pay to BicycleTx the following one-time, non-refundable, non-creditable milestone payments set forth in the table below following the end of the Calendar Quarter in which the first achievement by or on behalf of Ionis, its Affiliates or Sublicensees of the corresponding milestone event occurred:

[***]		Milestone Payment Amount
1.	[***]	[***]
2.	[***]	[***]

6.5.2 Notice and Payment. Ionis shall notify BicycleTx within [***] following the end of the Calendar Quarter in which such milestone event in the table above was achieved. Ionis shall pay to BicycleTx the applicable milestone payment within [***] after receipt of an invoice for the achievement of the applicable milestone event.

6.6 Royalties.

6.6.1 Royalty Rates. As further consideration for the rights granted to Ionis under this Agreement, subject to the remainder of this Section 6.6, during the Royalty Term, Ionis shall make quarterly, non-refundable (except as the result of an overpayment under Section 6.11), non-creditable royalty payments to BicycleTx on the annual Net Sales of each Licensed Product sold by or on behalf of Ionis, its Affiliates or Sublicensees in the Territory at the applicable rate set forth below:

Annual Net Sales in the Territory of a given Licensed Product in a Calendar Year	Royalty Rate
[***]	[***]
[***]	[***]

6.6.2 Royalty Term. Royalties shall be paid on a Licensed Product-by-Licensed Product and country-by-country basis in the Territory from the First Commercial Sale of such Licensed Product in a country by or on behalf of Ionis, its Affiliates, or Sublicensees, until the expiration of the Royalty Term for such Licensed Product in such country.

6.6.3 Permitted Reductions.

(a) On a Licensed Product-by-Licensed Product basis, if [***] to the extent necessary such that [***] for such Licensed Product in such Calendar Quarter, after giving effect to [***];

provided that during the [***] following the First Commercial Sale of such Licensed Product in [***] (each such period, a "Royalty Floor Period") in no event will the foregoing operate to reduce the royalty paid to BicycleTx on the Net Sales of such Licensed Product in any [***] of the amount that BicycleTx otherwise would have received on the Net Sales of such Licensed Product in [***] had no such reduction occurred.

(b) If following the Royalty Floor Period the amount of royalties paid to BicycleTx by Ionis is reduced as described in Section 6.6.3(a), Ionis will also pay to BicycleTx [***] sale of the applicable Licensed Product following the Royalty Floor Period until [***] of the amount that BicycleTx [***] after the Royalty Floor Period ***minus*** (ii) the royalty payments received by BicycleTx for such Net Sales in such countries. [***]. For instance, [***]. At the end of the quarter, [***].

Notwithstanding the foregoing, Ionis will use commercially reasonable efforts to obtain a minimum of a [***] royalty from its Sublicensees so that no reduction to the royalty payable to BicycleTx pursuant to Section 6.6.3(a) is implemented.

(c) Except as set forth in the foregoing Section 6.6.3(a), the royalties payable by Ionis to BicycleTx pursuant to Section 6.6.1 shall [***].

6.7 Royalty Payments and Reports. Ionis shall calculate all amounts payable to BicycleTx pursuant to Section 6.6 at the end of each Calendar Quarter, which amounts shall be converted to Dollars, in accordance with Section 6.8. Ionis shall pay to BicycleTx the royalty amounts due with respect to a given Calendar Quarter within [***] after the end of each Calendar Quarter. Each payment of royalties due to BicycleTx shall be accompanied by a report setting forth the Net Sales of the Licensed Products by Ionis and its Affiliates and Sublicensees in the Territory in sufficient detail to permit confirmation of the accuracy of the royalty payment made, including [***].

6.8 Mode of Payment. All payments to BicycleTx under this Agreement shall be made by deposit of Dollars in the requisite amount to such bank account as BicycleTx may from time to time designate by written notice to Ionis. For the purpose of calculating any sums due under, or otherwise reimbursable pursuant to, this Agreement (including the calculation of Net Sales expressed in currencies other than Dollars), a Party shall convert any amount expressed in a foreign currency into Dollar equivalents using its, its Affiliate's, or Sublicensee's standard conversion methodology consistent with Accounting Standards.

6.9 Taxes.

6.9.1 Taxes on Income. Except as provided herein, each Party shall be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.9.2 Withholding Amounts. If any sum due to be paid to BicycleTx under this Agreement is subject to any withholding or similar tax, the Parties shall use their commercially reasonable efforts to do all such acts and to sign all such documents as will enable them to take advantage of any applicable double taxation agreement or treaty. If there is no applicable double taxation agreement or treaty, or if an applicable double taxation agreement or treaty reduces but does not eliminate such withholding or similar tax, Ionis shall remit such withholding or similar tax to the appropriate government authority and any tax paid or required to be withheld by Ionis for the benefit of BicycleTx on account of any payments to BicycleTx under this Agreement will be deducted from the amount of royalties or other payments otherwise due. Ionis will secure and send to BicycleTx the best available proof of any such taxes so

withheld and paid by Ionis for the benefit of BicycleTx. If withholding or similar taxes are paid to a government authority, each Party will provide the other such assistance as is reasonably required to obtain a refund of the withheld or similar taxes, or to obtain a credit with respect to such taxes paid.

6.9.3 Withholding Actions. Notwithstanding the foregoing, the Parties acknowledge and agree that if Ionis (or its assignee pursuant to Section 12.9) is required by Applicable Law to withhold taxes in respect of any amount payable under this Agreement, and if such withholding obligation arises as a result any action by Ionis, including any assignment of this Agreement by Ionis as permitted under Section 12.9, a change in tax residency of Ionis, or payments arise or are deemed to arise through a branch of Ionis and such withholding taxes exceed the amount of withholding taxes that would have been applicable if such action had not occurred (each, an "**Ionis Withholding Tax Action**"), then, notwithstanding anything to the contrary herein, any such amount payable to BicycleTx under this Agreement shall be increased to take into account such increased withholding taxes as may be necessary so that, after making all required withholdings, BicycleTx (or its assignee pursuant to Section 12.9) receives an amount equal to the sum it would have received had no such Ionis Withholding Tax Action occurred. BicycleTx shall (a) use its commercially reasonable efforts to obtain an exemption of such withheld amounts to the extent practicable under Applicable Law and (b) cooperate with Ionis, at Ionis' reasonable expense, to obtain a reduction or refund of such withheld amounts. Notwithstanding the foregoing, the Parties acknowledge and agree that as of the date of this Agreement and under Applicable Laws, no withholding tax will be applicable to payments made to BicycleTx pursuant to this Agreement provided BicycleTx provides Ionis with a completed IRS form W-8BEN-E claiming the benefits of the United States – United Kingdom Income Tax Convention. The failure by BicycleTx to provide the tax forms described herein shall not relieve Ionis (or its assignee pursuant to Section 12.9) of its obligations pursuant to this Section 6.9.3 unless Ionis has requested the applicable tax forms in writing sufficiently in advance of a payment so as to allow the BicycleTx a reasonable amount of time to obtain and provide the required forms. Notwithstanding the foregoing, if the increase in the withholding tax is directly a result of the transfer or assignment by BicycleTx of any intellectual property or a portion of the rights under this license Ionis will only be obligated to pay BicycleTx such gross up to the extent such transfer or assignment by BicycleTx did not cause such increase in the withholding tax.

6.9.4 Tax Credits. During the Term, to the extent of, and if directly as a result of, an additional payment paid to BicycleTx pursuant to Section 6.9.3, BicycleTx is able to utilize a foreign tax credit or claim a deduction in the year of any such payment or any later year to actually reduce otherwise payable cash taxes, BicycleTx will refund to Ionis an amount equal to the actual cash tax savings obtained by BicycleTx directly related to the increased payment BicycleTx received pursuant to Section 6.9.3 as reasonably determined in good faith by BicycleTx and supported by BicycleTx's tax records. Except in the case of a dispute between the Parties under this Section 6.9.4, BicycleTx will not be required to provide Ionis with any tax returns or other confidential tax, accounting, or financial information.

6.10 Interest on Late Payments. If any undisputed payment due to either Party under this Agreement is not paid when due, then such paying Party shall pay interest thereon (before and after any judgment, but excluding the period during which termination is tolled pursuant to Section 11.3.1) at [***], such interest to run from the date [***] until [***]. For the purposes of this Agreement, [***].

6.11 Audit. Ionis shall keep, and shall require its Affiliates and Sublicensees to keep, complete and accurate records pertaining to the sale or other disposition of Licensed Products in sufficient detail to permit BicycleTx to confirm the accuracy of any milestone payment due under Section 6.5 and royalty payment due under Section 6.6. Ionis will keep such books and records for [***] following the Calendar Year to which they pertain, or such longer period of time as may be required by Applicable Law. Upon

reasonable prior notice and during regular business hours at such place or places where such records are customarily kept, such records may be inspected on BicycleTx's behalf by an independent certified public accountant (the "**Auditor**") selected by BicycleTx and reasonably acceptable to Ionis for the sole purpose of verifying for BicycleTx the accuracy of any payments made, or required to be made, to BicycleTx pursuant to this Agreement. Before beginning its audit, the Auditor shall execute an undertaking reasonably acceptable to each Party by which the Auditor agrees to keep confidential all information reviewed during the audit. Such audits shall be limited to [***] each Calendar Year and [***]. Such auditor shall not disclose Ionis' Confidential Information to BicycleTx except to the extent necessary to confirm the accuracy of the financial reports and payments furnished by Ionis under this Agreement and the amount of any discrepancies. If the final result of the inspection reveals an undisputed underpayment, the underpaid amount shall be paid within [***] after the Auditor's report. If the final result of the inspection reveals an undisputed overpayment, the overpaid amount shall be applied as a credit against future royalty payments by Ionis. BicycleTx shall bear the full cost of such audit unless such audit reveals an underpayment owed by Ionis of more than [***] from the reported amounts, in which case Ionis shall bear the cost of such audit.

ARTICLE 7
INTELLECTUAL PROPERTY

7.1 Ownership of Intellectual Property.

7.1.1 United States Law. The determination of whether an Invention is discovered, made, conceived, or reduced to practice by a Party for the purpose of allocating proprietary rights (including Patent, copyright, or other intellectual property rights) therein, shall, for purposes of this Agreement, be made in accordance with Applicable Law in the United States.

7.1.2 Inventions.

(a) **Sole Ownership**. As between the Parties, (i) BicycleTx, or an Affiliate designated by BicycleTx, shall own all right, title, and interest in and to any and all TfR1 BicycleTx Inventions and (ii) with respect to all other Inventions, each Party shall solely own any Inventions made solely by its and its Affiliates' employees, agents, or independent contractors.

(b) **Joint Ownership**. Subject to Section 7.1.2(a)(i), the Parties shall jointly own any Inventions that are made jointly by employees, agents, or independent contractors of one Party and its Affiliates together with employees, agents, or independent contractors of the other Party and its Affiliates ("**Joint Inventions**"). Subject to the licenses granted under Section 2.1 and Section 2.3, and BicycleTx's Exclusivity Obligations hereunder, each Party shall have the right to Exploit the Joint Patents and Joint Inventions without a duty of seeking consent from or accounting to the other Party.

7.1.3 Assignment Obligation.

(a) Each Party shall cause all Persons who perform activities for such Party under this Agreement to be under an obligation to assign (or, if such Party is unable to cause such Person to agree to such assignment obligation despite such Party's using commercially reasonable efforts to negotiate such assignment obligation, provide a license under) their rights in any Inventions resulting therefrom to such Party, except where Applicable Law requires otherwise and except in the case of governmental, not-for-profit, and public institutions which have standard policies against such an assignment (in which case a suitable license, or right to obtain such a license, shall be obtained).

(b) Ionis will promptly disclose to BicycleTx in writing any TfR1 BicycleTx Inventions made (either solely or jointly) by Persons (other than BicycleTx) who perform activities for Ionis under this Agreement. Ionis, for itself and on behalf of its Affiliates, hereby assigns (and to the extent a present assignment of future rights is prohibited by Applicable Law, hereby agrees to and shall assign) to BicycleTx all of its right, title, and interest in and to any and all TfR1 BicycleTx Inventions (and any BicycleTx Patents relating thereto). Ionis will execute and record assignments and other necessary documents consistent with such ownership promptly upon BicycleTx's request.

(c) Each Party will promptly disclose to the other Party, in writing, the conception, discovery, development, generation, making or creation of any Joint Inventions made by Persons who perform activities for it under this Agreement. Each Party will execute and record assignments and other necessary documents consistent with such ownership promptly upon such other Party's request.

7.2 Patent Prosecution and Maintenance.

7.2.1 BicycleTx Patents other than BicycleTx Product Patents.

(a) BicycleTx shall have the sole right, but not the obligation, through the use of internal or outside counsel of its choice, to prepare, file, prosecute, and maintain (a) the BicycleTx Platform Patents, and (b) the BicycleTx Patents that do not Cover any Compound or Licensed Product worldwide, at BicycleTx's expense.

(b) BicycleTx shall have the first right, but not the obligation, through the use of internal or outside counsel of its choice, to prepare, file, prosecute, and maintain any BicycleTx Patent that Cover any Compound or Licensed Product, but which Patent is not a BicycleTx Product Patent (each, a "**BicycleTx Relevant Patent**") worldwide, at BicycleTx's expense. With respect to any BicycleTx Relevant Patents that [***], BicycleTx shall keep Ionis reasonably informed of all material steps with regard to the preparation, filing, prosecution, and maintenance of any such claims of such BicycleTx Relevant Patents, including by providing Ionis with a copy of material communications to and from any patent authority in the Territory regarding such claims of such BicycleTx Relevant Patents, and by providing Ionis drafts of any material filings to be made to such patent authorities in the Territory sufficiently in advance of submitting such filings so as to allow for a reasonable opportunity for Ionis to review and comment on such claims. Upon Ionis' request during the Term, BicycleTx shall use reasonable efforts, to the extent reasonably practicable under applicable patent law, to separate [***] from any BicycleTx Relevant Patent, and to file one or more divisional or continuation patent applications that [***] shall be deemed BicycleTx Product Patents hereunder as of the date of filing, and shall thereafter be subject to Section 7.2.3. For clarity, all Patents that issue from such [***], shall be included as BicycleTx Product Patents under this Agreement.

(c) If, in the reasonable opinion of BicycleTx's patent counsel, [***], BicycleTx shall consider in good faith the requests and suggestions of Ionis with respect to such BicycleTx drafts and with respect to strategies for filing and prosecuting such Patents in the Territory. If BicycleTx decides not to prosecute, or maintain any BicycleTx Relevant Patents that [***] in a country or other jurisdiction in the Territory, BicycleTx shall provide reasonable prior written notice to Ionis of such intention (which notice shall, in any event, be given no later than [***] prior to the next deadline for any action that may be taken with respect to such BicycleTx Relevant Patents that [***] in such country or other jurisdiction), and BicycleTx shall reasonably consider a request by Ionis to assume the control and direction of the preparation, filing, prosecution, and maintenance of such Patent at its sole cost and expense in such country or other jurisdiction. For clarity, BicycleTx shall [***]. If BicycleTx grants its consent to Ionis'

assumption of such activities, Ionis shall assume the responsibility and control for the preparation, filing, prosecution, and maintenance of such BicycleTx Relevant Patent. In such event, Bicycle shall reasonably cooperate with Ionis with respect to such Patent in such country or other jurisdiction as provided under Section 7.2.4.

7.2.2 Ionis Patents. Ionis shall have the sole right, but not the obligation, through the use of internal or outside counsel, to prepare, file, prosecute, and maintain the Ionis Patents, BicycleTx Product Patents, and Joint Product Patents worldwide, at Ionis' expense.

7.2.3 BicycleTx Product Patents and Joint Patents. Ionis shall have the first right, but not the obligation, through the use of internal counsel, or outside counsel reasonably acceptable to BicycleTx, to prepare, file, prosecute, and maintain the BicycleTx Product Patents and the Joint Patents worldwide, at Ionis' expense. Ionis shall keep BicycleTx reasonably informed of all material steps with regard to the preparation, filing, prosecution, and maintenance of the BicycleTx Product Patents and Joint Patents, including by providing BicycleTx with a copy of material communications to and from any patent authority in the Territory regarding such Patents, and by providing BicycleTx drafts of any material filings to be made to such patent authorities in the Territory sufficiently in advance of submitting such filings so as to allow for a reasonable opportunity for BicycleTx to review and comment thereon. Ionis shall consider in good faith the requests and suggestions of BicycleTx with respect to such Ionis drafts and with respect to strategies for filing and prosecuting such Patents in the Territory. If Ionis decides not to prepare, file, prosecute, or maintain any BicycleTx Product Patent or Joint Patent in a country or other jurisdiction in the Territory, Ionis shall provide reasonable prior written notice to BicycleTx of such intention (which notice shall, in any event, be given no later than [***] prior to the next deadline for any action that may be taken with respect to such BicycleTx Product Patent or Joint Patent in such country or other jurisdiction), and BicycleTx shall thereupon have the option, in its sole discretion, to assume the control and direction of the preparation, filing, prosecution, and maintenance of such Patent at its sole cost and expense in such country or other jurisdiction. Upon BicycleTx's written acceptance of such option, BicycleTx shall assume the responsibility and control for the preparation, filing, prosecution, and maintenance of such BicycleTx Product Patent or Joint Patent, as applicable. In such event, Ionis shall reasonably cooperate with BicycleTx with respect to such Patent in such country or other jurisdiction as provided under Section 7.2.4. Notwithstanding the foregoing, following the termination of Oligo Exclusivity, BicycleTx shall assume sole responsibility for the prosecution and maintenance of BicycleTx Product Patents that solely Cover Licensed Products and Compounds directed to any Target that is not a Collaboration Target, and Ionis will reasonably cooperate with BicycleTx to transfer responsibility for such prosecution and maintenance activities to BicycleTx for any such BicycleTx Product Patents promptly following the loss of Oligo Exclusivity.

7.2.4 Cooperation. The Parties agree to cooperate fully in the preparation, filing, prosecution, and maintenance of the Product Patents and Joint Patents in the Territory under this Agreement. Cooperation shall include:

(a) without limiting any other rights and obligations of the Parties under this Agreement, cooperating with respect to the timing, scope, and filing of such Patents to preserve and enhance the patent protection for Compounds and Licensed Products, including the manufacture and use thereof;

(b) executing all papers and instruments, or requiring its employees or contractors to execute such papers and instruments, so as to (i) effectuate the ownership of intellectual property set forth in Section 7.1.2; (ii) enable the other Party to apply for and to prosecute Patent applications in the Territory; and (iii) obtain and maintain any Patent extensions, supplementary protection

certificates, and the like with respect to the Product Patents and Joint Patents in the Territory, in each case ((i), (ii), and (iii)) to the extent provided for in this Agreement;

(c) consistent with this Agreement, assisting in any license registration processes with applicable governmental authorities that may be available in the Territory for the protection of a Party's interests in this Agreement; and

(d) promptly informing the other Party of any matters coming to such Party's attention that may materially affect the preparation, filing, prosecution, or maintenance of any such Patents in the Territory.

7.2.5 CREATE Act. It is the intention of the Parties that this Agreement is a "joint research agreement" as that phrase is defined in 35 USC § 102(c) (AIA) or 35 USC § 103(c) (pre-AIA). In the event that either Party to this Agreement intends to overcome a rejection of a claimed invention within the Joint Patents or Product Patents under this Agreement pursuant to the provisions of 35 USC § 102(c) or 35 USC § 103(c), such Party shall first obtain the prior written consent of the other Party. Following receipt of such written consent, such Party shall limit any amendment to the specification or statement to the patent office with respect to this Agreement to that which is strictly required by 35 USC § 102(c) or 35 USC § 103(c) and the rules and regulations promulgated thereunder and which is consistent with the terms and conditions of this Agreement. If the Parties agree that, in order to overcome a rejection of a claimed invention within the Joint Patents or Product Patents pursuant to the provisions of the CREATE Act, the filing of a terminal disclaimer is required or advisable, the Parties shall first agree on terms and conditions under which the patent application subject to such terminal disclaimer and the patent or application over which such application is disclaimed shall be jointly enforced, if and to the extent that the Parties have not previously agreed to such terms and conditions. If Ionis enters into an agreement with a Third Party with respect to the further Research, Development, or Commercialization of a Compound or Licensed Product, BicycleTx shall, upon Ionis' request, similarly enter into such agreement with such Third Party for the purposes of furthering the Parties' objectives under this Agreement, provided that such agreement is consistent with the rights of BicycleTx under this Section 7.2.5 and does not place any material obligation on BicycleTx.

7.2.6 Patent Term Extension and Supplementary Protection Certificate. Ionis shall have authority and sole discretion for making decisions regarding patent term extensions, including supplementary protection certificates and any other extensions that are now or become available in the future, wherever applicable, for Ionis Patents, Product Patents, and Joint Patents in any country or other jurisdiction and for applying for any extension or supplementary protection certificate with respect to such Patents in the Territory. BicycleTx shall provide prompt and reasonable assistance, as requested by Ionis, including by taking such action as patent holder as is required under any Applicable Law to obtain such patent extension or supplementary protection certificate. If Ionis desires that a patent term extension should be applied for a BicycleTx Patent other than a BicycleTx Product Patent, BicycleTx and Ionis shall discuss in good faith such patent term extension, provided that such decision shall be at BicycleTx's sole discretion. Ionis shall pay all expenses (including any expenses incurred by BicycleTx) with respect to obtaining any extension or supplementary protection certificate in the Territory requested by Ionis.

7.2.7 Patent Listings. Ionis will have the sole right to make all filings with Regulatory Authorities in the Territory with respect to Ionis Patents, Product Patents, and Joint Patents, including as required or allowed under Applicable Law, provided that with respect to Joint Patents and BicycleTx Product Patents, such right shall be solely with respect to Licensed Products. Ionis shall notify BicycleTx in writing of any BicycleTx Patents other than BicycleTx Product Patents that it intends to list with

Regulatory Authorities related to the Licensed Products and, prior to filing any such listing, consult with and consider in good faith the requests and suggestions of BicycleTx regarding the same.

7.3 Patent Enforcement.

7.3.1 BicycleTx Patents other than BicycleTx Product Patents. Each Party shall promptly notify the other Party in writing of any alleged or threatened infringement of a BicycleTx Patent other than a BicycleTx Product Patent by a Third Party in the Territory of which such Party becomes aware based on the development or commercialization of, or an application to market a product containing, a Compound or a Licensed Product in the Territory. BicycleTx shall have the sole right, but not the obligation, to prosecute any such infringement involving any claims of BicycleTx Patents (other than BicycleTx Product Patents) for which it is responsible for prosecution and maintenance activities pursuant to Section 7.2.1, at its sole expense and BicycleTx shall retain control of prosecution of each such claim, suit, or proceeding. For clarity, Ionis shall have the first right, but not the obligation to prosecute any such infringement of BicycleTx Patents for which Ionis has assumed responsibility for prosecution and maintenance pursuant to Section 7.2.1.

7.3.2 Ionis Patents, Product Patents, and Joint Patents.

(a) Each Party shall promptly notify the other Party in writing of any alleged or threatened infringement of an Ionis Patent, a Product Patent, or a Joint Patent by a Third Party in the Territory of which such Party becomes aware (including alleged or threatened infringement based on the development or commercialization of, or an application to market a product containing, a Compound or Licensed Product in the Territory).

(b) Ionis shall have the sole right, but not the obligation, to prosecute any such infringement of Ionis Patents in the Territory at its sole expense, and Ionis shall retain control of the prosecution of such claim, suit, or proceeding.

(c) Ionis shall have the first right, but not the obligation, to prosecute any such infringement of BicycleTx Product Patents and Joint Patents, in each case for which it is responsible for prosecution and maintenance activities under Section 7.2.3, in each case in the Territory at its sole expense, and Ionis shall retain control of the prosecution of such claim, suit, or proceeding. If Ionis prosecutes any such infringement, BicycleTx shall have the right to join as a party to such claim, suit, or proceeding in the Territory and participate with its own counsel at its own expense; provided that Ionis shall retain control of the prosecution of such claim, suit, or proceeding. If Ionis does not take commercially reasonable steps to prosecute the alleged or threatened infringement in the Territory with respect to any such BicycleTx Product Patent or Joint Patent (i) within [***] following the first notice provided above with respect to such alleged infringement, or (ii) [***] before the time limit, if any, set forth in appropriate laws and regulations for filing of such actions, whichever comes first, then BicycleTx may prosecute the alleged or threatened infringement in the Territory at its own expense. For clarity, BicycleTx shall have the first right, but not the obligation to prosecute any such infringement of Joint Patents and BicycleTx Product Patents for which BicycleTx has assumed responsibility for prosecution and maintenance, including any such BicycleTx Product Patents following termination of Oligo Exclusivity.

7.3.3 Cooperation. The Parties agree to cooperate fully in any infringement action pursuant to this Section 7.3. To the extent necessary for a Party to bring such an action, the other Party shall, where necessary, furnish a power of attorney solely for such purpose or shall join in, or be named as a necessary party to, such action. Unless otherwise set forth herein, the Party entitled to bring any patent

infringement litigation in accordance with this Section 7.3 shall have the right to settle such claim; provided that neither Party shall have the right to settle any patent infringement litigation under this Section 7.3 in a manner that materially diminishes or has a material adverse effect on the rights or interest of the other Party, or in a manner that imposes any costs or liability on, or involves any admission by, the other Party, without the express written consent of such other Party. The Party commencing the litigation shall provide the other Party with copies of all pleadings and other documents filed with the court and shall consider reasonable input from the other Party during the course of the proceedings.

7.3.4 Recovery. Any recovery realized as a result of such litigation described in Section 7.3.1 or Section 7.3.2 (whether by way of settlement or otherwise) shall be first allocated to reimburse the Parties for their costs and expenses in making such recovery (which amounts shall be allocated pro rata if insufficient to cover the totality of such expenses). Any remainder after [***].

7.4 Infringement Claims by Third Parties. If the manufacture, sale, or use of a Licensed Product in the Territory pursuant to this Agreement results in, or may result in, any claim, suit, or proceeding by a Third Party alleging patent infringement by Ionis (or its Affiliates or Sublicensees), Ionis shall promptly notify BicycleTx thereof in writing. Ionis shall have the first right, but not the obligation, to defend and control the defense of any such claim, suit, or proceeding at its own expense, using counsel of its own choice. BicycleTx may participate in any such claim, suit, or proceeding with counsel of its choice at its own expense. Without limitation of the foregoing, if Ionis finds it necessary or desirable to join BicycleTx as a party to any such action, BicycleTx shall, at Ionis' expense, execute all papers and perform such acts as reasonably required. If Ionis elects (in a written communication submitted to BicycleTx within a reasonable amount of time after notice of the alleged patent infringement) not to defend or control the defense of, or otherwise fails to initiate and maintain the defense of, any such claim, suit, or proceeding, within such time periods so that BicycleTx is not prejudiced by any delays, BicycleTx may conduct and control the defense of any such claim, suit, or proceeding at its own expense. Each Party shall keep the other Party reasonably informed of all material developments in connection with any such claim, suit, or proceeding. Any recoveries by Ionis of any sanctions awarded to Ionis and against a party asserting a claim being defended under this Section 7.4 shall be applied first to reimburse each Party for its reasonable out-of-pocket costs of defending or participating in such claim, suit, or proceedings, on a pro rata basis. The balance of any such recoveries shall [***].

7.5 Invalidity or Unenforceability Defenses or Actions.

7.5.1 Notice. Each Party shall promptly notify the other Party in writing of any alleged or threatened assertion of invalidity or unenforceability of any of the BicycleTx Patents that Cover a Compound or Licensed Product, Ionis Patents, or Joint Patents by a Third Party, in each case in the Territory and of which such Party becomes aware.

7.5.2 BicycleTx Patents other than BicycleTx Product Patents. BicycleTx shall have the sole right, but not the obligation, to defend and control the defense of the validity and enforceability of the BicycleTx Patents other than the BicycleTx Product Patents at its own expense in the Territory.

7.5.3 Ionis Patents. Ionis shall have the sole right, but not the obligation, to defend and control the defense of the validity and enforceability of the Ionis Patents at its own expense in the Territory.

7.5.4 BicycleTx Product Patents and Joint Patents. Ionis shall have the first right, but not the obligation, to defend and control the defense of the validity and enforceability of the BicycleTx Product Patents and Joint Patents at its own expense in the Territory, in each case for which it is responsible

for prosecution and maintenance activities under Section 7.2.3. BicycleTx may participate in any such claim, suit, or proceeding in the Territory related to the BicycleTx Product Patents and Joint Patents with counsel of its choice at its own expense; provided that Ionis shall retain control of the defense in such claim, suit, or proceeding. If Ionis elects not to defend or control the defense of the BicycleTx Product Patents or Joint Patents in a suit brought in the Territory, or otherwise fails to initiate and maintain the defense of any such claim, suit, or proceeding, then BicycleTx may conduct and control the defense of any such claim, suit, or proceeding, at its own expense; provided, that BicycleTx shall obtain the written consent of Ionis prior to settling or compromising such defense, such consent not to be unreasonably withheld, conditioned, or delayed. For clarity, BicycleTx shall have the first right, but not the obligation to defend and control the defense of the validity and enforceability of BicycleTx Product Patents and Joint Patents for which BicycleTx has assumed responsibility for prosecution and maintenance, including any such BicycleTx Product Patents following termination of Oligo Exclusivity.

7.5.5 Cooperation. Each Party shall assist and cooperate with the other Party as such other Party may reasonably request from time to time in connection with its activities set forth in this Section 7.5, including by being joined as a party plaintiff in such action or proceeding, providing access to relevant documents and other evidence, and making its employees available at reasonable business hours. In connection with any such defense or claim or counterclaim, the controlling Party shall consider in good faith any comments from the other Party, shall keep the other Party reasonably informed of any steps taken, and shall provide copies of all documents filed, in connection with such defense, claim, or counterclaim. In connection with the activities set forth in this Section 7.5, each Party shall consult with the other as to the strategy for the defense of the BicycleTx Patents, Ionis Patents, and Joint Patents.

7.6 Inventor's Remuneration. Each Party shall be solely responsible for any remuneration that may be due such Party's inventors under any applicable inventor remuneration laws.

7.7 Common Interest. All information exchanged between the Parties regarding the prosecution, maintenance, enforcement and defense of Patents under this ARTICLE 7 will be deemed to be Confidential Information of the disclosing Party. In addition, the Parties acknowledge and agree [***]. The Parties agree and acknowledge [***]. Notwithstanding anything to the contrary in this Agreement, to the extent a Party has a good faith belief that any information required to be disclosed by such Party to the other Party under this ARTICLE 7 is protected by attorney-client privilege or any other applicable legal privilege or immunity, such Party shall not be required to disclose such information and the Parties shall in good faith cooperate to agree upon a procedure (including entering into a specific common interest agreement or disclosing such information on a "for counsel eyes only" basis or similar procedure) under which such information may be disclosed without waiving or breaching such privilege or immunity.

ARTICLE 8
CONFIDENTIALITY AND NON-DISCLOSURE

8.1 Confidentiality Obligations. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing by the Parties, during the Term and for [***] thereafter, the receiving Party shall keep confidential and shall not publish or otherwise disclose, and shall not use for any purpose other than as expressly provided for in this Agreement, any Confidential Information furnished or otherwise made known to it, directly or indirectly, by the other Party, and each Party shall keep confidential and shall not publish or otherwise disclose the terms of this Agreement except as permitted herein. Each Party may use the other Party's Confidential Information only to the extent required to accomplish the purposes of this Agreement, including exercising its rights and performing its obligations under this Agreement. Each Party will use at least the same standard of care as it uses to protect its own proprietary or confidential information

(but no less than reasonable care) to ensure that its employees, agents, consultants, contractors, and other representatives do not disclose or make any unauthorized use of the other Party's Confidential Information. Each Party will promptly notify the other upon discovery of any loss or unauthorized use or disclosure of the other Party's Confidential Information.

8.2 Exceptions. The obligations of confidentiality and non-use set forth in Section 8.1 above shall not apply to any information that the receiving Party can demonstrate by written evidence:

8.2.1 is already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the disclosing Party;

8.2.2 is now, or hereafter becomes, generally available to the public or otherwise part of the public domain through no fault of the receiving Party;

8.2.3 is disclosed to the receiving Party by a Third Party who had no obligation to the disclosing Party not to disclose such information to others; or

8.2.4 was independently discovered or developed by the receiving Party without the use of Confidential Information belonging to the disclosing Party.

Specific aspects or details of Confidential Information shall not be deemed to be within the public domain or in the possession of the receiving Party merely because the Confidential Information is embraced by more general information in the public domain or in the possession of the receiving Party. Further, any combination of Confidential Information shall not be considered in the public domain or in the possession of the receiving Party merely because individual elements of such Confidential Information are in the public domain or in the possession of the receiving Party unless the combination and its principles are in the public domain or in the possession of the receiving Party.

8.3 Permitted Disclosures.

8.3.1 Pursuant to Applicable Law. Each Party may disclose Confidential Information to the extent that such disclosure is, in the reasonable opinion of the receiving Party's legal counsel, required to be disclosed pursuant to law, regulation, or a valid order of a court of competent jurisdiction or other supra-national, federal, national, regional, state, provincial, or local governmental body of competent jurisdiction, provided that the receiving Party shall first have given prompt written notice (and to the extent possible, at least [***] notice) to the disclosing Party and given the disclosing Party a reasonable opportunity to take whatever action it deems necessary to protect its Confidential Information. If no protective order or other remedy is obtained, or the disclosing Party waives compliance with the terms of this Agreement, the receiving Party shall furnish only that portion of Confidential Information which the receiving Party is advised by counsel is legally required to be disclosed; for clarity, disclosures required in the reasonable opinion of the receiving Party's legal counsel to the U.S. Securities and Exchange Commission (or equivalent foreign agency) shall be subject to the following Section 8.3.2.

8.3.2 Securities Exchange Filings. The Parties acknowledge that either or both Parties (or its Affiliates) may be obligated to make one or more filings (including to file a copy of this Agreement or Stock Purchase Agreement) with the U.S. Securities and Exchange Commission (or equivalent foreign agency) or a governmental authority. Each Party will be entitled to make such a required filing, provided that if such filing includes a copy of this Agreement it will (a) submit in connection with such filing a copy of this Agreement in a form mutually agreed by the Parties in advance or, if, despite the reasonable efforts

of the filing Party a form mutually agreed by the Parties cannot be agreed in advance, redacted to the extent permitted by Applicable Law, based on advice of filing Party's counsel (the "**Redacted Agreement**"), (b) request, and use reasonable efforts consistent with Applicable Laws to obtain, confidential treatment of all terms redacted in the Redacted Agreement, for a period of at least [***], (c) unless otherwise agreed in writing by the other Party, request an appropriate extension of the term of the confidential treatment period if legally justifiable. For clarity, following a request from a governmental authority to change the redactions requested by a Party in the Redacted Agreement, a Party will not be in breach of this Section 8.3.2 for unredacting those redactions rejected by the applicable governmental authority, provided that such Party shall provide the other Party with a notice of the required change(s) and a copy of the revised redactions. Each Party will be responsible for its own legal and other external costs in connection with any such filing, registration, or notification.

8.3.3 Additional Permitted Disclosures. In addition to disclosures pursuant to Sections 8.3.1 and 8.3.2 and as otherwise expressly permitted by this Agreement, each Party may disclose Confidential Information belonging to the other Party if and to the extent such disclosure is reasonably necessary in the following instances:

(a) under appropriate conditions of confidentiality and on a need-to-know basis to its legal and financial advisors;

(b) under appropriate conditions of confidentiality in connection with an actual or potential (i) permitted license or sublicense of its rights hereunder, (ii) debt, lease, or equity financing of such Party, (iii) merger, acquisition, consolidation, share exchange, or other similar transaction involving such Party and a Third Party, and (iv) co-funding or financing arrangement, provided that in each case ((i) to (iv)) the receiving Party takes reasonable and lawful actions to minimize the degree of such disclosure;

(c) under appropriate conditions of confidentiality to any Third Party that is or may be engaged to perform services in connection with the Development, Manufacturing, or Commercialization of the Licensed Products as necessary to enable such Third Party to perform such services;

(d) to any government agency or authority in connection with seeking government funding, support, or grants;

(e) filing, prosecuting, and maintaining Patents, and prosecuting and defending litigation, in each case as permitted by this Agreement;

(f) obtaining and maintaining Regulatory Approvals for, and conducting preclinical studies or Clinical Trials of, Licensed Products that such Party has a license or right to Develop or Commercialize under this Agreement in a given country or jurisdiction; and

(g) in the case of Confidential Information pertaining to TfR1 Bicycles, BicycleTx may disclose such information to [***], and *provided* that BicycleTx does not [***].

8.4 Use of Name. Except as expressly provided herein, neither Party shall mention or otherwise use the name, logo, or trademark of the other Party or any of its Affiliates (or any abbreviation or adaptation thereof) in any publication, press release, marketing and promotional material, or other form of publicity without the prior written approval of such other Party in each instance. The restrictions imposed

by this Section 8.4 shall not prohibit either Party from making any disclosure identifying the other Party that, in the opinion of the disclosing Party's counsel, is required by Applicable Law; provided that such Party shall submit the proposed disclosure identifying the other Party in writing to the other Party as far in advance as reasonably practicable (and in no event less than five Business Days prior to the anticipated date of disclosure) so as to provide a reasonable opportunity to comment thereon.

8.5 Press Releases. The Parties agree to issue separate, mutually approved press releases at or shortly after the Effective Date within the time-period as required by relevant securities laws. It is understood that each Party may desire or be required to issue subsequent press releases relating to this Agreement or activities hereunder. The Parties agree to consult with each other reasonably and in good faith with respect to the text and timing of such press releases prior to the issuance thereof. Notwithstanding the foregoing, neither Party may unreasonably withhold, condition, or delay consent to such releases by more than five Business Days, and either Party may issue such press releases or make such disclosures to the U.S. Securities and Exchange Commission (or equivalent foreign agency) as it determines, based on advice of counsel, is reasonably necessary to comply with Applicable Laws or for appropriate market disclosure. Each Party shall provide the other Party with advance notice of legally required disclosures to the extent practicable, and to the extent possible, at least [***] prior to such disclosure. Following the initial joint press release announcing this Agreement, either Party shall be free to disclose, without the other Party's prior written consent, the existence of this Agreement, the identity of the other Party, and those terms of the Agreement which have already been publicly disclosed in accordance with this Section 8.5.

8.6 Publications. During the Term, the disclosure by either Party relating to any Compound or Licensed Product in any publication or presentation shall be in accordance with the procedure set forth in this Section 8.6. A Party ("**Publishing Party**") shall provide the other Party with a copy of any proposed publication or presentation at least [***] prior to submission for publication so as to provide such other Party with an opportunity to recommend any changes to the Publishing Party that it reasonably believes are necessary to continue to maintain such Party's Confidential Information in accordance with the requirements of this Agreement. The incorporation of such recommended changes shall not be unreasonably refused; and if such other Party notifies ("**Publishing Notice**") the Publishing Party in writing, within [***] after receipt of the copy of the proposed publication or presentation, that such publication or presentation in its reasonable judgment (a) contains an Invention, solely or jointly conceived or reduced to practice by the other Party, for which the other Party reasonably desires to obtain patent protection or (b) could be expected to have a material adverse effect on the commercial value of any Confidential Information disclosed by the other Party to the Publishing Party, the Publishing Party shall prevent such publication or delay such publication for a mutually agreed period of time. In the case of Inventions, a delay shall be for a period reasonably sufficient to permit the timely preparation and filing of a patent application(s) on such Invention, and in no event less than [***] from the date of the Publishing Notice.

8.7 Destruction or Return of Confidential Information. Upon the effective date of the termination of this Agreement for any reason, each Party shall, as soon as reasonably practicable, with respect to Confidential Information to which such Party does not retain rights under the surviving provisions of this Agreement, either return to the disclosing Party or destroy (at the receiving Party's election) all copies of such Confidential Information in the possession of the receiving Party, and confirm such destruction or complete return in writing to the disclosing Party, provided that the receiving Party shall be permitted to retain one copy of such Confidential Information for the sole purpose of performing any continuing obligations hereunder, as required by Applicable Law, or for archival purposes. Notwithstanding the foregoing, the receiving Party also shall be permitted to retain such additional copies of or any computer records or files containing such Confidential Information that have been created solely by such Party's

automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with such Party's standard archiving and back-up procedures, but not for any other use or purpose. If the termination this Agreement is with respect to one or more Terminated Targets but not in its entirety, the obligations under this Section 8.7 shall apply solely to the extent the applicable Confidential Information of the disclosing Party relates to such Terminated Targets and Terminated Assets, as applicable, and to the extent that such Confidential Information cannot be separated from information that relates to Targets and Licensed Products and Compounds other than the Terminated Targets and Terminated Assets, the receiving Party shall have no rights to use or disclose such Confidential Information in connection with Terminated Assets or Terminated Targets following the effective date of termination.

ARTICLE 9
REPRESENTATIONS AND WARRANTIES

9.1 Mutual Representations and Warranties. BicycleTx and Ionis each represents and warrants to the other, as of the Effective Date, as follows:

9.1.1 Organization. It is a corporation duly incorporated, validly existing, and in good standing under the laws of the jurisdiction of its incorporation, and has all requisite corporate power and authority, to execute, deliver, and perform this Agreement.

9.1.2 Authorization. The execution and delivery of this Agreement and the performance by it of the transactions contemplated hereby have been duly authorized by all necessary corporate action and do not violate (a) such Party's charter documents, bylaws, or other organizational documents, (b) in any material respect, any agreement, instrument, or contractual obligation to which such Party is bound, (c) any requirement of any Applicable Law, or (d) any order, writ, judgment, injunction, decree, determination, or award of any court or governmental agency presently in effect applicable to such Party.

9.1.3 Binding Agreement. This Agreement is a legal, valid, and binding obligation of such Party enforceable against it in accordance with its terms and conditions, subject to the effects of bankruptcy, insolvency, or other laws of general application affecting the enforcement of creditor rights, judicial principles affecting the availability of specific performance, and general principles of equity (whether enforceability is considered a proceeding at law or equity).

9.1.4 No Inconsistent Obligation. It is not under any obligation, contractual or otherwise, to any Person that conflicts with or is inconsistent in any material respect with the terms of this Agreement or that would impede the diligent and complete fulfillment of its obligations hereunder.

9.2 Additional Representations, Warranties, and Covenants of Bicycle. BicycleTx further represents, warrants, and covenants to Ionis, as of the Effective Date, as follows:

9.2.1 All BicycleTx Patents that Cover a TfR1 Bicycle existing as of the Effective Date are listed on Schedule 9.2.1 (the "**Existing Patents**").

9.2.2 There are no judgments, or settlements against, or amounts with respect thereto, owed by BicycleTx or any of its Affiliates relating to the Existing Patents. No claim or litigation has been brought or threatened in writing or any other form by any Person alleging, and BicycleTx has no knowledge of any claim, whether or not asserted, that the Existing Patents are invalid or unenforceable.

9.2.3 To BicycleTx's knowledge, no Person is infringing or threatening to infringe or misappropriating or threatening to misappropriate the Existing Patents.

9.2.4 To BicycleTx's knowledge, [***].

9.2.5 The [***].

9.2.6 BicycleTx is [***].

9.2.7 [***].

9.2.8 BicycleTx is the sole and exclusive owner of the entire right, title, and interest in the Existing Patents, and BicycleTx is entitled to grant the license granted to Ionis herein.

9.2.9 [***]

9.2.10 With respect to the BicycleTx Patents, all applicable official fees, maintenance fees and annuities for the BicycleTx Patents have been paid as of the Effective Date.

9.2.11 All employees and contractors of BicycleTx performing activities under the Option Agreement or this Agreement on behalf of BicycleTx (including for any Affiliate) will be obligated (or were obligated as the case may be) to assign all rights, title and interests in and to any inventions developed by them, whether or not patentable, to BicycleTx or such Affiliate, respectively, as the sole owner thereof, prior to performing any such activities, or otherwise grant to BicycleTx or such Affiliate sufficient rights to such inventions to the extent necessary to effect the license and ownership provisions of the Option Agreement or this Agreement.

9.2.12 During the Term, BicycleTx covenants that it will not enter into or amend any agreement, whether written or oral, that would conflict with or otherwise diminish the rights granted to Ionis hereunder.

9.2.13 Neither BicycleTx nor any of its employees is debarred or disqualified under the U.S. Federal Food, Drug and Cosmetic Act, as may be amended, or comparable laws in any country or jurisdiction other than the U.S., and it does not, and will not during the Research Term, employ or use the services of any person who is debarred or disqualified in connection with activities relating to the TfR1 Bicycles. If BicycleTx becomes aware of the debarment or disqualification or threatened debarment or disqualification of any Person providing services to BicycleTx, including BicycleTx itself or its or its Affiliate's employees or agents, that directly or indirectly relate to activities contemplated by this Agreement, BicycleTx shall immediately notify Ionis in writing and BicycleTx shall cease employing, contracting with, or retaining any such Person to perform any such services.

9.3 Additional Representations, Warranties and Covenants of Ionis. Ionis represents, warrants, and covenants to BicycleTx, as of the Effective Date, as follows:

9.3.1 Ionis is entitled to grant BicycleTx the license as specified in Section 2.2 with regard to Ionis Intellectual Property Controlled by Ionis or any of its Affiliates on the Effective Date.

9.3.2 Neither Ionis nor any of its employees is debarred or disqualified under the U.S. Federal Food, Drug and Cosmetic Act, as may be amended, or comparable laws in any country or jurisdiction other than the U.S., and it does not, and will not during the Term, employ or use the services of

any person who is debarred or disqualified in connection with activities relating to the Compounds and Licensed Products. If Ionis becomes aware of the debarment or disqualification or threatened debarment or disqualification of any Person providing services to Ionis, including Ionis itself or its or its Affiliate's employees or agents, that directly or indirectly relate to activities contemplated by this Agreement, Ionis shall immediately notify BicycleTx in writing and Ionis shall cease employing, contracting with, or retaining any such Person to perform any such services.

9.4 DISCLAIMER OF WARRANTIES. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH HEREIN, NEITHER PARTY MAKES ANY REPRESENTATIONS OR GRANTS ANY WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND EACH PARTY SPECIFICALLY DISCLAIMS ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 10
INDEMNIFICATION; INSURANCE

10.1 Indemnification of Bicycle. Ionis shall indemnify, defend, and hold harmless BicycleTx, its Affiliates, and its and their respective directors, officers, employees, and agents (the "**BicycleTx Indemnitees**") from and against any and all losses, damages, liabilities, penalties, settlements, costs, taxes (including penalties and interest) and expenses (including reasonable attorneys' fees and other expenses of litigation) (collectively, "**Losses**") in connection with any and all suits, investigations, claims, or demands of Third Parties (collectively, "**Third Party Claims**") incurred by or rendered against the BicycleTx Indemnitees to the extent arising from or occurring as a result of: (a) the breach by Ionis or its Affiliates of this Agreement; (b) the negligence, recklessness, or willful misconduct on the part of Ionis or its Affiliates or their respective directors, officers, employees, and agents in performing any of its or their obligations under this Agreement; or (c) the Research or Exploitation of any Compounds or Licensed Products by Ionis or its Affiliates or Sublicensees; except in each case ((a) – (c)) to the extent that BicycleTx has an obligation to indemnify Ionis pursuant to Section 10.2.

10.2 Indemnification of Ionis. BicycleTx shall indemnify, defend, and hold harmless Ionis, its Affiliates and its and their respective directors, officers, employees, and agents (the "**Ionis Indemnitees**") from and against any and all Losses in connection with any and all Third Party Claims incurred by or rendered against the Ionis Indemnitees to the extent arising from or occurring as a result of: (a) the breach by BicycleTx or its Affiliates of this Agreement; or (b) the negligence, recklessness, or willful misconduct on the part of BicycleTx or its Affiliates or its or their respective directors, officers, employees, and agents in performing its obligations under this Agreement; except in each case ((a) – (b)) to the extent that Ionis has an obligation to indemnify BicycleTx pursuant to Section 10.1.

10.3 Notice of Claim. All indemnification claims in respect of a Party, its Affiliates, or its or their respective directors, officers, employees and agents shall be made solely by such Party to this Agreement (the "**Indemnified Party**"). The Indemnified Party shall give the indemnifying Party (the "**Indemnifying Party**") prompt written notice (an "**Indemnification Claim Notice**") of any Losses or discovery of fact upon which such Indemnified Party intends to base a request for indemnification under this ARTICLE 10, but in no event shall the Indemnifying Party be liable for any Losses that result from any delay by the Indemnified Party in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party shall furnish promptly to the

Indemnified Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

10.4 Control of Defense. The Indemnifying Party shall have the right, but not the obligation, to conduct and control, through counsel of its choosing, any action for which indemnification is sought, and if the Indemnifying Party elects to assume the defense thereof, the Indemnifying Party shall not be liable to the Indemnified Party for any legal expenses of other legal counsel or any other expenses subsequently incurred by such Indemnified Party in connection with the defense thereof. The Indemnifying Party may settle any action, claim, or suit for which the Indemnified Party is seeking indemnification; provided that the Indemnifying Party shall first give the Indemnified Party advance written notice of any proposed compromise or settlement and such Indemnified Party provides prior written approval, such approval not to be unreasonably conditioned, withheld or delayed. The Parties and their employees shall cooperate fully with each other and their legal representatives in the investigation, defense, prosecution, negotiation, or settlement of any such claim or suit. Each Party's indemnification obligations under this ARTICLE 10 shall not apply to amounts paid by an Indemnified Party in settlement of any action with respect to a Third Party claim, if such settlement is effected without the prior written consent of the Indemnifying Party, which consent shall not be unreasonably conditioned, withheld or delayed. In no event shall the Indemnifying Party settle or abate any Third Party Claim in a manner that would diminish the rights or interests of the Indemnified Party, admit any liability, fault, or guilt by the Indemnified Party, or obligate the Indemnified Party to make any payment, take any action, or refrain from taking any action, without the prior written approval of the Indemnified Party.

10.5 Limitation of Liability. EXCEPT FOR DAMAGES PAYABLE FOR A PARTY'S BREACH OF ITS OBLIGATIONS UNDER ARTICLE 8 (BASED ON REASONABLE WRITTEN EVIDENCE) OR REQUIRED TO BE PAID PURSUANT TO A PARTY'S INDEMNIFICATION OBLIGATIONS UNDER THIS ARTICLE 10, NEITHER PARTY NOR ANY OF ITS AFFILIATES SHALL BE LIABLE FOR INDIRECT, INCIDENTAL, SPECIAL, EXEMPLARY, PUNITIVE, OR CONSEQUENTIAL DAMAGES, INCLUDING LOSS OF PROFITS OR BUSINESS INTERRUPTION, HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY, WHETHER IN CONTRACT, TORT, NEGLIGENCE, BREACH OF STATUTORY DUTY OR OTHERWISE IN CONNECTION WITH THIS AGREEMENT OR THE EXERCISE OF ANY LICENSE GRANTED HERUNDER, EVEN IF ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

10.6 Insurance. Each Party shall maintain, at its own expense, commercial general liability insurance and other appropriate insurance in an amount consistent with sound business practice and reasonable in light of its obligations under this Agreement. Each Party shall maintain such insurance for the period commencing promptly after the Effective Date until [***] the Term. Each Party shall provide a certificate of insurance evidencing such coverage to the other Party upon request. It is understood that such insurance shall not be construed to create any limit of either Party's obligations or liabilities with respect to its indemnification obligations under this Agreement. Without limiting the generality of the foregoing, Ionis shall maintain, at a minimum, [***].

ARTICLE 11
TERM AND TERMINATION

11.1 Term. This Agreement shall commence on the Effective Date and, unless earlier terminated in accordance herewith, shall continue in force and effect on a Licensed Product-by-Licensed Product and country-by-country basis, until the expiration of the Royalty Term for such Licensed Product in such country (such period, the "**Term**"). Upon the expiration of the Term for a particular Licensed

Product in a particular country, the license grant to Ionis in Section 2.1 shall become non-exclusive, fully-paid, royalty-free, and irrevocable with respect to such Licensed Product in such country.

11.2 Termination for Convenience. Ionis may terminate this Agreement in its entirety or on a Target-by-Target basis (i.e. with respect to all Compounds and Licensed Products directed to such Target), for any or no reason, upon:

11.2.1 [***] prior written notice to BicycleTx if termination occurs [***]; and

11.2.2 [***] prior written notice to BicycleTx if termination occurs [***].

For clarity, with regard to termination of the Agreement in its entirety pursuant to this Section 11.2, the required notice period shall be that period that is applicable to the Licensed Product that is furthest advanced at the time of such termination.

11.3 Termination for Uncured Material Breach.

11.3.1 Material Breach. If either Party (the "**Non-Breaching Party**") believes that the other Party (the "**Breaching Party**") has materially breached one or more of its material obligations under this Agreement (other than for failure to achieve a diligence milestone under Section 4.5.2 the remedy for which is set forth in Section 4.5.4), then the Non-Breaching Party may deliver notice of such material breach to the Breaching Party (a "**Breach Notice**"). If (a) the Breaching Party does not dispute that it has committed a material breach of one or more of its material obligations under this Agreement, and (b) either (i) the Breaching Party fails to cure such breach within [***] ([***] with respect to any payment breach) after receipt of the Breach Notice ("**Breach Cure Period**"), or (ii) a cure cannot be fully achieved within such Breach Cure Period and the Breaching Party has failed to commence to cure or has failed to use diligent efforts to achieve a full cure within the Breach Cure Period, then the Non-Breaching Party may terminate this Agreement in whole or in part upon written notice to the Breaching Party, effective upon receipt by the Breaching Party, provided that if the Breaching Party is Ionis and such material breach relates solely to a Licensed Product and/or its corresponding Target (but not to all Licensed Products or Targets), then BicycleTx will only have the right to terminate the License Agreement solely with respect to such Licensed Product (and the corresponding Target) to which such material breach relates. If the Breaching Party disputes in good faith that it has materially breached one or more of its material obligations under this Agreement or that it has failed to timely or diligently cure such material breach, the Dispute shall be resolved pursuant to Section 12.2 and the Breach Cure Period shall be tolled until such dispute is so resolved. Upon a determination of material breach or failure to cure, the Breaching Party may have the remainder of the Breach Cure Period to cure such material breach. If such material breach is not cured within the Breach Cure Period, then absent withdrawal of the Non-Breaching Party's request for termination, this Agreement shall terminate, effective as of the expiration of the Breach Cure Period.

11.3.2 Adverse Ruling. Furthermore, if as a result of the application Section 12.2, the Breaching Party is determined to be in material breach of one or more of its material obligations under this Agreement (other than for failure to achieve a diligence milestone under Section 4.5.2 the remedy for which is set forth in Section 4.5.4), such that the Non-Breaching Party has the right to terminate this Agreement in whole or with respect to a particular Licensed Product and/or its corresponding Target (an "**Adverse Ruling**") and the Breaching Party fails to complete the actions specified in such Adverse Ruling, or to cure such material breach within [***] ([***] with respect to any payment breach) after such Adverse Ruling, or such other period (which may be shorter) as the arbitrators may provide in such Adverse Ruling, then the Non-Breaching Party may terminate this Agreement in whole or in part upon written notice to the

Breaching Party, provided that if the Breaching Party is Ionis and such Adverse Ruling relates solely to a Licensed Product and/or its corresponding Target (but not to all Licensed Products or Targets), then BicycleTx will only have the right to terminate the License Agreement solely with respect to the Licensed Product (and the corresponding Target) to which such Adverse Ruling relates.

11.4 Termination for Insolvency. If either Party (a) files for protection under bankruptcy or insolvency laws, (b) makes an assignment for the benefit of creditors, (c) appoints or suffers appointment of a receiver or trustee over substantially all of its property that is not discharged within [***] after such filing, (d) is a party to any dissolution or liquidation, (e) files a petition under any bankruptcy or insolvency act or has any such petition filed against it that is not discharged within [***] of the filing thereof, or (f) admits in writing its inability generally to meet its obligations as they fall due in the general course, then the other Party may terminate this Agreement in its entirety effective immediately upon written notice to such Party.

11.5 Rights in Bankruptcy.

11.5.1 Applicability of 11 U.S.C. § 365(n). All rights and licenses (collectively, the "**Intellectual Property**") granted under or pursuant to this Agreement, including all rights and licenses to use improvements or enhancements developed during the Term, are intended to be, and shall otherwise be deemed to be, for purposes of Section 365(n) of the United States Bankruptcy Code (the "**Bankruptcy Code**") or any analogous provisions in any other country or jurisdiction, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Bankruptcy Code. The Parties agree that the licensee of such Intellectual Property under this Agreement shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code, including Section 365(n) of the Bankruptcy Code, or any analogous provisions in any other country or jurisdiction. All of the rights granted to either Party under this Agreement shall be deemed to exist immediately before the occurrence of any bankruptcy case in which the other Party is the debtor.

11.5.2 Rights of non-Debtor Party in Bankruptcy. If a bankruptcy proceeding is commenced by or against either Party under the Bankruptcy Code or any analogous provisions in any other country or jurisdiction, the non-debtor Party shall be entitled to a complete duplicate of (or complete access to, as appropriate) any Intellectual Property and all embodiments of such Intellectual Property, which, if not already in the non-debtor Party's possession, shall be delivered to the non-debtor Party within five Business Days of such request; provided, that the debtor Party is excused from its obligation to deliver the Intellectual Property to the extent the debtor Party continues to perform all of its obligations under this Agreement and the Agreement has not been rejected pursuant to the Bankruptcy Code or any analogous provision in any other country or jurisdiction.

11.6 Effects of Termination. Upon any termination of this Agreement in its entirety by either Party, the following terms will apply. Upon any termination of this Agreement with respect to a particular Target (such terminated Target, a "**Terminated Target**"), the following terms will apply solely with respect to such Terminated Target and corresponding Terminated Assets. For clarity, during the pendency of any dispute regarding material breach and/or any Breach Cure Period, all of the terms and conditions of this Agreement shall remain in effect and the Parties shall continue to perform all of their respective obligations hereunder.

11.6.1 Licenses. All licenses granted by either Party will automatically terminate.

11.6.2 Sublicenses. Any Ionis Sublicensee will, from the effective date of such termination, automatically become a direct licensee of BicycleTx, provided that such Sublicensee is not then in default of its sublicense agreement and such sublicense was granted in accordance with Section 2.4, and provided further that: (a) such direct license shall not obligate (i) such Sublicensee to perform contractual obligations greater than those set forth in the applicable sublicense or (ii) BicycleTx to perform contractual obligations greater than those set forth herein, (b) the scope of such direct license shall be consistent with the scope of the license sublicensed to such Sublicensee, and (c) the amounts payable to BicycleTx by such Sublicensee under such direct license shall be equivalent to the amounts BicycleTx would have received from Ionis under this Agreement as a result of such Sublicensee's activities had this Agreement remained in effect and such Sublicensee performed such activity under the sublicense agreement with Ionis.

11.6.3 Confidential Information. Each Party shall return or cause to be returned to the other Party or destroy (and certify such destruction to such other Party) all Confidential Information and all substances or compositions of the other Party or its Affiliates delivered or provided by or on behalf of such other Party in accordance with Section 8.7.

11.7 Accrued Rights; Surviving Obligations. Termination or expiration of this Agreement (either in its entirety or with respect to one or more Terminated Targets and Terminated Asset) for any reason shall be without prejudice to any rights that shall have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration shall not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. Without limiting the foregoing, the following Articles and Sections of this Agreement shall survive the termination or expiration of this Agreement for any reason: Articles 1 (to the extent applicable to other surviving Sections or Articles), 8 (excluding Section 8.6), 10, and 12 (excluding Section 12.6), and Section 4.12, Sections 6.4.4, 6.5.2, and 6.7 (in each case solely with respect to amounts accrued or owing as of the effective date of termination), 6.8, 6.9, 6.10, 6.11, 7.1, 7.7, 9.4, 11.1(last sentence only), 11.5, 11.6, 11.7.

ARTICLE 12
MISCELLANEOUS

12.1 Governing Law and Service.

12.1.1 Governing Law. This Agreement and the performance, enforcement, breach, and termination hereof shall be interpreted, governed by, and construed in accordance with the laws of the State of New York, United States excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Agreement to the substantive law of another jurisdiction; provided, that all questions concerning (a) inventorship of Patents under this Agreement shall be determined in accordance with Section 7.1.1 and (b) the construction or effect of Patents shall be determined in accordance with the laws of the country or other jurisdiction in which the particular Patent has been filed or granted, as the case may be. The Parties agree to exclude the application to this Agreement of the United Nations Convention on Contracts for the International Sale of Goods.

12.1.2 Service. Each Party further agrees that service of any process, summons, notice, or document by registered mail to its address set forth in Section 12.10 shall be effective service of process for any action, suit, or proceeding brought against it by the other Party under this Agreement in any such court.

12.2 Dispute Resolution. Except as provided in Section 3.3 and Section 12.2.2, any dispute arising out of or relating to this Agreement that has not been resolved at the JSC or otherwise under the terms of this Agreement, including the determination of the scope or applicability of this Section 12.2 and the agreement to arbitrate, or any document or instrument delivered in connection herewith (a "**Dispute**"), shall be resolved pursuant to this Section 12.2.

12.2.1 General. Any Dispute shall first be referred to the Alliance Managers who will seek to resolve the issue within [***]. If no resolution is obtained, the issue will be elevated to the Senior Officers of the Parties, who shall confer in good faith on the resolution of the issue. Without limiting Section 12.5, any final decision mutually agreed to by the Senior Officers shall be conclusive and binding on the Parties. If the Senior Officers are not able to agree on the resolution of any such issue within [***] (or such other period of time as mutually agreed by the Senior Officers) after such issue was first referred to them, then, except as otherwise set forth in Section 12.2.2, the Dispute shall be finally settled by arbitration as set forth in Section 12.2.3. Any dispute concerning the commencement of the arbitration shall be finally settled by the arbitrators.

12.2.2 Intellectual Property Disputes. If a Dispute arises with respect to the validity, scope, enforceability, inventorship, or ownership of any Patent, trademark, or other intellectual property right, and such Dispute cannot be resolved in accordance with Section 12.2.1, then, unless otherwise agreed by the Parties in writing, such Dispute shall not be submitted to an arbitration proceeding in accordance with Section 12.2.3 and instead either Party may initiate litigation in a court of competent jurisdiction, notwithstanding Section 12.1, in any country or other jurisdiction in which such rights apply; provided, however, that the Parties expressly waive any right to a jury trial in connection with disputes under this Section 12.2.2. In case of a Dispute between the Parties with respect to inventorship, the Parties shall jointly select an independent Third Party patent attorney registered before the United States Patent and Trademark Office who has appropriate professional credentials in the relevant subject matter and jurisdiction and submit such Dispute to the mutually-selected independent Third Party patent attorney for resolution by expert determination under United States patent law. The decision of such patent attorney with respect to inventorship shall be final, and the Parties agree to be bound by the decision and share equally the expenses of such patent attorney. If within [***] after the Senior Officers have failed to settle a Dispute regarding inventorship the Parties have not been able to mutually agree on the selection of an independent Third Party patent attorney for such expert determination, each Party shall appoint a patent counsel within [***] and both Party-appointed patent counsels shall, within [***] following the last appointment of a patent counsel by a Party, nominate the patent counsel who will conduct the expert determination under this Section 12.2.2.

12.2.3 Arbitration. Any arbitration shall take place in accordance with Schedule 12.2.3.

12.2.4 Adverse Ruling. Any determination pursuant to this Section 12.2 that a Party is in material breach of its material obligations hereunder shall specify a (nonexclusive) set of actions to be taken to cure such material breach, if feasible.

12.2.5 Interim Relief. Notwithstanding anything herein to the contrary in this Section 12.2, in the event that a Party reasonably requires relief on a more expedited basis than would be possible pursuant to the procedure set forth in this ARTICLE 12, such Party may seek interim or provisional relief, including a temporary restraining order, preliminary injunction, or other interim equitable relief concerning a Dispute, if necessary to protect the interests of such Party. This Section 12.2.5 shall be specifically enforceable.

12.2.6 Pending Dispute. During a pending Dispute, where this Agreement has not yet been terminated, each Party shall continue to perform in good faith its obligations under this Agreement.

12.3 Entire Agreement; Amendments. This Agreement and the Stock Purchase Agreement, including any schedules, constitute the entire, final, and complete agreement and understanding between the Parties with respect to its subject matter and replaces and supersedes all prior discussions and agreements between them with respect to the subject matter hereof. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth in this Agreement. No modification of any terms or conditions hereof shall be effective unless made in writing and signed by a duly authorized representative of each Party.

12.4 Severability. If any provision of this Agreement is, becomes, or is deemed invalid or unenforceable by any court or other competent authority having jurisdiction, the remainder of this Agreement shall remain unimpaired and the Parties shall promptly negotiate in good faith to amend such invalid or unenforceable provision to conform to applicable laws so as to be valid and enforceable and best accomplish the original intent of the Parties.

12.5 Waiver and Non-Exclusion of Remedies. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver shall be effective unless it is in writing and signed by the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach by such other Party whether of a similar nature or otherwise. The rights and remedies provided herein are cumulative and do not exclude any other right or remedy provided by Applicable Law or otherwise available except as expressly set forth herein.

12.6 Force Majeure. Each Party shall be excused from liability for the failure or delay in performance of any obligation under this Agreement (other than a payment obligation) by reason of any event beyond such Party's reasonable control, including acts of God, fire, flood, explosion, earthquake, epidemic or pandemic (including quarantine, lock-down, movement restriction or similar orders imposed by any governmental authority as of or after the Effective Date in connection therewith), or other natural forces, war, civil unrest, acts of terrorism, accident, destruction, or other casualty, any lack or failure of transportation facilities, any lack or failure of supply of raw materials or supplies, or any other event similar to those enumerated above. Such excuse from liability shall be effective to the extent and duration of the event(s) causing the failure or delay in performance and provided that the Party has not caused such event(s) to occur. Notice of a Party's failure or delay in performance due to force majeure must be given to the other Party as soon as reasonably practicable after its occurrence.

12.7 Export Control. This Agreement is made subject to any restrictions concerning the export of products or technical information from the United States or other countries that may be imposed on the Parties from time to time. Each Party agrees that it will not export, directly or indirectly, any technical information acquired from the other Party under this Agreement or any products using such technical information to a location or in a manner that at the time of export requires an export license or other governmental approval, without first obtaining the written consent to do so from the appropriate agency or other governmental entity in accordance with Applicable Law.

12.8 Relationship of the Parties. The relationship of the Parties is that of independent contractors, and nothing in this Agreement shall be construed to create a partnership, joint venture, franchise, employment, or agency relationship between the Parties. Neither Party shall be considered the agent of the other Party for any purpose whatsoever and neither Party has any authority to enter into any

contract or assume any obligation for the other Party or to make any warranty or representation on behalf of the other Party. All persons employed by a Party shall be employees of such Party and not of the other Party and all costs and obligations incurred by reason of any such employment shall be for the account and expense of such Party. The Parties (and any successor, assignee, transferee, or Affiliate of a Party) shall (a) use commercially reasonable efforts to structure the arrangement and activities contemplated by this Agreement to avoid the arrangement contemplated by this Agreement being treated as a partnership that is engaged in a "United States trade or business" for United States tax purposes and (b) not treat or report the relationship between the Parties arising under this Agreement as a partnership for United States tax purposes without the prior written consent of the other Party unless required by a final "determination" as defined in Section 1313 of the United States Internal Revenue Code of 1986, as amended.

12.9 Assignment. Neither Party shall sell, transfer, assign, delegate, pledge, or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or obligations hereunder without the prior written consent of the other Party, such consent not to be unreasonably withheld, conditioned, or delayed; provided, that either Party may make such a transfer or assignment without the other Party's consent (a) to its Affiliate, provided that if the entity to which this Agreement is assigned ceases to be an Affiliate of the assigning Party, this Agreement will be automatically assigned back to the assigning Party or its successor or (b) to a successor in interest by way of merger, consolidation, sale of stock, or sale of all or substantially all of its business to which this Agreement relates. Any purported assignment or delegation in violation of this Section 12.9 shall be null and void. All validly assigned and delegated rights and obligations of the Parties hereunder shall be binding upon and inure to the benefit of and be enforceable by and against the successors and permitted assigns of BicycleTx or Ionis, as the case may be. The permitted assignee or transferee shall assume all obligations of its assignor or transferor under this Agreement. Without limiting the generality of the foregoing, the grant of rights set forth in this Agreement shall be binding upon any successor or permitted assignee of BicycleTx, and the obligations of Ionis (including all payment obligations) shall run in favor of any such successor or permitted assignee of BicycleTx's benefits under this Agreement. Notwithstanding the foregoing, all rights to Know-How, Patents, materials, and other intellectual property Controlled by a Third Party permitted assignee of a Party (or any of such Third Party's affiliates immediately prior to the closing of such assignment) immediately prior to such assignment shall be automatically excluded from the rights licensed or granted to the other Party under this Agreement.

12.10 Notices. Any notice required or permitted pursuant to this Agreement shall be in writing and delivered by personal delivery, overnight express courier service, electronic mail, facsimile transmission, or by certified or registered mail, return receipt requested, and shall be deemed given upon personal delivery, upon acknowledgement of receipt fax or electronic transmission, on the next Business Day after deposit if sent by overnight express courier service, or five days after deposit in the mail. Notices will be sent to the following addresses or such other address as either Party may specify in writing pursuant to this Section 12.10. BicycleTx will promptly provide notice information for the Gatekeeper once available.

If to BicycleTx, to:

BicycleTx Limited
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: Chief Operating Officer

with a copy (which shall not constitute notice) to:

BicycleTx Limited
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: General Counsel

Email: [***]

If to Ionis, to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
U.S.A.
Attention: Executive Vice President, Research

With a copy (which shall not constitute notice) to:

Attention: General Counsel
Email: [***]

12.11 English Language. This Agreement shall be written and executed in, and all other communications under or in connection with this Agreement shall be in, the English language. Any translation into any other language shall not be an official version thereof, and in the event of any conflict in interpretation between the English version and such translation, the English version shall control.

12.12 Performance by Affiliates. Each Party may use one (1) or more of its Affiliates to perform its obligations and duties hereunder and such Affiliates are expressly granted certain rights herein to perform such obligations and duties; provided that each such Affiliate shall be bound by the corresponding obligations of such Party; and provided further that such Party, subject to an assignment to such Affiliate pursuant to Section 12.9, shall remain liable hereunder for the prompt payment and performance of its obligations hereunder.

12.13 Construction. The terms of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each Party hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement. Except as otherwise explicitly specified to the contrary, (a) references to a Section, exhibit, appendix, or schedule means a Section of, or exhibit, appendix, or schedule to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "will" and "shall" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f)

references to a particular person include such person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United States dollars, (h) the headings contained in this Agreement, in any exhibit, appendix, or schedule to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement, (i) the word "or" means "and/or" unless the context dictates otherwise because the subjects of the conjunction are mutually exclusive, (j) the words "herein", "hereof", and "hereunder" and other words of similar import refer to this Agreement as a whole and not to any particular Section or other subdivision, and (k) all references to days mean calendar days, unless otherwise specified.

12.14 Schedules. In the event of any inconsistencies between this Agreement and any schedules or other attachments hereto, the terms of this Agreement shall control.

12.15 Further Assurance. Each Party agrees to execute, acknowledge, and deliver such further instruments, and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of this Agreement.

12.16 No Benefit to Third Parties. Except as provided in ARTICLE 10, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they shall not be construed as conferring any rights on any other Persons.

12.17 Counterparts. This Agreement may be executed in one or more counterparts in original, facsimile, PDF, or other electronic format, each of which shall be an original, and all of which together shall constitute one instrument.

[***]

THIS COLLABORATION AND LICENSE AGREEMENT is executed by the authorized representatives of the Parties as of the Effective Date.

BICYCLETX LIMITED	**IONIS PHARMACEUTICALS, INC.**
By: /s/ Kevin Lee	By: /s/ Brett Monia
Name: Kevin Lee	Name: Brett Monia
Title: Dr	Title: CEO

Schedule 1.22

[***]

Schedule 9.2.1

[***]

Schedule 12.2.3

[***]

Exhibit 6.2

SHARE PURCHASE AGREEMENT

THIS SHARE PURCHASE AGREEMENT ("***Agreement***") is entered into as of _____, 2021 (the "***Execution Date***"), by and between **Bicycle Therapeutics plc**, a company incorporated under the laws of England and Wales having an office at Building 900, Babraham Research Campus, Cambridge, United Kingdom CB22 3AT (the "***Company***"), and **Ionis Pharmaceuticals, Inc.** a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA (the "***Purchaser***"). The capitalized terms used herein and not otherwise defined have the meanings given to them in Appendix 1.

RECITALS

BicycleTx Limited ("***BicycleTx***"), an affiliate of the Company, and Purchaser entered into that certain Evaluation and Option Agreement dated as of December 31, 2020 (the "***Option Agreement***") pursuant to which BicycleTx granted to the Purchaser an exclusive option to obtain an exclusive license under BicycleTx's technology to research, develop, manufacture, and commercialize products incorporating TfR1 Bicycles (as defined in the Collaboration Agreement (as defined below)) and Purchaser has exercised such option in accordance with the terms of the Option Agreement. Pursuant to the exercise of such option and contemporaneously with execution of this Agreement, BicycleTx and Purchaser are entering into that certain Collaboration and Licensing Agreement (the "***Collaboration Agreement***").

Pursuant to the Option Agreement, and as partial consideration for the Collaboration Agreement, the Company has agreed to sell, and the Purchaser has agreed to purchase, ordinary shares, nominal value £0.01 per share, of the Company (the "***Ordinary Shares***"), subject to and in accordance with the terms and provisions of this Agreement.

AGREEMENT

For good and valuable consideration, the Purchaser and the Company agree as follows:

1. Sale and Purchase of Ordinary Shares

1.1 Purchase of Ordinary Shares. Subject to the terms and conditions of this Agreement, at the Closing, the Company will issue and sell to the Purchaser, and the Purchaser will purchase from the Company, a number of Ordinary Shares equal to $11,000,000 divided by the Share Value, rounded down to the nearest whole share (such Ordinary Shares, the "***Shares***"). The aggregate purchase price shall equal the number of Shares multiplied by the Share Value, rounded to the nearest cent (the "***Purchase Price***"), *provided, however*, that if the number of Shares calculated in accordance with the preceding clause of this Section 1.1 exceeds the Share Cap, the Company will issue and sell to Purchaser, and the Purchaser will purchase from the Company, the number of Ordinary Shares equal to the Share Cap, at the Share Value, and shall pay to the Company in cash the difference between (i) $11,000,000 and (ii) the product of the Share Value multiplied by the Share Cap (any such amount, the "***Closing Cash***"**)**. In the event the Share Cap is applicable, the term "***Shares***" shall refer to the number of Ordinary Shares equal to the Share Cap, and the term "***Purchase Price***" shall refer to the product of the Share Value and the Share Cap.

1.2 Payment. At the Closing, Purchaser will pay the Purchase Price and the Closing Cash, if any, by wire transfer of immediately available funds in accordance with wire instructions, which instructions will have been provided by the Company to Purchaser at least three (3) Business Days prior to

the Closing, and the Company will cause its registrar and transfer agent to issue such Shares in restricted book entry form registered in the name of the Purchaser.

1.3 Closing.

(a) Closing. The closing of the transaction contemplated by Section 1.1 (the "***Closing***") will be held at the offices of the Company or through the electronic exchange of documents and signatures, as promptly as practicable and upon the satisfaction of the closing conditions set forth in Section 6 hereof, and in no event more than ten (10) Business Days after the Execution Date.

(b) Closing Deliverables.

(i) At the Closing, the Company will deliver to Purchaser:

(1) a duly executed cross-receipt in form and substance reasonably satisfactory to each party (the "***Cross-Receipt***");

(2) a certificate in form and substance reasonably satisfactory to Purchaser and duly executed on behalf of the Company by an authorized officer of the Company, certifying that the conditions to the Closing set forth in Sections 6.2(a), (b), (c) and (d) of this Agreement have been fulfilled; and

(3) a certificate of the secretary of the Company dated as of the Closing Date certifying that attached thereto is a true and complete copy of all resolutions adopted by the Board authorizing the execution, delivery and performance of this Agreement and the transactions contemplated herein and that all such resolutions are in full force and effect and are all the resolutions adopted in connection with the transactions contemplated hereby as of the Closing Date.

(ii) At the Closing, Purchaser will deliver to the Company:

(1) a duly-executed Cross-Receipt; and

(2) a certificate in form and substance reasonably satisfactory to the Company and duly executed on behalf of Purchaser by an authorized officer of Purchaser, certifying that the conditions to the Closing set forth in Section 6.1(b) and (c) of this Agreement have been fulfilled.

2. Representations and Warranties of the Company

Except as otherwise specifically contemplated by this Agreement, the Company hereby represents and warrants to Purchaser that:

2.1 Private Placement. Neither the Company nor any Person acting on its behalf, has, directly or indirectly, made any offers or sales of any security or solicited any offers to buy any security, under any circumstances that would require registration of the Shares under the Securities Act. Subject to the accuracy of the representations made by Purchaser in Section 3, the Shares will be issued and sold to Purchaser in compliance with applicable exemptions from the registration and prospectus delivery requirements of the Securities Act and the registration and qualification requirements of all applicable securities Laws of the states of the United States. The Company has not engaged any brokers, finders or agents, or incurred, or will incur, directly or indirectly, any liability for brokerage or finder's fees or agents' commissions or any similar charges in connection with this Agreement and the transactions contemplated hereby.

2.2 Corporate Power and Qualification. The Company has full corporate power and authority to conduct its business as currently conducted. The Company is duly qualified to do business and is in good standing in every jurisdiction in which the nature of the business conducted by it or property owned by it makes such qualification necessary, except where the failure to be so qualified or in good standing, as the case may be, would not reasonably be expected to have a Material Adverse Effect on the Company.

2.3 Authorization; Enforcement. The Company has all requisite corporate power and authority to enter into and to perform its obligations under this Agreement, to consummate the transactions contemplated hereby and to issue the Shares in accordance with the terms and conditions hereof. The execution, delivery and performance of this Agreement by the Company and the consummation by it of the transactions contemplated hereby (including the issuance of the Shares at the Closing in accordance with the terms and conditions hereof) have been duly authorized by the Board and no further consent or authorization of the Company, the Board, or its shareholders is required. This Agreement has been duly executed by the Company and constitutes a legal, valid and binding obligation of the Company enforceable against the Company in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

2.4 Issuance of Shares. The Shares, upon issuance in accordance with the terms of this Agreement, will be validly issued, fully paid and non-assessable and will not be subject to preemptive rights or other similar rights of shareholders of the Company.

2.5 SEC Documents, Financial Statements.

(a) The American Depositary Shares are registered pursuant to Section 12(b) or 12(g) of the Exchange Act. The Company has delivered or made available (by filing on the SEC's electronic data gathering and retrieval system (EDGAR)) to Purchaser complete copies of its most recent Annual Report on Form 10-K and each subsequent Quarterly Report on Form 10-Q, and any report on Form 8-K, in each case filed with the SEC prior to the Execution Date (the "***SEC Documents***"). As of its date, each SEC Document complied in all material respects with the requirements of the Exchange Act, and other Laws applicable to it, and, as of its date, such SEC Document did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading. No inquiries or any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

(b) There are no outstanding or unresolved comments in comment letters received from the SEC or its staff.

(c) As of the Execution Date, other than the transactions that are the subject of this Agreement and the Collaboration Agreement, no material fact or circumstance exists that would be required to be disclosed in a current report on Form 8-K or in a registration statement filed under the Securities Act, were such a registration statement filed on the date hereof, that has not been disclosed in an SEC Document.

(d) The financial statements, together with the related notes, of the Company included in the SEC Documents comply as to form in all material respects with all applicable accounting requirements and the published rules and regulations of the SEC and all other applicable rules and regulations with respect thereto. Such financial statements, together with the related notes and schedules,

have been prepared in accordance with GAAP applied on a consistent basis during the periods involved (except (i) as may be otherwise indicated in such financial statements or the notes thereto or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes or may be condensed or summary statements), and fairly present in all material respects the financial condition of the Company and its consolidated subsidiaries as of the dates thereof and the results of operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal year-end audit adjustments).

(e) The American Depositary Shares are listed on Nasdaq, and the Company has taken no action designed to, or that to its knowledge is likely to have the effect of, terminating the registration of the American Depositary Shares under the Exchange Act or delisting the American Depositary Shares from Nasdaq. As of the Execution Date, the Company has not received any notification that, and has no knowledge that, the SEC or Nasdaq is contemplating terminating such registration or listing.

2.6 Internal Controls; Disclosure Controls and Procedures. The Company maintains internal control over financial reporting as defined in Rule 13a-15(f) under the Exchange Act. The Company has implemented the "disclosure controls and procedures" (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) required in order for the principal executive officer and principal financial officer of the Company to engage in the review and evaluation process mandated by the Exchange Act, and is in compliance with such disclosure controls and procedures in all material respects. Each of the principal executive officer and the principal financial officer of the Company has made all certifications required by Sections 302 and 906 of the Sarbanes-Oxley Act of 2002 with respect to all reports, schedules, forms, statements and other documents required to be filed by the Company with the SEC.

2.7 Voting Rights.

(a) All of the Ordinary Shares are entitled to one (1) vote per share.

(b) Except as described or referred to in the SEC Documents, as of the Execution Date, there were not: (i) any outstanding equity securities, options, warrants, rights (including conversion or preemptive rights) or other agreements pursuant to which the Company is or may become obligated to issue, sell or repurchase any ordinary shares, ADSs or any other securities of the Company other than equity securities that may have been granted pursuant to its equity incentive plans, which plans are described in the SEC Documents; or (ii) any restrictions on the transfer of share capital of the Company other than pursuant to applicable U.K. or U.S. federal or state securities Laws or as set forth in this Agreement.

(c) The Company is not a party to or subject to any agreement or understanding relating to the voting of shares of or other securities of the Company or the giving of written consents by a shareholder or director of the Company.

2.8 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by the Company and the consummation by the Company of the transactions contemplated hereby (including the issuance of the Shares) will not (i) conflict with or result in a violation of any provision of the Company's Articles of Association, as in effect on the date hereof, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which the Company is a party, or (iii) subject to Section 2.8(b), result in a violation of any Law (including United States federal, state and U.K. securities Laws and regulations and regulations of any self-regulatory organizations) applicable to the Company, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as would not reasonably be expected to have, a Material Adverse Effect on the Company or result in a liability for Purchaser.

(b) The Company is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to issue and sell the Shares in accordance with the terms and conditions hereof other than such as have been made or obtained, and except for any post-closing filings required to be made under federal, national or state securities Laws.

2.9 Litigation. Other than as set forth in the SEC Documents filed prior to the Execution Date, there is no action, suit, proceeding or investigation pending (of which the Company has received notice or otherwise has knowledge) or, to the Company's knowledge, threatened, against the Company or that the Company intends to initiate, except where such action, suit, proceeding or investigation, as the case may be, and would not reasonably be expected to have a Material Adverse Effect.

2.10 Licenses and Other Rights; Compliance with Laws. The Company has all franchises, permits, licenses and other rights and privileges ("***Permits***") necessary to permit it to own its properties and to conduct its business as presently conducted and is in compliance thereunder, except where the failure to be in compliance would not reasonably be expected to have a Material Adverse Effect. The Company has not taken any action that would interfere with its ability to renew all such Permit(s), except where the failure to renew such Permit(s) would not reasonably be expected to have, a Material Adverse Effect. The Company is and has been in compliance with all Laws applicable to its business, properties and assets, except where the failure to be in compliance has not had and would not reasonably be expected to have a Material Adverse Effect.

2.11 Intellectual Property.

(a) Other than as set forth in the SEC Documents filed prior to the Execution Date, the Intellectual Property that is owned by the Company or its subsidiaries is owned free from any Liens. All of the Company's material Intellectual Property Licenses are in full force and effect in accordance with their terms, are free of any Liens, and, to the Company's knowledge, neither the Company, nor any other party thereto, is in material breach of any such material Intellectual Property License. To the Company's knowledge, no event has occurred that with notice or lapse of time or both (i) would constitute a breach or default of any such material Intellectual Property License, (ii) would result in the termination thereof, or (iii) would cause or permit the acceleration or other change of any right or obligation or the loss of any benefit thereunder by the Company or its subsidiaries, except, in the case of each of clauses (i) through (iii), as would not reasonably be expected to have a Material Adverse Effect.

(b) Except as set forth in the SEC Documents, there is no legal claim or demand of any Person or any proceeding that is pending or threatened in writing, (i) challenging the right of the Company in respect of any Intellectual Property of the Company, or (ii) claiming that any default exists under any Intellectual Property License, except, in the case of clauses (i) and (ii) above, where any such claim, demand or proceeding has not had, and would notreasonably be expected to have, a Material Adverse Effect.

(c) Except as set forth in the SEC Documents: (i) the Company or one of its subsidiaries owns, free and clear of any Lien, or, to the Company's knowledge, has a valid license, or an enforceable right to use, as it is used or held for use, all U.S. and non-U.S. patents, trade secrets, know-how, trademarks, service marks, copyrights, and other proprietary and Intellectual Property rights, and all grants and applications with respect to the foregoing (collectively, the "***Proprietary Rights***") necessary for the conduct of the Company's business, except where the failure to own or have any of the foregoing would not reasonably be expected to have a Material Adverse Effect (such Proprietary Rights owned by or licensed to the Company collectively, the "***Company Rights***"); and (ii) the Company and its subsidiaries have taken

reasonable measures to protect the Company Rights, consistent with prudent commercial practices in the biotechnology industry, except where failure to take such measures has not had, and would not reasonably be expected to have, a Material Adverse Effect.

2.12 Health Care Matters. The Company: (i) has operated and currently operates its business in compliance in all material respects with applicable provisions of the Health Care Laws (as defined below) of the Food and Drug Administration ("***FDA***"), the Department of Health and Human Services and any comparable state, foreign or other regulatory authority to which they are subject (collectively, the "***Applicable Regulatory Authorities***") applicable to the ownership, testing, development, manufacture, packaging, processing, use, sale, promotion, distribution, storage, import, export or disposal of any of the Company's product candidates or any product manufactured or distributed by the Company; (ii) has not received any FDA Form 483, written notice of adverse finding, warning letter, untitled letter or other correspondence or written notice from any court or arbitrator or the Applicable Regulatory Authorities alleging or asserting non-compliance with any licenses, certificates, approvals, clearances, exemptions, authorizations, permits and supplements or amendments thereto required by any such Health Care Laws ("***Regulatory Authorizations***"); (iii) possesses all Regulatory Authorizations required to conduct its business as currently conducted and such Regulatory Authorizations are valid and in full force and effect and the Company is not in violation, in any material respect, of any term of any such Regulatory Authorizations; (iv) has not received notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any court or arbitrator or the Applicable Regulatory Authorities or any other third party alleging that any product operation or activity is in material violation of any Health Care Laws and has no knowledge that the Applicable Regulatory Authorities or any other third party is considering any such claim, litigation, arbitration, action, suit, investigation or proceeding; (v) has not received notice that any of the Applicable Regulatory Authorities has taken, is taking or intends to take action to limit, suspend, modify or revoke any material Regulatory Authorizations and has no knowledge that any of the Applicable Regulatory Authorities is considering such action; (vi) has filed, obtained, maintained or submitted all material reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Health Care Laws or Regulatory Authorizations and that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were materially complete and correct on the date filed (or were materially corrected or supplemented by a subsequent submission); (vii) is not a party to and does not have any ongoing reporting obligations pursuant to any corporate integrity agreements, deferred prosecution agreements, monitoring agreements, consent decrees, settlement orders, plans of correction or similar agreements with or imposed by any Applicable Regulatory Authority; and (viii) along with its employees, officers and directors, has not been excluded, disqualified, suspended or debarred from participation in any government health care program or human clinical research or, to the Company's knowledge, subject to a governmental inquiry, investigation, proceeding, or other similar action that could reasonably be expected to result in debarment, suspension, disqualification or exclusion.

2.13 Clinical Trials. None of the Company's product candidates has received marketing approval from any Applicable Regulatory Authority. All clinical and pre-clinical studies and trials conducted by or on behalf of or sponsored by the Company, or in which the Company has participated, with respect to the Company's product candidates, including any such studies and trials that are described in the SEC Documents, or the results of which are referred to in the SEC Documents, as applicable (collectively, "***Company Trials***"), were, and if still pending are, to the Company's knowledge, being conducted in all material respects in accordance with all applicable Health Care Laws of the Applicable Regulatory Authorities, including the FDA's current Good Clinical Practices and Good Laboratory Practices, standard medical and scientific research procedures and any applicable rules, regulations and policies of the jurisdiction in which such trials and studies are being conducted. The descriptions in the SEC Documents of the results of any Company Trials are accurate and complete descriptions in all material respects and fairly present the data derived therefrom as of the date of such SEC Documents. The Company

has no knowledge of any other studies or trials not described in the SEC Documents, the results of which are inconsistent with or call into question the results described or referred to in the SEC Documents. The Company has not received any written notices, correspondence or other communications from the Applicable Regulatory Authorities or any other governmental entity or any institutional review board ("***IRB***") or independent ethics committee ("***IEC***") requiring or threatening the termination, material modification or suspension of Company Trials, other than ordinary course communications with respect to modifications in connection with the design and implementation of such studies or trials, and, to the Company's knowledge, there are no reasonable grounds for the same. No investigational new drug application or comparable submission filed by or on behalf of the Company with the FDA has been terminated or suspended by the FDA or any other Applicable Regulatory Authority. The Company has obtained (or caused to be obtained) informed consent by or on behalf of each human subject who participated in a Company Trial, and the Company has obtained (or caused to be obtained) applicable IRB or IEC approvals for each Company Trial. To the Company's knowledge, none of the Company Trials involved any investigator who has been disqualified as a clinical investigator or has been found by the FDA to have engaged in scientific misconduct.

2.14 Absence of Certain Changes.

(a) Except as disclosed in the SEC Documents filed prior to the Execution Date, since March 31, 2021, no change or event has occurred, except where such change or event has not had, and would not reasonably be expected to have, a Material Adverse Effect on the Company.

(b) Except as set forth in the SEC Documents filed prior to the Execution Date or as contemplated by this Agreement or the Collaboration Agreement, since December 31, 2020, the Company has not (i) declared or paid any dividends, or authorized or made any distribution upon or with respect to any class or series of its share capital, or (ii) sold, exchanged or otherwise disposed of any of its material assets or rights.

(c) Since March 31, 2021, the Company has not admitted in writing its inability to pay its debts generally as they become due, filed or consented to the filing against it of a petition in bankruptcy or a petition to take advantage of any insolvency act, made an assignment for the benefit of creditors, consented to the appointment of a receiver for itself or for the whole or any substantial part of its property, or had a petition in bankruptcy filed against it, been adjudicated a bankrupt, or filed a petition or answer seeking reorganization or arrangement under the federal bankruptcy Laws or any other Laws of the United States or any other jurisdiction.

2.15 Not an Investment Company. The Company is not, and after receipt of the Purchase Price, will not be, an "investment company" as defined in the Investment Company Act of 1940, as amended.

2.16 Critical Technology. The Company does not produce, design, test, manufacture, fabricate, or develop one or more "critical technologies" within the meaning of the Defense Production Act of 1950, as amended, including all implementing regulations thereof.

2.17 No Integration. The Company has not, directly or through any agent, sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in the Securities Act) that is or will be integrated with the Shares sold pursuant to this Agreement in a manner that would require the registration of the Shares under the Securities Act.

3. Representations and Warranties of Purchaser

Except as otherwise specifically contemplated by this Agreement, Purchaser hereby represents and warrants to the Company that:

3.1 Authorization; Enforcement. Purchaser has the requisite corporate or other similar power and authority to enter into this Agreement and to consummate the transactions contemplated hereby. Purchaser has taken all necessary corporate or other similar action to authorize the execution, delivery and performance of this Agreement. Upon the execution and delivery of this Agreement, this Agreement will constitute a valid and binding obligation of Purchaser enforceable against Purchaser in accordance with its terms and conditions, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

3.2 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Purchaser and the consummation by Purchaser of the transactions contemplated hereby (including the purchase of the Shares) will not (i) conflict with or result in a violation of any provision of Purchaser's memorandum and articles of association or equivalent organizational documents, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which Purchaser is a party, or (iii) result in a violation of any Law (including U.S. federal and state securities Laws and regulations and regulations of any self-regulatory organizations) applicable to Purchaser, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as have not had, and would not reasonably be expected to have, a Material Adverse Effect on Purchaser or result in a liability for the Company.

(b) Purchaser is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to purchase the Shares in accordance with the terms and conditions hereof, other than such as have been made or obtained, except if and to the extent applicable for compliance with any requirements of the HSR Act and any other antitrust Law.

3.3 Investment Purpose. Purchaser is purchasing the Shares for its own account and not with a present view toward the public distribution thereof and has no arrangement or understanding with any other Persons regarding the distribution of such Shares except as would not result in a violation of the Securities Act. Without limiting Section 5.1 and Section 5.2, Purchaser will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) any of the Shares except in accordance with the Securities Act.

3.4 Reliance on Exemptions. Purchaser understands that the Company intends for the Shares to be offered and sold to it in reliance upon specific exemptions from the registration requirements of United States federal and state securities Laws and that the Company is relying upon the truth and accuracy of, and Purchaser's compliance with, the representations, warranties, agreements, acknowledgments and understandings of Purchaser set forth herein in order to determine the availability of such exemptions and the eligibility of Purchaser to acquire the Shares.

3.5 Accredited Investor; Access to Information. Purchaser is an "accredited investor" as defined in Regulation D under the Securities Act and is knowledgeable, sophisticated and experienced in making, and is qualified to make, decisions with respect to investments in shares presenting an investment decision like that involved in the purchase of the Shares. Purchaser has been furnished with materials relating to the offer and sale of the Shares that have been requested by Purchaser, including the SEC Documents, and Purchaser has had the opportunity to review the SEC Documents. Purchaser has been

afforded the opportunity to ask questions of the Company. Neither such inquiries nor any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

3.6 Restricted Securities. Purchaser understands that the Shares will be characterized as "restricted securities" under the U.S. federal securities Laws inasmuch as they are being acquired from the Company in a private placement under Section 4(a)(2) of the Securities Act and that under such Laws and applicable regulations such Shares may be resold without registration under the Securities Act only in certain limited circumstances.

3.7 Governmental Review. Purchaser understands that no U.S. federal or state or U.K. agency or any other Governmental Authority has passed upon or made any recommendation or endorsement of the Shares or an investment therein.

4. Standstill Agreement

4.1 During the period commencing on the date of this Agreement (the "***Standstill Commencement Date***") and ending on the 18-month anniversary of the Standstill Commencement Date (the "Standstill Period"), neither Purchaser, any of Purchaser's controlled Affiliates nor any of Purchaser's representatives acting on behalf of or in concert with Purchaser will, in any manner, directly or indirectly:

(a) make, effect, initiate, cause or participate in (i) any acquisition of beneficial ownership of any securities of the Company or any securities (including derivatives thereof) of any subsidiary or other controlled Affiliate of the Company, (ii) any acquisition of all or a material portion of the assets of the Company and its subsidiaries on a consolidated basis or (iii) any tender offer, exchange offer, merger, business combination, recapitalization, restructuring, liquidation, dissolution or extraordinary transaction involving the Company or any subsidiary or other controlled Affiliate of the Company or involving any securities or assets of the Company or any securities or assets of any subsidiary, division or other affiliate of the Company (provided that the Purchaser may tender its shares in any tender or exchange offer made by any third party provided that Ionis is not in breach of or won't be in breach of this Section 4.1 of this Agreement), or (iv) any "solicitation" of "proxies" (as those terms are used in the proxy rules of the SEC) or consents with respect to any securities of the Company;

(b) form, join or in any way participate in a "*group*" (as defined under the Exchange Act) with respect to the beneficial ownership of any securities of the Company or any subsidiary or division of the Company;

(c) otherwise act, alone or in concert with others, to seek to control or influence the management, Board or policies of the Company (other than such policies as may be within the scope of the Collaboration Agreement (including any amendments thereto));

(d) take any action that would reasonably be expected to require the Company to make a public announcement regarding any of the types of matters set forth in clause (a) above; or

(e) agree or offer to take, or knowingly encourage or propose (publicly or otherwise) the taking of, any action referred to in clauses (a), (b), (c), or (d) above;

(f) assist, induce or encourage any other Person to take any action of the type referred to in clauses (a), (b), (c), (d) or (e) above (provided that the Purchaser shall not be deemed to be in violation of this clause (f) unless the Person providing such assistance, inducement or encouragement knew or

reasonably should have known at the time he or she did so that doing so violated this clause (f), or knew or reasonably should have known after such time and did not attempt to halt such actions); or

(g) enter into any discussions, negotiations, arrangement or agreement with any other Person with the intent to effect any of the foregoing (provided that the Purchaser shall not be deemed to be in violation of this clause (g) with respect to discussions or negotiations unless the Person entering into such discussions or negotiations knew or reasonably should have known at the time he or she did so that doing so violated this clause (g) or knew or reasonably should have known after such time and did not attempt to halt such actions.

4.2 Purchaser also agrees during the Standstill Period not to request the Company (or its representatives), directly or indirectly, amend or waive any provision of this Section 4 other than by means of a confidential communication to the Company's Chairman of the Board or the Company's Chief Executive Officer.

4.3 Purchaser represents and warrants that, as of the Execution Date, neither Purchaser nor any of its Affiliates owns, of record or beneficially, any voting securities of the Company, or any securities convertible into or exercisable for any voting securities of the Company.

4.4 Notwithstanding the provisions set forth in Sections 4.1 and 4.2 (the "***Standstill Provisions***"), Purchaser shall immediately, and without any other action by the Company, be released from its obligations under the Standstill Provisions if: (a) the Company enters into a definitive written agreement with any Person other than the Purchaser (or any of its Affiliates) to consummate a merger, consolidation or similar transaction pursuant to which (i) any Person other than the Purchaser (or any of its Affiliates) will acquire 50% or more of the outstanding voting shares of the Company or (ii) the Company and its subsidiaries will sell to any Person other than the Purchaser (or any of its Affiliates) all or substantially all of the consolidated assets of the Company and its consolidated subsidiaries ((i) or (ii), a "***Company Sale***"), (ii) a Third Party makes a tender or exchange offer for securities of the Company and the Board either accepts such offer or fails to recommend that its shareholders reject such offer within 10 Business Days from the date of commencement of such offer, or (iii) the Company publicly announces that its Board is engaging in a formal process that is intended to result in a transaction that if consummated would constitute a Company Sale.

4.5 Notwithstanding any other provision of this Agreement to the contrary, nothing in this Agreement will be deemed to prohibit a party from confidentially communicating to the other party's board of directors or senior management or external financial advisors any non-public proposals regarding a possible transaction of any kind in such a manner as would not reasonably be expected to require public disclosure thereof under applicable Law or listing standards of any securities exchange, including Nasdaq.

5. Transfer, Resale, Legends, Deposit for American Depositary Shares

5.1 Transfer or Resale. Purchaser understands that:

(a) the Shares have not been and are not being registered under the Securities Act or any applicable state securities Laws and, consequently, Purchaser may have to bear the risk of owning the Shares for an indefinite period of time because the Shares may not be transferred unless (i) the resale of the Shares is registered pursuant to an effective registration statement under the Securities Act; (ii) Purchaser has delivered to the Company an opinion of counsel (in form, substance and scope customary for opinions of counsel in comparable transactions) to the effect that the Shares to be sold or transferred may be sold or transferred pursuant to an exemption from such registration; or (iii) the Shares are sold or transferred pursuant to Rule 144 under the Securities Act ("***Rule 144***"); and

(b) any sale of the Shares made in reliance on Rule 144 may be made only in accordance with the terms of Rule 144 and, if Rule 144 is not applicable, any resale of the Shares under circumstances in which the seller (or the Person through whom the sale is made) may be deemed to be an underwriter (as that term is defined in the Securities Act) may require compliance with some other exemption under the Securities Act or the rules and regulations of the SEC thereunder.

5.2 Lock-Up. Purchaser agrees that it will hold and will not sell any of the Shares (or otherwise make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale of the Shares) until the earlier of (i) the one-year anniversary of the Closing Date, and (ii) the termination of the Collaboration Agreement, provided that in the event the termination occurs less than six months after the Closing Date, the Purchaser shall hold and will not sell or otherwise enter into a transaction regarding the Shares until at least the date that is six months after the Closing Date. Notwithstanding the foregoing, this Section 5.2 will not preclude (i) distributions of Shares to general or limited partners, members, shareholders, Affiliates or wholly-owned subsidiaries of Purchaser or any investment fund or other entity controlled or managed by Purchaser; *provided*, in each case, that following any such transfer such Shares will remain subject to the provisions of this Section 5.2; or (ii) transfers pursuant to a *bona fide* third party tender offer for all outstanding Ordinary Shares, merger, consolidation or other similar transaction made to all holders of the Company's securities involving a change of control of the Company (including the entering into any lock-up, voting or similar agreement pursuant to which Purchaser may agree to transfer, sell, tender or otherwise dispose of Shares or other such securities in connection with such transaction, or vote any Shares or other such securities in favor of any such transaction); *provided*, that in the event that such tender offer, merger, consolidation or other such transaction is not completed, the Shares shall remain subject to the provisions of this Section 5.2.

5.3 Legends. Purchaser understands the Shares will bear restrictive legends in substantially the following form (and a stop-transfer order may be placed against transfer of the Shares):

THE SHARES HAVE NOT BEEN REGISTERED UNDER THE U.S. SECURITIES ACT OF 1933, AS AMENDED, OR ANY APPLICABLE STATE SECURITIES LAWS. THEY MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED OR HYPOTHECATED UNLESS (I) THE SHARES ARE REGISTERED PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT; (II) AN OPINION OF COUNSEL HAS BEEN DELIVERED (IN FORM, SUBSTANCE AND SCOPE CUSTOMARY FOR OPINIONS OF COUNSEL IN COMPARABLE TRANSACTIONS) TO THE EFFECT THAT THE SHARES TO BE SOLD OR TRANSFERRED MAY BE SOLD OR TRANSFERRED PURSUANT TO AN EXEMPTION FROM SUCH REGISTRATION; OR (III) THE SHARES ARE SOLD OR TRANSFERRED PURSUANT TO RULE 144 UNDER THE SECURITIES ACT.

THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THESE SECURITIES IS SUBJECT TO THE TERMS AND CONDITIONS OF A SHARE PURCHASE AGREEMENT DATED JULY 9, 2021 BETWEEN BICYCLE THERAPEUTICS PLC AND IONIS PHARMACEUTICALS, INC.

If such Shares may be transferred pursuant to Section 5.2 (excluding transfers pursuant to Section 5.2(i)), Purchaser may request that the Company remove, and the Company agrees to authorize and instruct (including by causing any required legal opinion to be provided) the removal of any legend from the Shares, if permitted by applicable securities Law, within two (2) Business Days of any such request; *provided, however*, that each party will be responsible for any fees it incurs in connection with such request and removal.

5.4 Deposit of Shares and Issuance of American Depositary Shares. Upon the written request of the Purchaser to the Company, and in accordance with the other limitations of this Agreement,

the Company will deposit or cause to be deposited such number of Shares with the Depositary as is requested by the Purchaser, and issue or cause to be issued to the Purchaser the corresponding American Depositary Shares, with any and all costs associated with such deposit and issuance paid for by the Purchaser. The Company shall (a) use its reasonable best efforts to (i) register or qualify its American Depositary Shares under the securities or blue sky Laws of such jurisdictions in the United States as the Purchaser reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable the Purchaser to consummate the disposition in such jurisdictions of the American Depositary Shares owned by the Purchaser in accordance with Rule 144 or some other exemption under the Securities Act or the rules and regulations of the SEC thereunder, provided that the Company shall not be required to register the Shares or any American Depositary Shares held by the Purchaser on a Registration Statement on Form S-1 or Registration Statement on Form S-3 and (ii) cause all such American Depositary Shares to be eligible and remain eligible for registration of the American Depositary Shares pursuant to Form F-6, and (b) cooperate with the Purchaser and the Depositary to facilitate the timely delivery of American Depositary Shares (in book entry or certificated form), which American Depositary Shares shall be free of all restrictive legends unless the Company reasonably determines on advice from legal counsel that such legends are required by applicable law (it being understood that the American Depositary Shares may be restricted American Depositary Shares subject to restrictions imposed by the Depositary if and for so long as the Purchaser is an Affiliate of the Company).

5.5 Rule 144 Reporting. With a view to making available to Purchaser the benefits of certain rules and regulations of the SEC that may permit the sale of registrable securities to the public without registration, the Company agrees to use its best efforts to:

(a) Make and keep public information available, as those terms are understood and defined in Rule 144 or any similar or analogous rule promulgated under the Securities Act, at all times after the effective date of the first registration filed by the Company for an offering of its securities to the general public;

(b) File with the SEC, in a timely manner, all reports and other documents required of the Company under the Exchange Act; and

(c) So long as Purchaser owns Shares, furnish to Purchaser upon request: a written statement by the Company as to its compliance with the reporting requirements of said Rule 144 of the Securities Act, and of the Exchange Act; a copy of the most recent annual or quarterly report of the Company filed with the Commission; and such other reports and documents as Purchaser may reasonably request in connection with availing itself of any rule or regulation of the SEC allowing it to sell any such securities without registration.

6. Conditions to Closing

6.1 Conditions to Obligations of the Company. The Company's obligation to complete the purchase and sale of the Shares and deliver the Shares to Purchaser is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Receipt of Funds. The Company will have received immediately available funds in the full amount of the Purchase Price for the Shares being purchased hereunder.

(b) Representations and Warranties. The representations and warranties made by Purchaser in Section 3 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(c) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by Purchaser on or prior to the Closing Date shall have been performed or complied with in all material respects.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) No Governmental Prohibition. The sale of the Shares by the Company and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(f) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(ii) shall have been delivered by Purchaser to the Company.

6.2 Conditions to Purchaser's Obligations at the Closing. Purchaser's obligation to complete the purchase and sale of the Shares is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Representations and Warranties. The representations and warranties made by the Company in Section 2 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(b) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by the Company on or prior to the Closing Date shall have been performed or complied with in all material respects.

(c) Transfer Agent Instructions. The Company will have delivered to its transfer agent and registrar irrevocable written instructions to issue the Shares to Purchaser in a form and substance acceptable to such transfer agent.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(f) No Governmental Prohibition. The sale of the Shares by the Company, and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(i) shall have been delivered by the Company to Purchaser.

7. Indemnification

7.1 Indemnification by the Company. The Company shall indemnify and hold harmless Purchaser and its Affiliates, and the directors, officers, employees and other agents and representatives of Purchaser and its Affiliates, from and against any and all liabilities, judgments, claims, settlements, losses, damages, fees, Liens, Taxes, penalties, obligations and expenses (including reasonable attorney's fees and expenses and costs and expenses of investigation) (collectively, "***Losses***") incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of the Company contained in this Agreement or any certificate delivered by the Company or on its behalf hereunder; and (b) the non-fulfillment or breach by the Company of any agreements or obligations under this Agreement.

7.2 Indemnification by Purchaser. Purchaser shall indemnify and hold harmless the Company and its Affiliates, and the directors, officers, employees and other agents and representatives of the Company and its Affiliates, from and against any and all Losses incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of Purchaser contained in this Agreement or any certificate delivered by the Purchaser or on its behalf hereunder; and (b) the non-fulfillment or breach by Purchaser of any agreements or obligations under this Agreement.

7.3 Calculation of Losses. Any indemnity payment hereunder shall be treated as an adjustment to the Purchase Price to the extent permitted by applicable Law. Where the receipt of any such payment is treated for Tax purposes in a manner other than as an adjustment to the Purchase Price, the amount of the payment shall be adjusted to take account of any net Tax cost actually incurred, or benefit actually enjoyed, by the Indemnified Party in respect thereof.

7.4 Certain Procedures for Indemnification.

(a) If any Person entitled to indemnification under this Agreement (an "***Indemnified Party***") asserts a claim for indemnification, or receives notice of the assertion of any claim or of the commencement of any action by any Person not a party to this Agreement against such Indemnified Party, for which a party to this Agreement is required to provide indemnification under this Section 7 (an "***Indemnifying Party***"), the Indemnified Party shall promptly notify the Indemnifying Party in writing of the claim or the commencement of that action; *provided*, *however*, that the failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party from any liability which it may have to the Indemnified Party, except to the extent that such failure materially prejudices the Indemnifying Party's ability to defend such action.

(b) With respect to third party claims for which indemnification is claimed hereunder, (i) the Indemnifying Party shall be entitled to participate in the defense of any such claim, and (ii) if, in the reasonable judgment of the Indemnified Party, such claim can properly be resolved by money damages alone and the Indemnifying Party has the financial resources to pay such damages, and the Indemnifying Party admits that this indemnity fully covers the claim or litigation, then the Indemnifying Party shall be entitled (y) to direct the defense of any claim at its sole cost and expense, but such defense shall be conducted by legal counsel reasonably satisfactory to the Indemnified Party, and (z) to settle and compromise any such claim or action for money damages alone; *provided*, *however*, that if the Indemnified Party has elected to be represented by separate counsel pursuant to the proviso below, or if such settlement or compromise does not include an unconditional release of the Indemnified Party for any liability arising out of such claim or action, such settlement or compromise shall be effected only with the written consent of the Indemnified Party. After notice from the Indemnifying Party to the Indemnified Party of its election to assume the defense of such claim or action, the Indemnifying Party shall not be liable to the Indemnified

Party under this Section 7.4 for any legal or other expenses subsequently incurred by the Indemnified Party in connection with the defense thereof other than reasonable costs of investigation or of assistance as contemplated by this Section 7.4; *provided, however,* that if, in the opinion of the Indemnified Party, it is advisable for the Indemnified Party to be represented by separate counsel due to actual or potential conflicts of interest, the Indemnified Party shall have the right to employ counsel to represent it and in that event the fees and expenses of such separate counsel shall be paid by the Indemnifying Party; *provided further,* that in no event shall the Indemnifying Party be responsible for the fees of more than one counsel to the Indemnified Party. The Indemnified Party and the Indemnifying Party shall each render to each other such assistance as may reasonably be requested in order to ensure the proper and adequate defense of any such claim or proceeding.

7.5 Survival; Expiration.

(a) Notwithstanding any investigation made by or on behalf of the Company or Purchaser prior to, on or after the Closing Date, the representations and warranties contained in this Agreement (including the exhibits and schedules hereto) and any certificate delivered hereunder shall survive the Closing and shall terminate on the second anniversary of the Closing Date.

(b) The covenants of the parties hereto shall survive until fully performed and discharged, unless otherwise expressly provided herein.

(c) Any right of indemnification or reimbursement pursuant to this Section 7 with respect to a claimed breach, inaccuracy or non-fulfillment of any representation, warranty, agreement or obligation shall expire on the applicable date of termination of the representation, warranty or covenant claimed to be breached (the "***Expiration Date***"), unless on or prior to the applicable Expiration Date, the Indemnifying Party has received written notice from the Indemnified Party of such breach, inaccuracy or non-fulfillment from the Indemnified Party or is based on fraud or intentional or willful breach of the Indemnifying Party, in which case the Indemnified Party may continue to pursue its right of indemnification or reimbursement hereunder beyond the Expiration Date of the applicable representation, warranty, agreement or obligation. For the avoidance of doubt, no claims based on fraud or intentional or willful breach will be subject to any of the limitations set forth in this Section 7.5.

8. Dispute Resolution

8.1 (a) If the parties cannot amicably resolve any dispute (a "***Dispute***") arising under this Agreement, then a party seeking further resolution of such Dispute shall submit such Dispute to final and binding arbitration conducted in accordance with the terms of this Section 8.1. The party initiating arbitration will give written notice to that effect to the other party. The legal seat of arbitration will be New York City, New York, U.S., and the arbitration will be administered by JAMS according to the JAMS International Arbitration Rules applicable at the time of commencement of the arbitration except as otherwise provided herein and applying the substantive law specified in Section 10.1. The arbitration will be conducted by a single arbitrator appointed in accordance with the Rules, provided that such arbitrator must have significant business or legal experience in the pharmaceutical industry and the applicable law concerning the subject matter of the dispute. In any case, the arbitrator will not be an Affiliate, employee, consultant, officer, director, shareholder or stockholder of either party, or otherwise have any current or previous relationship with either party or their respective Affiliates. After conducting any hearing and taking any evidence deemed appropriate for consideration, the arbitrator will render a written opinion within 30 days after the final arbitration hearing. The arbitrator's decision will include findings of fact and conclusions of law. The determination of the arbitrator as to the resolution of any Dispute will be binding and conclusive on the parties. Judgment on the award so rendered may be entered in any court of competent jurisdiction, and the parties undertake to carry out any award without delay. Nothing contained herein will

be construed to permit the arbitrator to award punitive, exemplary, or any similar damages and any arbitral award that purports to award such damages is expressly prohibited and void *ab initio*. Each party will bear its own attorneys' fees, costs and disbursements arising out of the arbitration and will pay an equal share of the fees and costs of the arbitrator. Except to the extent necessary to confirm, enforce, or challenge an award of the arbitration, to protect or pursue a legal right, or as otherwise required by applicable law or regulation, no party nor the arbitrator may disclose the existence, content, or results of an arbitration under this Section 8.1 without the express, prior written consent of each of the parties. In no event shall any party initiate arbitration after the date when commencement of a legal or equitable proceeding based on the Dispute, controversy, or claim would be barred by the applicable New York statute of limitations. Any Disputes concerning the propriety of the commencement of the arbitration, or the validity or application of this Section 8.1, shall be finally settled by the arbitrator. Nothing in this Section 8.1 shall preclude either party from (a) seeking interim or provisional relief, including a temporary restraining order, preliminary injunction, or other interim equitable relief concerning a dispute in any court of competent jurisdiction, before or after the initiation of an arbitration as set forth in this Section 8.1, if necessary to protect the interests of such party, or (b) bringing an action in any court of competent jurisdiction to resolve a dispute regarding the intellectual property rights hereunder, and this sentence shall be specifically enforceable.

(b) For the avoidance of doubt, any disputes with respect to the terms of the Collaboration Agreement shall be resolved in accordance with the dispute resolution provisions therein, and shall not be subject to the provisions of this Section 8.

9. Termination

9.1 Ability to Terminate. This Agreement may be terminated prior to the Closing:

(a) at any time by mutual written consent of the Company and Purchaser;

(b) by the Company, upon three (3) days' written notice to Purchaser, so long as the Company is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.1, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of Purchaser set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of Purchaser shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.1 could not be satisfied by the Termination Date;

(c) by Purchaser, upon three (3) days' written notice to the Company, so long as Purchaser is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.2 of this Agreement, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of the Company set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of the Company shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.2 of this Agreement could not be satisfied by the Termination Date;

(d) by either the Company or Purchaser, upon written notice to the other, if the Closing has not occurred on or before _____, 2021 (the "***Termination Date***").

9.2 Effect of Termination. In the event of the termination of this Agreement pursuant to Section 9, (a) this Agreement (except for this Section 9.2, and Section 7, Section 8, Section 10.1 and Sections 10.3 through 10.14 and any definitions set forth in this Agreement and used in such Sections) shall forthwith become void and have no effect, without any liability on the part of any party hereto or its Affiliates, and (b) any and all filings, applications and other submissions made pursuant to this Agreement,

to the extent practicable, shall be withdrawn from the agency or other Person to which they were made or appropriately amended to reflect the termination of the transactions contemplated hereby; *provided*, *however*, that nothing contained in this Section 10.2 shall relieve any party from liability for fraud or any intentional or willful breach of this Agreement.

10. Governing Law; Miscellaneous

10.1 Governing Law. This Agreement will be governed by and interpreted in accordance with the laws of the State of New York without regard to the principles of conflict of laws that would require the application of the substantive Laws of another jurisdiction.

10.2 Market Listing. From the Execution Date through the Closing, the Company shall use commercially reasonable efforts to maintain the listing and trading of the Company's American Depositary Shares on Nasdaq.

10.3 Counterparts; Electronic Signatures. This Agreement may be executed and delivered (including by facsimile transmission or PDF or any other electronically transmitted signatures) in two counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

10.4 Headings. The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

10.5 Rules of Construction.

(a) For purposes of this Agreement, whenever the context requires: the singular number shall include the plural, and vice versa; the masculine gender shall include the feminine and neuter genders; the feminine gender shall include the masculine and neuter genders; and the neuter gender shall include the masculine and feminine genders.

(b) As used in this Agreement, (i) the words "include" and "including," and variations thereof, shall not be deemed to be terms of limitation, but rather shall be deemed to be followed by the words "without limitation", (ii) the words "hereby," "herein," "hereunder" and "hereto" shall be deemed to refer to this Agreement in its entirety and not to any specific section of this Agreement and (iii) "or" has the inclusive meaning represented by the phrase "and/or".

(c) Except as otherwise indicated, all references in this Agreement to "Sections" and "Appendices" are intended to refer to Sections of this Agreement, as appropriate, and Appendices to this Agreement.

(d) As used in this Agreement, the term "days" means calendar days unless otherwise specified. When calculating the period of time before which, within which or following which any act is to be done or step taken pursuant to this Agreement, the date that is the reference date in calculating such period shall be excluded. If the last day of such period is a non-Business Day, the period in question shall end on the next succeeding Business Day.

(e) Unless otherwise indicated, all monetary amounts herein are in United States dollars.

10.6 Severability. If any provision of this Agreement should be held invalid, illegal or unenforceable in any jurisdiction, the parties will negotiate in good faith a valid, legal and enforceable

substitute provision that most nearly reflects the original intent of the parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

10.7 Entire Agreement; Amendments. This Agreement, the Option Agreement, and the Collaboration Agreement (including any schedules, appendices and exhibits hereto or thereto and any certificates delivered hereunder) constitute the entire agreement between the parties hereto with respect to the subject matter hereof and thereof. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein or therein. This Agreement supersedes all prior agreements and understandings between the parties hereto with respect to the subject matter hereof. No provision of this Agreement may be waived or amended other than by an instrument in writing signed by the party to be charged with enforcement. Any amendment or waiver effected in accordance with this Section 10.7 shall be binding upon Purchaser and the Company.

10.8 Notices. All notices required or permitted hereunder will be in writing and will be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed email if sent during normal business hours of the recipient, if not, then on the next Business Day, or (c) one Business Day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. The addresses for such communications are:

If to the Company, to:

Bicycle Therapeutics plc
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: General Counsel
Email:

with a copy (which shall not constitute notice) to:

Cooley LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
Attention: Laura Berezin
E-mail:

If to the Purchaser, to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Financial Officer
Email:

With a copy (which shall not constitute notice) to:

Attention: General Counsel
Email:

10.9 Successors and Assigns. This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. The Company will not assign this Agreement or any rights or obligations hereunder without the prior written consent of Purchaser, and Purchaser will not assign this Agreement or any rights or obligations hereunder without the prior written consent of the Company.

10.10 Third Party Beneficiaries. This Agreement is intended for the benefit of the parties hereto, their respective permitted successors and assigns, and is not for the benefit of, nor may any provision hereof be enforced by, any other Person.

10.11 Further Assurances. Each party will do and perform, or cause to be done and performed, all such further acts and things, and will execute and deliver all other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

10.12 No Strict Construction. The language used in this Agreement is deemed to be the language chosen by the parties to express their mutual intent, and no rules of strict construction will be applied against a party.

10.13 Equitable Relief. The Company recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to Purchaser. The Company therefore agrees that Purchaser is entitled to seek temporary and permanent injunctive relief or specific performance in any such case. Purchaser also recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to the Company. Purchaser therefore agrees that the Company is entitled to seek temporary and permanent injunctive relief or specific performance in any such case.

10.14 Expenses. The Company and Purchaser are each liable for, and will pay, their own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement, including attorneys' and consultants' fees and expenses.

10.15 Public Disclosure. On or shortly after the Effective Date, the Company and Purchaser shall issue a joint press release in a form mutually agreed to by the Company and Purchaser. In addition, the Company shall file a Current Report on Form 8-K with the SEC within the time period required by such form and including such disclosures as required by such form with respect to this Agreement and the transactions contemplated herein, such Current Report on Form 8-K to be in a form mutually agreed to by the Company and Purchaser. No other written release, public announcement, disclosure or filing concerning the purchase of the Shares, this Agreement or the transactions contemplated hereby or thereby shall be issued, filed or furnished, as the case may be, by any party without the prior written consent of the other party (which consent shall not be unreasonably withheld, conditioned or delayed) and, except as set forth in this Section 10.15, the parties agree to keep the terms of this Agreement confidential. Notwithstanding the foregoing, the parties acknowledge and agree that applicable Law or the requirements of a national securities exchange or another similar regulatory body may require either party to file or otherwise disclose a copy of this Agreement. The party required to make such filing or otherwise disclose shall notify the other party and shall, to the extent possible, provide the other party with at least five (5) Business Days to request redactions thereof prior to making such filing or disclosure. The disclosing party shall use commercially reasonable efforts to procure confidential treatment of such proposed redactions pursuant to the Securities Act and the Exchange Act, in each case as amended, and the rules, regulations and guidelines promulgated thereunder, or any other applicable Law or the rules, regulations or guidelines promulgated hereunder; *provided* that the foregoing shall not prevent the party from making such public disclosures as it must make to comply with applicable Law.

[Remainder of page intentionally left blank.]

IN WITNESS WHEREOF, Purchaser and the Company have caused this Agreement to be duly executed as of the date first above written.

COMPANY:

BICYCLE THERAPEUTICS PLC

By: _____

Name: _____

Title: _____

PURCHASER:

IONIS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

APPENDIX 1

DEFINED TERMS

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity that directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with it. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities, capital stock or share capital (or such lesser percentage that is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the preamble.

"***American Depositary Shares***" shall mean shares issued by the Depositary pursuant to the Deposit Agreement, each representing one Ordinary Share.

"***Applicable Regulatory Authorities***" has the meaning set forth in Section 2.12.

"***BicycleTx***" has the meaning set forth in the recitals.

"***Board***" means the board of directors of the Company.

"***Business Day***" means a day Monday through Friday on which banks are generally open for business in the State of California, the State of New York and London, England.

"***Change of Control Transaction***" has the meaning set forth in Section 5.2.

"***Closing***" has the meaning set forth in Section 1.3(a).

"***Closing Cash***" has the meaning set forth in Section 1.1.

"***Closing Date***" means the date on which the Closing actually occurs.

"***Collaboration Agreement***" has the meaning set forth in the recitals.

"***Company Rights***" has the meaning set forth in Section 2.11(c).

"***Company Sale***" has the meaning set forth in Section 4.4.

"***Company Trials***" has the meaning set forth in Section 2.13.

"***Cross-Receipt***" has the meaning set forth in Section 1.3(b)(i)(A).

"***Deposit Agreement***" means the Deposit Agreement, dated as May 28, 2019, as amended from time to time, among the Company, the Depositary, and holders from time to time of the American Depositary Shares.

"***Depositary***" means mean Citibank, N.A.

"***Dispute***" has the meaning set forth in Section 8.1.

"***DOJ***" means the U.S. Department of Justice.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC thereunder.

"***Execution Date***" has the meaning set forth in the preamble.

"***Expiration Date***" has the meaning set forth in Section 7.5(c).

"***FDA***" has the meaning set forth in Section 2.12.

"***FTC***" means the U.S. Federal Trade Commission.

"***GAAP***" means generally accepted accounting principles in the United States of America.

"Good Clinical Practices" means the legal, scientific and ethical standards for the performance of clinical research on medicinal products involving humans, including as reflected in the regulations of the FDA at 21 C.F.R. parts 50, 54, 56, and 312.

"Good Laboratory Practices" means the legal, scientific and ethical standards for the performance of nonclinical laboratory studies, including as set out in the regulations of the FDA at 21 C.F.R. part 58.

"***Governmental Authority***" means any federal, state, provincial, local, municipal, foreign or other governmental or quasi-governmental authority, including any arbitrator and applicable securities exchanges, or any department, minister, agency, commission, commissioner, board, subdivision, bureau, agency, instrumentality, court or other tribunal of any of the foregoing.

"***Health Care Laws***" means Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395-1395lll (the Medicare statute); Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396w-5 (the Medicaid statute); the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b); the civil False Claims Act, 31 U.S.C. §§ 3729 et seq.; the criminal False Claims Act 42 U.S.C. 1320a-7b(a); any other criminal laws relating to health care fraud and abuse, including but not limited to 18 U.S.C. Sections 286 and 287 and the health care fraud criminal provisions under the Health Insurance Portability and Accountability Act of 1996, 42 U.S.C. §§ 1320d et seq., ("***HIPAA***"); the Civil Monetary Penalties Law, 42 U.S.C. §§ 1320a-7a; the Physician Payments Sunshine Act, 42 U.S.C. § 1320a-7h; the Exclusion Laws, 42 U.S.C. § 1320a-7; HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, 42 U.S.C. §§ 17921 et seq.; the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 et seq.; the Public Health Service Act, 42 U.S.C. §§ 201 et seq.; the regulations promulgated pursuant to such laws; and any similar federal, state and local laws and regulations, each and all as may be amended from time to time.

"***HIPAA***" has the meaning set forth in the definition of "Health Care Laws."

"***IEC***" has the meaning set forth in Section 2.13.

"***Indemnified Party***" has the meaning set forth in Section 7.4(a).

"***Indemnifying Party***" has the meaning set forth in Section 7.4(a).

"***Intellectual Property***" shall mean trademarks, trade names, trade dress, service marks, copyrights, and similar rights (including registrations and applications to register or renew the registration of any of the foregoing), patents and patent applications, trade secrets, and any other similar intellectual property rights.

"***Intellectual Property License***" shall mean any license, permit, authorization, approval, contract or consent granted, issued by or with any Person relating to the use of Intellectual Property.

"***IRB***" has the meaning set forth in Section 2.13.

"***Law***" means any federal, state, local or foreign constitution, treaty, law, statute, ordinance, rule, regulation, interpretation, directive, policy, order, writ, decree, injunction, judgment, stay or restraining order of any Governmental Authority, the terms of any permit, and any other ruling or decision of, agreement with or by, or any other requirement of, any Governmental Authority.

"***Lien***" means any lien (statutory or otherwise), charge, security interest, pledge, mortgage, restriction on use or transfer, financing statement or similar encumbrance of any kind or nature whatsoever (including any conditional sale or other title retention agreement and any lease having substantially the same effect as any of the foregoing and any assignment or deposit arrangement in the nature of a security device).

"***Losses***" has the meaning set forth in Section 7.1.

"***Material Adverse Effect***" means any change, effect or circumstance, individually or in the aggregate, (a) that is reasonably likely to be materially adverse to the business, operations, assets or financial condition of the Company or Purchaser, as the case may be, taken as a whole, or (b) that materially impairs the ability of the Company or Purchaser to perform its obligations pursuant to the transactions contemplated by this Agreement or the Collaboration Agreement; *provided however*, that, none of the following (alone or when aggregated with any other effects), shall be deemed to be a Material Adverse Effect, and none of the following (alone or when aggregated with any other effects), shall be taken into account for purposes of clause (a) above: (A) (1) general market, economic or political conditions or (2) conditions (or any changes therein) in the industries in which the Company or Purchaser conducts business, in each case, including any acts of terrorism or war, weather conditions, global virus pandemics, epidemics or other force majeure events, in the case of each of clauses (1) and (2), solely to the extent that such effects do not have and are not reasonably likely to have a material disproportionate impact on the Company or Purchaser, as the case may be; (B) this Agreement, the Collaboration Agreement (including any amendments thereto), and the transactions contemplated hereby and thereby; or (C) changes in the trading price or volume of the American Depositary Shares or the Purchaser's ordinary shares, in and of themselves.

"***Nasdaq***" means The Nasdaq Global Select Market.

"***Option Agreement***" has the meaning set forth in the recitals.

"***Ordinary Shares***" has the meaning set forth in the recitals.

"***Purchaser***" has the meaning set forth in the preamble.

"***Permits***" has the meaning set forth in Section 2.10.

"***Person***" means a human being, labor organization, partnership, firm, enterprise, association, joint venture, corporation, limited liability company, cooperative, legal representative, foundation, society, political party, estate, trust, trustee, trustee in bankruptcy, receiver or any other organization or entity whatsoever, including any Governmental Authority.

"***Proprietary Rights***" has the meaning set forth in Section 2.11(c).

"***Purchase Price***" has the meaning set forth in Section 1.1.

"***Regulatory Authorizations***" has the meaning set forth in Section 2.12.

"***Rule 144***" has the meaning set forth in Section 5.1(a).

"***SEC***" means the United States Securities and Exchange Commission or any successor entity.

"***SEC Documents***" has the meaning set forth in Section 2.5(a).

"***Securities Act***" means the Securities Act of 1933, as amended, and the rules and regulations of the SEC thereunder.

"***Share Cap***" means a number of Ordinary Shares equal to 9.99% of the Ordinary Shares issued and outstanding on the Execution Date, rounded down to nearest number of Ordinary Shares.

"***Share Value***" means a price per Share (rounded to the nearest cent) equal to the product of (a) 1.3 and (b) the volume weighted average price per American Depositary Share as displayed under the heading "Bloomberg VWAP" on Bloomberg page "BCYC AQR" (or its equivalent successor if such page is not available) for a twenty (20) Trading Day period, starting with the scheduled opening of trading on the twentieth (20th) Trading Day prior to the date of the Purchaser's exercise of its option under the Option Agreement and ending with the scheduled close of trading of the primary trading session on the Trading Day prior to date of Purchaser's exercise of its option under the Option Agreement, as reported on Nasdaq.com, without regard to after-hours trading or any other trading outside of the regular trading session trading hours; *provided* that the Share Value shall in no event be lower than the Minimum Price (as defined in accordance with the rules and regulations of Nasdaq) on the Execution Date.

"***Shares***" has the meaning set forth in Section 1.1.

"***Standstill Period***" has the meaning set forth in Section 4.1.

"***Standstill Provisions***" has the meaning set forth in Section 4.4.

"***Tax***" means any federal, state, local, or foreign income, gross receipts, license, payroll, employment, excise, severance, stamp, occupation, premium, windfall profits, environmental (including taxes under Section 59A of the Internal Revenue Code of 1986, as amended), customs duties, capital stock, share capital, franchise, profits, withholding, social security (or similar), unemployment, disability, real property, personal property, sales, use, transfer, registration, value added, alternative or add-on minimum, estimated, or other tax of any kind whatsoever, including any interest, penalty, or addition thereto, whether disputed or not.

"***Termination Date***" has the meaning set forth in Section 9.1(d).

"Third Party" means any entity other than BicycleTx, the Company, the Purchaser or an Affiliate of BicycleTx, the Company, or the Purchaser.

"***Trading Day***" means a day on which Nasdaq is open for trading.

"***The Company***" has the meaning set forth in the preamble.

Exhibit 10.2

Execution Version

SHARE PURCHASE AGREEMENT

THIS SHARE PURCHASE AGREEMENT ("***Agreement***") is entered into as of July 9, 2021 (the "***Execution Date***"), by and between **Bicycle Therapeutics plc**, a company incorporated under the laws of England and Wales having an office at Building 900, Babraham Research Campus, Cambridge, United Kingdom CB22 3AT (the "***Company***"), and **Ionis Pharmaceuticals, Inc.** a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA (the "***Purchaser***"). The capitalized terms used herein and not otherwise defined have the meanings given to them in Appendix 1.

RECITALS

BicycleTx Limited ("***BicycleTx***"), an affiliate of the Company, and Purchaser entered into that certain Evaluation and Option Agreement dated as of December 31, 2020 (the "***Option Agreement***") pursuant to which BicycleTx granted to the Purchaser an exclusive option to obtain an exclusive license under BicycleTx's technology to research, develop, manufacture, and commercialize products incorporating TfR1 Bicycles (as defined in the Collaboration Agreement (as defined below)) and Purchaser has exercised such option in accordance with the terms of the Option Agreement. Pursuant to the exercise of such option and contemporaneously with execution of this Agreement, BicycleTx and Purchaser are entering into that certain Collaboration and Licensing Agreement (the "***Collaboration Agreement***").

Pursuant to the Option Agreement, and as partial consideration for the Collaboration Agreement, the Company has agreed to sell, and the Purchaser has agreed to purchase, ordinary shares, nominal value £0.01 per share, of the Company (the "***Ordinary Shares***"), subject to and in accordance with the terms and provisions of this Agreement.

AGREEMENT

For good and valuable consideration, the Purchaser and the Company agree as follows:

SECTION 1. SALE AND PURCHASE OF ORDINARY SHARES

1.1 Purchase of Ordinary Shares. Subject to the terms and conditions of this Agreement, at the Closing, the Company will issue and sell to the Purchaser, and the Purchaser will purchase from the Company, a number of Ordinary Shares equal to $11,000,000 divided by the Share Value, rounded down to the nearest whole share (such Ordinary Shares, the "***Shares***"). The aggregate purchase price shall equal the number of Shares multiplied by the Share Value, rounded to the nearest cent (the "***Purchase Price***"), *provided*, *however*, that if the number of Shares calculated in accordance with the preceding clause of this Section 1.1 exceeds the Share Cap, the Company will issue and sell to Purchaser, and the Purchaser will purchase from the Company, the number of Ordinary Shares equal to the Share Cap, at the Share Value, and shall pay to the Company in cash the difference between (i) $11,000,000 and (ii) the product of the Share Value multiplied by the Share Cap (any such amount, the "***Closing Cash***"**)**. In the event the Share Cap is applicable, the term "***Shares***" shall refer to the number of Ordinary Shares equal to the Share

Cap, and the term "***Purchase Price***" shall refer to the product of the Share Value and the Share Cap.

1.2 Payment. At the Closing, Purchaser will pay the Purchase Price and the Closing Cash, if any, by wire transfer of immediately available funds in accordance with wire instructions, which instructions will have been provided by the Company to Purchaser at least three (3) Business Days prior to the Closing, and the Company will cause its registrar and transfer agent to issue such Shares in restricted book entry form registered in the name of the Purchaser.

1.3 Closing.

(a) Closing. The closing of the transaction contemplated by Section 1.1 (the "***Closing***") will be held at the offices of the Company or through the electronic exchange of documents and signatures, as promptly as practicable and upon the satisfaction of the closing conditions set forth in Section 6 hereof, and in no event more than ten (10) Business Days after the Execution Date.

(b) Closing Deliverables.

(i) At the Closing, the Company will deliver to Purchaser:

A. a duly executed cross-receipt in form and substance reasonably satisfactory to each party (the "***Cross-Receipt***");

B. a certificate in form and substance reasonably satisfactory to Purchaser and duly executed on behalf of the Company by an authorized officer of the Company, certifying that the conditions to the Closing set forth in Sections 6.2(a), (b), (c) and (d) of this Agreement have been fulfilled; and

C. a certificate of the secretary of the Company dated as of the Closing Date certifying that attached thereto is a true and complete copy of all resolutions adopted by the Board authorizing the execution, delivery and performance of this Agreement and the transactions contemplated herein and that all such resolutions are in full force and effect and are all the resolutions adopted in connection with the transactions contemplated hereby as of the Closing Date.

(ii) At the Closing, Purchaser will deliver to the Company:

A. a duly-executed Cross-Receipt; and

B. a certificate in form and substance reasonably satisfactory to the Company and duly executed on behalf of Purchaser by an authorized officer of Purchaser, certifying that the conditions to the Closing set forth in Section 6.1(b) and (c) of this Agreement have been fulfilled.

SECTION 2. REPRESENTATIONS AND WARRANTIES OF THE COMPANY

Except as otherwise specifically contemplated by this Agreement, the Company hereby represents and warrants to Purchaser that:

2.1 Private Placement. Neither the Company nor any Person acting on its behalf, has, directly or indirectly, made any offers or sales of any security or solicited any offers to buy any security, under any circumstances that would require registration of the Shares under the Securities Act. Subject to the accuracy of the representations made by Purchaser in Section 3, the Shares will be issued and sold to Purchaser in compliance with applicable exemptions from the registration and prospectus delivery requirements of the Securities Act and the registration and qualification requirements of all applicable securities Laws of the states of the United States. The Company has not engaged any brokers, finders or agents, or incurred, or will incur, directly or indirectly, any liability for brokerage or finder's fees or agents' commissions or any similar charges in connection with this Agreement and the transactions contemplated hereby.

2.2 Corporate Power and Qualification. The Company has full corporate power and authority to conduct its business as currently conducted. The Company is duly qualified to do business and is in good standing in every jurisdiction in which the nature of the business conducted by it or property owned by it makes such qualification necessary, except where the failure to be so qualified or in good standing, as the case may be, would not reasonably be expected to have a Material Adverse Effect on the Company.

2.3 Authorization; Enforcement. The Company has all requisite corporate power and authority to enter into and to perform its obligations under this Agreement, to consummate the transactions contemplated hereby and to issue the Shares in accordance with the terms and conditions hereof. The execution, delivery and performance of this Agreement by the Company and the consummation by it of the transactions contemplated hereby (including the issuance of the Shares at the Closing in accordance with the terms and conditions hereof) have been duly authorized by the Board and no further consent or authorization of the Company, the Board, or its shareholders is required. This Agreement has been duly executed by the Company and constitutes a legal, valid and binding obligation of the Company enforceable against the Company in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

2.4 Issuance of Shares. The Shares, upon issuance in accordance with the terms of this Agreement, will be validly issued, fully paid and non-assessable and will not be subject to preemptive rights or other similar rights of shareholders of the Company.

2.5 SEC Documents, Financial Statements.

(a) The American Depositary Shares are registered pursuant to Section 12(b) or 12(g) of the Exchange Act. The Company has delivered or made available (by filing on the SEC's electronic data gathering and retrieval system (EDGAR)) to Purchaser complete copies of its most recent Annual Report on Form 10-K and each subsequent Quarterly Report on Form 10-Q, and any report on Form 8-K, in each case filed with the SEC prior to the Execution Date (the "***SEC Documents***"). As of its date, each SEC Document complied in all material respects with the requirements of the Exchange Act, and other Laws applicable to it, and, as of its date, such

SEC Document did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading. No inquiries or any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

(b) There are no outstanding or unresolved comments in comment letters received from the SEC or its staff.

(c) As of the Execution Date, other than the transactions that are the subject of this Agreement and the Collaboration Agreement, no material fact or circumstance exists that would be required to be disclosed in a current report on Form 8-K or in a registration statement filed under the Securities Act, were such a registration statement filed on the date hereof, that has not been disclosed in an SEC Document.

(d) The financial statements, together with the related notes, of the Company included in the SEC Documents comply as to form in all material respects with all applicable accounting requirements and the published rules and regulations of the SEC and all other applicable rules and regulations with respect thereto. Such financial statements, together with the related notes and schedules, have been prepared in accordance with GAAP applied on a consistent basis during the periods involved (except (i) as may be otherwise indicated in such financial statements or the notes thereto or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes or may be condensed or summary statements), and fairly present in all material respects the financial condition of the Company and its consolidated subsidiaries as of the dates thereof and the results of operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal year-end audit adjustments).

(e) The American Depositary Shares are listed on Nasdaq, and the Company has taken no action designed to, or that to its knowledge is likely to have the effect of, terminating the registration of the American Depositary Shares under the Exchange Act or delisting the American Depositary Shares from Nasdaq. As of the Execution Date, the Company has not received any notification that, and has no knowledge that, the SEC or Nasdaq is contemplating terminating such registration or listing.

2.6 Internal Controls; Disclosure Controls and Procedures. The Company maintains internal control over financial reporting as defined in Rule 13a-15(f) under the Exchange Act. The Company has implemented the "disclosure controls and procedures" (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) required in order for the principal executive officer and principal financial officer of the Company to engage in the review and evaluation process mandated by the Exchange Act, and is in compliance with such disclosure controls and procedures in all material respects. Each of the principal executive officer and the principal financial officer of the Company has made all certifications required by Sections 302 and 906 of the Sarbanes-Oxley Act of 2002 with respect to all reports, schedules, forms, statements and other documents required to be filed by the Company with the SEC.

2.7 Voting Rights.

(a) All of the Ordinary Shares are entitled to one (1) vote per share.

(b) Except as described or referred to in the SEC Documents, as of the Execution Date, there were not: (i) any outstanding equity securities, options, warrants, rights (including conversion or preemptive rights) or other agreements pursuant to which the Company is or may become obligated to issue, sell or repurchase any ordinary shares, ADSs or any other securities of the Company other than equity securities that may have been granted pursuant to its equity incentive plans, which plans are described in the SEC Documents; or (ii) any restrictions on the transfer of share capital of the Company other than pursuant to applicable U.K. or U.S. federal or state securities Laws or as set forth in this Agreement.

(c) The Company is not a party to or subject to any agreement or understanding relating to the voting of shares of or other securities of the Company or the giving of written consents by a shareholder or director of the Company.

2.8 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by the Company and the consummation by the Company of the transactions contemplated hereby (including the issuance of the Shares) will not (i) conflict with or result in a violation of any provision of the Company's Articles of Association, as in effect on the date hereof, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which the Company is a party, or (iii) subject to Section 2.8(b), result in a violation of any Law (including United States federal, state and U.K. securities Laws and regulations and regulations of any self-regulatory organizations) applicable to the Company, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as would not reasonably be expected to have, a Material Adverse Effect on the Company or result in a liability for Purchaser.

(b) The Company is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to issue and sell the Shares in accordance with the terms and conditions hereof other than such as have been made or obtained, and except for any post-closing filings required to be made under federal, national or state securities Laws.

2.9 Litigation. Other than as set forth in the SEC Documents filed prior to the Execution Date, there is no action, suit, proceeding or investigation pending (of which the Company has received notice or otherwise has knowledge) or, to the Company's knowledge, threatened, against the Company or that the Company intends to initiate, except where such action, suit, proceeding or investigation, as the case may be, and would not reasonably be expected to have a Material Adverse Effect.

2.10 Licenses and Other Rights; Compliance with Laws. The Company has all franchises, permits, licenses and other rights and privileges ("***Permits***") necessary to permit it to

own its properties and to conduct its business as presently conducted and is in compliance thereunder, except where the failure to be in compliance would not reasonably be expected to have a Material Adverse Effect. The Company has not taken any action that would interfere with its ability to renew all such Permit(s), except where the failure to renew such Permit(s) would not reasonably be expected to have, a Material Adverse Effect. The Company is and has been in compliance with all Laws applicable to its business, properties and assets, except where the failure to be in compliance has not had and would not reasonably be expected to have a Material Adverse Effect.

2.11 Intellectual Property.

(a) Other than as set forth in the SEC Documents filed prior to the Execution Date, the Intellectual Property that is owned by the Company or its subsidiaries is owned free from any Liens. All of the Company's material Intellectual Property Licenses are in full force and effect in accordance with their terms, are free of any Liens, and, to the Company's knowledge, neither the Company, nor any other party thereto, is in material breach of any such material Intellectual Property License. To the Company's knowledge, no event has occurred that with notice or lapse of time or both (i) would constitute a breach or default of any such material Intellectual Property License, (ii) would result in the termination thereof, or (iii) would cause or permit the acceleration or other change of any right or obligation or the loss of any benefit thereunder by the Company or its subsidiaries, except, in the case of each of clauses (i) through (iii), as would not reasonably be expected to have a Material Adverse Effect.

(b) Except as set forth in the SEC Documents, there is no legal claim or demand of any Person or any proceeding that is pending or threatened in writing, (i) challenging the right of the Company in respect of any Intellectual Property of the Company, or (ii) claiming that any default exists under any Intellectual Property License, except, in the case of clauses (i) and (ii) above, where any such claim, demand or proceeding has not had, and would notreasonably be expected to have, a Material Adverse Effect.

(c) Except as set forth in the SEC Documents: (i) the Company or one of its subsidiaries owns, free and clear of any Lien, or, to the Company's knowledge, has a valid license, or an enforceable right to use, as it is used or held for use, all U.S. and non-U.S. patents, trade secrets, know-how, trademarks, service marks, copyrights, and other proprietary and Intellectual Property rights, and all grants and applications with respect to the foregoing (collectively, the "***Proprietary Rights***") necessary for the conduct of the Company's business, except where the failure to own or have any of the foregoing would not reasonably be expected to have a Material Adverse Effect (such Proprietary Rights owned by or licensed to the Company collectively, the "***Company Rights***"); and (ii) the Company and its subsidiaries have taken reasonable measures to protect the Company Rights, consistent with prudent commercial practices in the biotechnology industry, except where failure to take such measures has not had, and would not reasonably be expected to have, a Material Adverse Effect.

2.12 Health Care Matters. The Company: (i) has operated and currently operates its business in compliance in all material respects with applicable provisions of the Health Care Laws (as defined below) of the Food and Drug Administration ("***FDA***"), the Department of Health and Human Services and any comparable state, foreign or other regulatory authority to which they are

subject (collectively, the "***Applicable Regulatory Authorities***") applicable to the ownership, testing, development, manufacture, packaging, processing, use, sale, promotion, distribution, storage, import, export or disposal of any of the Company's product candidates or any product manufactured or distributed by the Company; (ii) has not received any FDA Form 483, written notice of adverse finding, warning letter, untitled letter or other correspondence or written notice from any court or arbitrator or the Applicable Regulatory Authorities alleging or asserting non-compliance with any licenses, certificates, approvals, clearances, exemptions, authorizations, permits and supplements or amendments thereto required by any such Health Care Laws ("***Regulatory Authorizations***"); (iii) possesses all Regulatory Authorizations required to conduct its business as currently conducted and such Regulatory Authorizations are valid and in full force and effect and the Company is not in violation, in any material respect, of any term of any such Regulatory Authorizations; (iv) has not received notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any court or arbitrator or the Applicable Regulatory Authorities or any other third party alleging that any product operation or activity is in material violation of any Health Care Laws and has no knowledge that the Applicable Regulatory Authorities or any other third party is considering any such claim, litigation, arbitration, action, suit, investigation or proceeding; (v) has not received notice that any of the Applicable Regulatory Authorities has taken, is taking or intends to take action to limit, suspend, modify or revoke any material Regulatory Authorizations and has no knowledge that any of the Applicable Regulatory Authorities is considering such action; (vi) has filed, obtained, maintained or submitted all material reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Health Care Laws or Regulatory Authorizations and that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were materially complete and correct on the date filed (or were materially corrected or supplemented by a subsequent submission); (vii) is not a party to and does not have any ongoing reporting obligations pursuant to any corporate integrity agreements, deferred prosecution agreements, monitoring agreements, consent decrees, settlement orders, plans of correction or similar agreements with or imposed by any Applicable Regulatory Authority; and (viii) along with its employees, officers and directors, has not been excluded, disqualified, suspended or debarred from participation in any government health care program or human clinical research or, to the Company's knowledge, subject to a governmental inquiry, investigation, proceeding, or other similar action that could reasonably be expected to result in debarment, suspension, disqualification or exclusion.

2.13 Clinical Trials. None of the Company's product candidates has received marketing approval from any Applicable Regulatory Authority. All clinical and pre-clinical studies and trials conducted by or on behalf of or sponsored by the Company, or in which the Company has participated, with respect to the Company's product candidates, including any such studies and trials that are described in the SEC Documents, or the results of which are referred to in the SEC Documents, as applicable (collectively, "***Company Trials***"), were, and if still pending are, to the Company's knowledge, being conducted in all material respects in accordance with all applicable Health Care Laws of the Applicable Regulatory Authorities, including the FDA's current Good Clinical Practices and Good Laboratory Practices, standard medical and scientific research procedures and any applicable rules, regulations and policies of the jurisdiction in which such trials and studies are being conducted. The descriptions in the SEC Documents of the results of any Company Trials are accurate and complete descriptions in all material respects and fairly present the data derived therefrom as of the date of such SEC Documents. The Company has no

knowledge of any other studies or trials not described in the SEC Documents, the results of which are inconsistent with or call into question the results described or referred to in the SEC Documents. The Company has not received any written notices, correspondence or other communications from the Applicable Regulatory Authorities or any other governmental entity or any institutional review board ("***IRB***") or independent ethics committee ("***IEC***") requiring or threatening the termination, material modification or suspension of Company Trials, other than ordinary course communications with respect to modifications in connection with the design and implementation of such studies or trials, and, to the Company's knowledge, there are no reasonable grounds for the same. No investigational new drug application or comparable submission filed by or on behalf of the Company with the FDA has been terminated or suspended by the FDA or any other Applicable Regulatory Authority. The Company has obtained (or caused to be obtained) informed consent by or on behalf of each human subject who participated in a Company Trial, and the Company has obtained (or caused to be obtained) applicable IRB or IEC approvals for each Company Trial. To the Company's knowledge, none of the Company Trials involved any investigator who has been disqualified as a clinical investigator or has been found by the FDA to have engaged in scientific misconduct.

2.14 Absence of Certain Changes.

(a) Except as disclosed in the SEC Documents filed prior to the Execution Date, since March 31, 2021, no change or event has occurred, except where such change or event has not had, and would not reasonably be expected to have, a Material Adverse Effect on the Company.

(b) Except as set forth in the SEC Documents filed prior to the Execution Date or as contemplated by this Agreement or the Collaboration Agreement, since March 31, 2021 the Company has not (i) declared or paid any dividends, or authorized or made any distribution upon or with respect to any class or series of its share capital, or (ii) sold, exchanged or otherwise disposed of any of its material assets or rights.

(c) Since March 31, 2021, the Company has not admitted in writing its inability to pay its debts generally as they become due, filed or consented to the filing against it of a petition in bankruptcy or a petition to take advantage of any insolvency act, made an assignment for the benefit of creditors, consented to the appointment of a receiver for itself or for the whole or any substantial part of its property, or had a petition in bankruptcy filed against it, been adjudicated a bankrupt, or filed a petition or answer seeking reorganization or arrangement under the federal bankruptcy Laws or any other Laws of the United States or any other jurisdiction.

2.15 Not an Investment Company. The Company is not, and after receipt of the Purchase Price, will not be, an "investment company" as defined in the Investment Company Act of 1940, as amended.

2.16 Critical Technology. The Company does not produce, design, test, manufacture, fabricate, or develop one or more "critical technologies" within the meaning of the Defense Production Act of 1950, as amended, including all implementing regulations thereof.

2.17 No Integration. The Company has not, directly or through any agent, sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in

the Securities Act) that is or will be integrated with the Shares sold pursuant to this Agreement in a manner that would require the registration of the Shares under the Securities Act.

SECTION 3. REPRESENTATIONS AND WARRANTIES OF PURCHASER

Except as otherwise specifically contemplated by this Agreement, Purchaser hereby represents and warrants to the Company that:

3.1 Authorization; Enforcement. Purchaser has the requisite corporate or other similar power and authority to enter into this Agreement and to consummate the transactions contemplated hereby. Purchaser has taken all necessary corporate or other similar action to authorize the execution, delivery and performance of this Agreement. Upon the execution and delivery of this Agreement, this Agreement will constitute a valid and binding obligation of Purchaser enforceable against Purchaser in accordance with its terms and conditions, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

3.2 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Purchaser and the consummation by Purchaser of the transactions contemplated hereby (including the purchase of the Shares) will not (i) conflict with or result in a violation of any provision of Purchaser's memorandum and articles of association or equivalent organizational documents, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which Purchaser is a party, or (iii) result in a violation of any Law (including U.S. federal and state securities Laws and regulations and regulations of any self-regulatory organizations) applicable to Purchaser, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as have not had, and would not reasonably be expected to have, a Material Adverse Effect on Purchaser or result in a liability for the Company.

(b) Purchaser is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to purchase the Shares in accordance with the terms and conditions hereof, other than such as have been made or obtained, except if and to the extent applicable for compliance with any requirements of the HSR Act and any other antitrust Law.

3.3 Investment Purpose. Purchaser is purchasing the Shares for its own account and not with a present view toward the public distribution thereof and has no arrangement or understanding with any other Persons regarding the distribution of such Shares except as would not result in a violation of the Securities Act. Without limiting Section 5.1 and Section 5.2, Purchaser will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) any of the Shares except in accordance with the Securities Act.

3.4 Reliance on Exemptions. Purchaser understands that the Company intends for the Shares to be offered and sold to it in reliance upon specific exemptions from the registration requirements of United States federal and state securities Laws and that the Company is relying upon the truth and accuracy of, and Purchaser's compliance with, the representations, warranties, agreements, acknowledgments and understandings of Purchaser set forth herein in order to determine the availability of such exemptions and the eligibility of Purchaser to acquire the Shares.

3.5 Accredited Investor; Access to Information. Purchaser is an "accredited investor" as defined in Regulation D under the Securities Act and is knowledgeable, sophisticated and experienced in making, and is qualified to make, decisions with respect to investments in shares presenting an investment decision like that involved in the purchase of the Shares. Purchaser has been furnished with materials relating to the offer and sale of the Shares that have been requested by Purchaser, including the SEC Documents, and Purchaser has had the opportunity to review the SEC Documents. Purchaser has been afforded the opportunity to ask questions of the Company. Neither such inquiries nor any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

3.6 Restricted Securities. Purchaser understands that the Shares will be characterized as "restricted securities" under the U.S. federal securities Laws inasmuch as they are being acquired from the Company in a private placement under Section 4(a)(2) of the Securities Act and that under such Laws and applicable regulations such Shares may be resold without registration under the Securities Act only in certain limited circumstances.

3.7 Governmental Review. Purchaser understands that no U.S. federal or state or U.K. agency or any other Governmental Authority has passed upon or made any recommendation or endorsement of the Shares or an investment therein.

SECTION 4. STANDSTILL AGREEMENT

4.1 During the period commencing on the date of this Agreement (the "***Standstill Commencement Date***") and ending on the 18-month anniversary of the Standstill Commencement Date (the "Standstill Period"), neither Purchaser, any of Purchaser's controlled Affiliates nor any of Purchaser's representatives acting on behalf of or in concert with Purchaser will, in any manner, directly or indirectly:

(a) make, effect, initiate, cause or participate in (i) any acquisition of beneficial ownership of any securities of the Company or any securities (including derivatives thereof) of any subsidiary or other controlled Affiliate of the Company, (ii) any acquisition of all or a material portion of the assets of the Company and its subsidiaries on a consolidated basis or (iii) any tender offer, exchange offer, merger, business combination, recapitalization, restructuring, liquidation, dissolution or extraordinary transaction involving the Company or any subsidiary or other controlled Affiliate of the Company or involving any securities or assets of the Company or any securities or assets of any subsidiary, division or other affiliate of the Company (provided that the Purchaser may tender its shares in any tender or exchange offer made by any third party provided that Ionis is not in breach of or won't be in breach of this Section 4.1 of this Agreement), or (iv)

any "solicitation" of "proxies" (as those terms are used in the proxy rules of the SEC) or consents with respect to any securities of the Company;

(b) form, join or in any way participate in a "*group*" (as defined under the Exchange Act) with respect to the beneficial ownership of any securities of the Company or any subsidiary or division of the Company;

(c) otherwise act, alone or in concert with others, to seek to control or influence the management, Board or policies of the Company (other than such policies as may be within the scope of the Collaboration Agreement (including any amendments thereto));

(d) take any action that would reasonably be expected to require the Company to make a public announcement regarding any of the types of matters set forth in clause (a) above; or

(e) agree or offer to take, or knowingly encourage or propose (publicly or otherwise) the taking of, any action referred to in clauses (a), (b), (c), or (d) above;

(f) assist, induce or encourage any other Person to take any action of the type referred to in clauses (a), (b), (c), (d) or (e) above (provided that the Purchaser shall not be deemed to be in violation of this clause (f) unless the Person providing such assistance, inducement or encouragement knew or reasonably should have known at the time he or she did so that doing so violated this clause (f), or knew or reasonably should have known after such time and did not attempt to halt such actions); or

(g) enter into any discussions, negotiations, arrangement or agreement with any other Person with the intent to effect any of the foregoing (provided that the Purchaser shall not be deemed to be in violation of this clause (g) with respect to discussions or negotiations unless the Person entering into such discussions or negotiations knew or reasonably should have known at the time he or she did so that doing so violated this clause (g) or knew or reasonably should have known after such time and did not attempt to halt such actions.

4.2 Purchaser also agrees during the Standstill Period not to request the Company (or its representatives), directly or indirectly, amend or waive any provision of this Section 44 other than by means of a confidential communication to the Company's Chairman of the Board or the Company's Chief Executive Officer.

4.3 Purchaser represents and warrants that, as of the Execution Date, neither Purchaser nor any of its Affiliates owns, of record or beneficially, any voting securities of the Company, or any securities convertible into or exercisable for any voting securities of the Company.

4.4 Notwithstanding the provisions set forth in Sections 4.1 and 4.2 (the "***Standstill Provisions***"), Purchaser shall immediately, and without any other action by the Company, be released from its obligations under the Standstill Provisions if: (a) the Company enters into a definitive written agreement with any Person other than the Purchaser (or any of its Affiliates) to consummate a merger, consolidation or similar transaction pursuant to which (i) any Person other than the Purchaser (or any of its Affiliates) will acquire 50% or more of the outstanding voting shares of the Company or (ii) the Company and its subsidiaries will sell to any Person

other than the Purchaser (or any of its Affiliates) all or substantially all of the consolidated assets of the Company and its consolidated subsidiaries ((i) or (ii), a "***Company Sale***"), (ii) a Third Party makes a tender or exchange offer for securities of the Company and the Board either accepts such offer or fails to recommend that its shareholders reject such offer within 10 Business Days from the date of commencement of such offer, or (iii) the Company publicly announces that its Board is engaging in a formal process that is intended to result in a transaction that if consummated would constitute a Company Sale.

4.5 Notwithstanding any other provision of this Agreement to the contrary, nothing in this Agreement will be deemed to prohibit a party from confidentially communicating to the other party's board of directors or senior management or external financial advisors any non-public proposals regarding a possible transaction of any kind in such a manner as would not reasonably be expected to require public disclosure thereof under applicable Law or listing standards of any securities exchange, including Nasdaq.

SECTION 5. TRANSFER, RESALE, LEGENDS, DEPOSIT FOR AMERICAN DEPOSITARY SHARES

5.1 Transfer or Resale. Purchaser understands that:

(a) the Shares have not been and are not being registered under the Securities Act or any applicable state securities Laws and, consequently, Purchaser may have to bear the risk of owning the Shares for an indefinite period of time because the Shares may not be transferred unless (i) the resale of the Shares is registered pursuant to an effective registration statement under the Securities Act; (ii) Purchaser has delivered to the Company an opinion of counsel (in form, substance and scope customary for opinions of counsel in comparable transactions) to the effect that the Shares to be sold or transferred may be sold or transferred pursuant to an exemption from such registration; or (iii) the Shares are sold or transferred pursuant to Rule 144 under the Securities Act ("***Rule 144***"); and

(b) any sale of the Shares made in reliance on Rule 144 may be made only in accordance with the terms of Rule 144 and, if Rule 144 is not applicable, any resale of the Shares under circumstances in which the seller (or the Person through whom the sale is made) may be deemed to be an underwriter (as that term is defined in the Securities Act) may require compliance with some other exemption under the Securities Act or the rules and regulations of the SEC thereunder.

5.2 Lock-Up. Purchaser agrees that it will hold and will not sell any of the Shares (or otherwise make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale of the Shares) until the earlier of (i) the one-year anniversary of the Closing Date, and (ii) the termination of the Collaboration Agreement, provided that in the event the termination occurs less than six months after the Closing Date, the Purchaser shall hold and will not sell or otherwise enter into a transaction regarding the Shares until at least the date that is six months after the Closing Date. Notwithstanding the foregoing, this Section 5.2 will not preclude (i) distributions of Shares to general or limited partners, members, shareholders, Affiliates or wholly-owned subsidiaries of Purchaser or any investment fund or other entity controlled or managed by Purchaser; *provided*, in each case, that

following any such transfer such Shares will remain subject to the provisions of this Section 5.2; or (ii) transfers pursuant to a *bona fide* third party tender offer for all outstanding Ordinary Shares, merger, consolidation or other similar transaction made to all holders of the Company's securities involving a change of control of the Company (including the entering into any lock-up, voting or similar agreement pursuant to which Purchaser may agree to transfer, sell, tender or otherwise dispose of Shares or other such securities in connection with such transaction, or vote any Shares or other such securities in favor of any such transaction); *provided*, that in the event that such tender offer, merger, consolidation or other such transaction is not completed, the Shares shall remain subject to the provisions of this Section 5.2.

5.3 Legends. Purchaser understands the Shares will bear restrictive legends in substantially the following form (and a stop-transfer order may be placed against transfer of the Shares):

THE SHARES HAVE NOT BEEN REGISTERED UNDER THE U.S. SECURITIES ACT OF 1933, AS AMENDED, OR ANY APPLICABLE STATE SECURITIES LAWS. THEY MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED OR HYPOTHECATED UNLESS (I) THE SHARES ARE REGISTERED PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT; (II) AN OPINION OF COUNSEL HAS BEEN DELIVERED (IN FORM, SUBSTANCE AND SCOPE CUSTOMARY FOR OPINIONS OF COUNSEL IN COMPARABLE TRANSACTIONS) TO THE EFFECT THAT THE SHARES TO BE SOLD OR TRANSFERRED MAY BE SOLD OR TRANSFERRED PURSUANT TO AN EXEMPTION FROM SUCH REGISTRATION; OR (III) THE SHARES ARE SOLD OR TRANSFERRED PURSUANT TO RULE 144 UNDER THE SECURITIES ACT.

THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THESE SECURITIES IS SUBJECT TO THE TERMS AND CONDITIONS OF A SHARE PURCHASE AGREEMENT DATED JULY 9, 2021 BETWEEN BICYCLE THERAPEUTICS PLC AND IONIS PHARMACEUTICALS, INC.

If such Shares may be transferred pursuant to Section 5.2 (excluding transfers pursuant to Section 5.2(i)), Purchaser may request that the Company remove, and the Company agrees to authorize and instruct (including by causing any required legal opinion to be provided) the removal of any legend from the Shares, if permitted by applicable securities Law, within two (2) Business Days of any such request; *provided*, *however*, that each party will be responsible for any fees it incurs in connection with such request and removal.

5.4 Deposit of Shares and Issuance of American Depositary Shares. Upon the written request of the Purchaser to the Company, and in accordance with the other limitations of this Agreement, the Company will deposit or cause to be deposited such number of Shares with the Depositary as is requested by the Purchaser, and issue or cause to be issued to the Purchaser the corresponding American Depositary Shares, with any and all costs associated with such deposit and issuance paid for by the Purchaser. The Company shall (a) use its reasonable best efforts to (i) register or qualify its American Depositary Shares under the securities or blue sky Laws of such jurisdictions in the United States as the Purchaser reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable the Purchaser to consummate the disposition in such jurisdictions of the American Depositary Shares

owned by the Purchaser in accordance with Rule 144 or some other exemption under the Securities Act or the rules and regulations of the SEC thereunder, provided that the Company shall not be required to register the Shares or any American Depositary Shares held by the Purchaser on a Registration Statement on Form S-1 or Registration Statement on Form S-3 and (ii) cause all such American Depositary Shares to be eligible and remain eligible for registration of the American Depositary Shares pursuant to Form F-6, and (b) cooperate with the Purchaser and the Depositary to facilitate the timely delivery of American Depositary Shares (in book entry or certificated form), which American Depositary Shares shall be free of all restrictive legends unless the Company reasonably determines on advice from legal counsel that such legends are required by applicable law (it being understood that the American Depositary Shares may be restricted American Depositary Shares subject to restrictions imposed by the Depositary if and for so long as the Purchaser is an Affiliate of the Company).

5.5 Rule 144 Reporting. With a view to making available to Purchaser the benefits of certain rules and regulations of the SEC that may permit the sale of registrable securities to the public without registration, the Company agrees to use its best efforts to:

(a) Make and keep public information available, as those terms are understood and defined in Rule 144 or any similar or analogous rule promulgated under the Securities Act, at all times after the effective date of the first registration filed by the Company for an offering of its securities to the general public;

(b) File with the SEC, in a timely manner, all reports and other documents required of the Company under the Exchange Act; and

(c) So long as Purchaser owns Shares, furnish to Purchaser upon request: a written statement by the Company as to its compliance with the reporting requirements of said Rule 144 of the Securities Act, and of the Exchange Act; a copy of the most recent annual or quarterly report of the Company filed with the Commission; and such other reports and documents as Purchaser may reasonably request in connection with availing itself of any rule or regulation of the SEC allowing it to sell any such securities without registration.

SECTION 6. CONDITIONS TO CLOSING

6.1 Conditions to Obligations of the Company. The Company's obligation to complete the purchase and sale of the Shares and deliver the Shares to Purchaser is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Receipt of Funds. The Company will have received immediately available funds in the full amount of the Purchase Price for the Shares being purchased hereunder.

(b) Representations and Warranties. The representations and warranties made by Purchaser in Section 3 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(c) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by Purchaser on or prior to the Closing Date shall have been performed or complied with in all material respects.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) No Governmental Prohibition. The sale of the Shares by the Company and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(f) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(ii) shall have been delivered by Purchaser to the Company.

6.2 Conditions to Purchaser's Obligations at the Closing. Purchaser's obligation to complete the purchase and sale of the Shares is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Representations and Warranties. The representations and warranties made by the Company in Section 2 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(b) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by the Company on or prior to the Closing Date shall have been performed or complied with in all material respects.

(c) Transfer Agent Instructions. The Company will have delivered to its transfer agent and registrar irrevocable written instructions to issue the Shares to Purchaser in a form and substance acceptable to such transfer agent.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(f) No Governmental Prohibition. The sale of the Shares by the Company, and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(i) shall have been delivered by the Company to Purchaser.

SECTION 7. INDEMNIFICATION

7.1 Indemnification by the Company. The Company shall indemnify and hold harmless Purchaser and its Affiliates, and the directors, officers, employees and other agents and representatives of Purchaser and its Affiliates, from and against any and all liabilities, judgments, claims, settlements, losses, damages, fees, Liens, Taxes, penalties, obligations and expenses (including reasonable attorney's fees and expenses and costs and expenses of investigation) (collectively, "***Losses***") incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of the Company contained in this Agreement or any certificate delivered by the Company or on its behalf hereunder; and (b) the non-fulfillment or breach by the Company of any agreements or obligations under this Agreement.

7.2 Indemnification by Purchaser. Purchaser shall indemnify and hold harmless the Company and its Affiliates, and the directors, officers, employees and other agents and representatives of the Company and its Affiliates, from and against any and all Losses incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of Purchaser contained in this Agreement or any certificate delivered by the Purchaser or on its behalf hereunder; and (b) the non-fulfillment or breach by Purchaser of any agreements or obligations under this Agreement.

7.3 Calculation of Losses. Any indemnity payment hereunder shall be treated as an adjustment to the Purchase Price to the extent permitted by applicable Law. Where the receipt of any such payment is treated for Tax purposes in a manner other than as an adjustment to the Purchase Price, the amount of the payment shall be adjusted to take account of any net Tax cost actually incurred, or benefit actually enjoyed, by the Indemnified Party in respect thereof.

7.4 Certain Procedures for Indemnification.

(a) If any Person entitled to indemnification under this Agreement (an "***Indemnified Party***") asserts a claim for indemnification, or receives notice of the assertion of any claim or of the commencement of any action by any Person not a party to this Agreement against such Indemnified Party, for which a party to this Agreement is required to provide indemnification under this Section 7 (an "***Indemnifying Party***"), the Indemnified Party shall promptly notify the Indemnifying Party in writing of the claim or the commencement of that action; *provided, however*, that the failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party from any liability which it may have to the Indemnified Party, except to the extent that such failure materially prejudices the Indemnifying Party's ability to defend such action.

(b) With respect to third party claims for which indemnification is claimed hereunder, (i) the Indemnifying Party shall be entitled to participate in the defense of any such

claim, and (ii) if, in the reasonable judgment of the Indemnified Party, such claim can properly be resolved by money damages alone and the Indemnifying Party has the financial resources to pay such damages, and the Indemnifying Party admits that this indemnity fully covers the claim or litigation, then the Indemnifying Party shall be entitled (y) to direct the defense of any claim at its sole cost and expense, but such defense shall be conducted by legal counsel reasonably satisfactory to the Indemnified Party, and (z) to settle and compromise any such claim or action for money damages alone; *provided*, *however*, that if the Indemnified Party has elected to be represented by separate counsel pursuant to the proviso below, or if such settlement or compromise does not include an unconditional release of the Indemnified Party for any liability arising out of such claim or action, such settlement or compromise shall be effected only with the written consent of the Indemnified Party. After notice from the Indemnifying Party to the Indemnified Party of its election to assume the defense of such claim or action, the Indemnifying Party shall not be liable to the Indemnified Party under this Section 7.4 for any legal or other expenses subsequently incurred by the Indemnified Party in connection with the defense thereof other than reasonable costs of investigation or of assistance as contemplated by this Section 7.4; *provided*, *however*, that if, in the opinion of the Indemnified Party, it is advisable for the Indemnified Party to be represented by separate counsel due to actual or potential conflicts of interest, the Indemnified Party shall have the right to employ counsel to represent it and in that event the fees and expenses of such separate counsel shall be paid by the Indemnifying Party; *provided further*, that in no event shall the Indemnifying Party be responsible for the fees of more than one counsel to the Indemnified Party. The Indemnified Party and the Indemnifying Party shall each render to each other such assistance as may reasonably be requested in order to ensure the proper and adequate defense of any such claim or proceeding.

7.5 Survival; Expiration.

(a) Notwithstanding any investigation made by or on behalf of the Company or Purchaser prior to, on or after the Closing Date, the representations and warranties contained in this Agreement (including the exhibits and schedules hereto) and any certificate delivered hereunder shall survive the Closing and shall terminate on the second anniversary of the Closing Date.

(b) The covenants of the parties hereto shall survive until fully performed and discharged, unless otherwise expressly provided herein.

(c) Any right of indemnification or reimbursement pursuant to this Section 7 with respect to a claimed breach, inaccuracy or non-fulfillment of any representation, warranty, agreement or obligation shall expire on the applicable date of termination of the representation, warranty or covenant claimed to be breached (the "***Expiration Date***"), unless on or prior to the applicable Expiration Date, the Indemnifying Party has received written notice from the Indemnified Party of such breach, inaccuracy or non-fulfillment from the Indemnified Party or is based on fraud or intentional or willful breach of the Indemnifying Party, in which case the Indemnified Party may continue to pursue its right of indemnification or reimbursement hereunder beyond the Expiration Date of the applicable representation, warranty, agreement or obligation. For the avoidance of doubt, no claims based on fraud or intentional or willful breach will be subject to any of the limitations set forth in this Section 7.5.

SECTION 8. DISPUTE RESOLUTION

8.1 (a) If the parties cannot amicably resolve any dispute (a "***Dispute***") arising under this Agreement, then a party seeking further resolution of such Dispute shall submit such Dispute to final and binding arbitration conducted in accordance with the terms of this Section 8.1. The party initiating arbitration will give written notice to that effect to the other party. The legal seat of arbitration will be New York City, New York, U.S., and the arbitration will be administered by JAMS according to the JAMS International Arbitration Rules applicable at the time of commencement of the arbitration except as otherwise provided herein and applying the substantive law specified in Section 10.1. The arbitration will be conducted by a single arbitrator appointed in accordance with the Rules, provided that such arbitrator must have significant business or legal experience in the pharmaceutical industry and the applicable law concerning the subject matter of the dispute. In any case, the arbitrator will not be an Affiliate, employee, consultant, officer, director, shareholder or stockholder of either party, or otherwise have any current or previous relationship with either party or their respective Affiliates. After conducting any hearing and taking any evidence deemed appropriate for consideration, the arbitrator will render a written opinion within 30 days after the final arbitration hearing. The arbitrator's decision will include findings of fact and conclusions of law. The determination of the arbitrator as to the resolution of any Dispute will be binding and conclusive on the parties. Judgment on the award so rendered may be entered in any court of competent jurisdiction, and the parties undertake to carry out any award without delay. Nothing contained herein will be construed to permit the arbitrator to award punitive, exemplary, or any similar damages and any arbitral award that purports to award such damages is expressly prohibited and void *ab initio*. Each party will bear its own attorneys' fees, costs and disbursements arising out of the arbitration and will pay an equal share of the fees and costs of the arbitrator. Except to the extent necessary to confirm, enforce, or challenge an award of the arbitration, to protect or pursue a legal right, or as otherwise required by applicable law or regulation, no party nor the arbitrator may disclose the existence, content, or results of an arbitration under this Section 8.1 without the express, prior written consent of each of the parties. In no event shall any party initiate arbitration after the date when commencement of a legal or equitable proceeding based on the Dispute, controversy, or claim would be barred by the applicable New York statute of limitations. Any Disputes concerning the propriety of the commencement of the arbitration, or the validity or application of this Section 8.1, shall be finally settled by the arbitrator. Nothing in this Section 8.1 shall preclude either party from (a) seeking interim or provisional relief, including a temporary restraining order, preliminary injunction, or other interim equitable relief concerning a dispute in any court of competent jurisdiction, before or after the initiation of an arbitration as set forth in this Section 8.1, if necessary to protect the interests of such party, or (b) bringing an action in any court of competent jurisdiction to resolve a dispute regarding the intellectual property rights hereunder, and this sentence shall be specifically enforceable.

(b) For the avoidance of doubt, any disputes with respect to the terms of the Collaboration Agreement shall be resolved in accordance with the dispute resolution provisions therein, and shall not be subject to the provisions of this Section 8.

SECTION 9. TERMINATION

9.1 Ability to Terminate. This Agreement may be terminated prior to the Closing:

(a) at any time by mutual written consent of the Company and Purchaser;

(b) by the Company, upon three (3) days' written notice to Purchaser, so long as the Company is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.1, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of Purchaser set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of Purchaser shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.1 could not be satisfied by the Termination Date;

(c) by Purchaser, upon three (3) days' written notice to the Company, so long as Purchaser is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.2 of this Agreement, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of the Company set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of the Company shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.2 of this Agreement could not be satisfied by the Termination Date;

(d) by either the Company or Purchaser, upon written notice to the other, if the Closing has not occurred on or before July 23, 2021 (the "***Termination Date***").

9.2 Effect of Termination. In the event of the termination of this Agreement pursuant to Section 9, (a) this Agreement (except for this Section 9.2, and Section 7, Section 8, Section 10.1 and Sections 10.3 through 10.14 and any definitions set forth in this Agreement and used in such Sections) shall forthwith become void and have no effect, without any liability on the part of any party hereto or its Affiliates, and (b) any and all filings, applications and other submissions made pursuant to this Agreement, to the extent practicable, shall be withdrawn from the agency or other Person to which they were made or appropriately amended to reflect the termination of the transactions contemplated hereby; *provided*, *however*, that nothing contained in this Section 9.2 shall relieve any party from liability for fraud or any intentional or willful breach of this Agreement.

SECTION 10. GOVERNING LAW; MISCELLANEOUS

10.1 Governing Law. This Agreement will be governed by and interpreted in accordance with the laws of the State of New York without regard to the principles of conflict of laws that would require the application of the substantive Laws of another jurisdiction.

10.2 Market Listing. From the Execution Date through the Closing, the Company shall use commercially reasonable efforts to maintain the listing and trading of the Company's American Depositary Shares on Nasdaq.

10.3 Counterparts; Electronic Signatures. This Agreement may be executed and delivered (including by facsimile transmission or PDF or any other electronically transmitted signatures) in two counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

10.4 Headings. The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

10.5 Rules of Construction.

(a) For purposes of this Agreement, whenever the context requires: the singular number shall include the plural, and vice versa; the masculine gender shall include the feminine and neuter genders; the feminine gender shall include the masculine and neuter genders; and the neuter gender shall include the masculine and feminine genders.

(b) As used in this Agreement, (i) the words "include" and "including," and variations thereof, shall not be deemed to be terms of limitation, but rather shall be deemed to be followed by the words "without limitation", (ii) the words "hereby," "herein," "hereunder" and "hereto" shall be deemed to refer to this Agreement in its entirety and not to any specific section of this Agreement and (iii) "or" has the inclusive meaning represented by the phrase "and/or".

(c) Except as otherwise indicated, all references in this Agreement to "Sections" and "Appendices" are intended to refer to Sections of this Agreement, as appropriate, and Appendices to this Agreement.

(d) As used in this Agreement, the term "days" means calendar days unless otherwise specified. When calculating the period of time before which, within which or following which any act is to be done or step taken pursuant to this Agreement, the date that is the reference date in calculating such period shall be excluded. If the last day of such period is a non-Business Day, the period in question shall end on the next succeeding Business Day.

(e) Unless otherwise indicated, all monetary amounts herein are in United States dollars.

10.6 Severability. If any provision of this Agreement should be held invalid, illegal or unenforceable in any jurisdiction, the parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

10.7 Entire Agreement; Amendments. This Agreement, the Option Agreement, and the Collaboration Agreement (including any schedules, appendices and exhibits hereto or thereto and any certificates delivered hereunder) constitute the entire agreement between the parties hereto with respect to the subject matter hereof and thereof. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein or therein. This Agreement supersedes all prior agreements and understandings between the parties hereto with respect to the subject matter hereof. No provision of this Agreement may be waived or amended other than by an instrument in writing signed by the party to be charged with enforcement. Any amendment or waiver effected in accordance with this Section 10.7 shall be binding upon Purchaser and the Company.

10.8 Notices. All notices required or permitted hereunder will be in writing and will be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed email if sent during normal business hours of the recipient, if not, then on the next Business Day, or (c) one Business Day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. The addresses for such communications are:

If to the Company, to:

Bicycle Therapeutics plc
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: General Counsel
Email:

with a copy (which shall not constitute notice) to:

Cooley LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
Attention: Laura Berezin
E-mail:

If to the Purchaser, to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Financial Officer
Email:

With a copy (which shall not constitute notice) to:

Attention: General Counsel
Email:

10.9 Successors and Assigns. This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. The Company will not assign this Agreement or any rights or obligations hereunder without the prior written consent of Purchaser, and Purchaser will not assign this Agreement or any rights or obligations hereunder without the prior written consent of the Company.

10.10 Third Party Beneficiaries. This Agreement is intended for the benefit of the parties hereto, their respective permitted successors and assigns, and is not for the benefit of, nor may any provision hereof be enforced by, any other Person.

10.11 Further Assurances. Each party will do and perform, or cause to be done and performed, all such further acts and things, and will execute and deliver all other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

10.12 No Strict Construction. The language used in this Agreement is deemed to be the language chosen by the parties to express their mutual intent, and no rules of strict construction will be applied against a party.

10.13 Equitable Relief. The Company recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to Purchaser. The Company therefore agrees that Purchaser is entitled to seek temporary and permanent injunctive relief or specific performance in any such case. Purchaser also recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to the Company. Purchaser therefore agrees that the Company is entitled to seek temporary and permanent injunctive relief or specific performance in any such case.

10.14 Expenses. The Company and Purchaser are each liable for, and will pay, their own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement, including attorneys' and consultants' fees and expenses.

10.15 Public Disclosure. On or shortly after the Effective Date, the Company and Purchaser shall issue a joint press release in a form mutually agreed to by the Company and Purchaser. In addition, the Company shall file a Current Report on Form 8-K with the SEC within the time period required by such form and including such disclosures as required by such form with respect to this Agreement and the transactions contemplated herein, such Current Report on Form 8-K to be in a form mutually agreed to by the Company and Purchaser. No other written release, public announcement, disclosure or filing concerning the purchase of the Shares, this Agreement or the transactions contemplated hereby or thereby shall be issued, filed or furnished, as the case may be, by any party without the prior written consent of the other party (which consent shall not be unreasonably withheld, conditioned or delayed) and, except as set forth in this Section 10.15, the parties agree to keep the terms of this Agreement confidential. Notwithstanding the foregoing, the parties acknowledge and agree that applicable Law or the requirements of a national securities exchange or another similar regulatory body may require either party to file or otherwise disclose a copy of this Agreement. The party required to make such filing or otherwise disclose shall notify the other party and shall, to the extent possible, provide the other party with at least five (5) Business Days to request redactions thereof prior to making such filing or disclosure. The disclosing party shall use commercially reasonable efforts to procure confidential treatment of such proposed redactions pursuant to the Securities Act and the Exchange Act, in each case as amended, and the rules, regulations and guidelines promulgated thereunder, or any other applicable Law or the rules, regulations or guidelines promulgated hereunder; *provided* that the foregoing shall not prevent the party from making such public disclosures as it must make to comply with applicable Law.

[Remainder of page intentionally left blank.]

IN WITNESS WHEREOF, Purchaser and the Company have caused this Agreement to be duly executed as of the date first above written.

COMPANY:

BICYCLE THERAPEUTICS PLC

By: /s/ Kevin Lee

Name: Kevin Lee

Title: Chief Executive Officer, Director

PURCHASER:

IONIS PHARMACEUTICALS, INC.

By: /s/ Brett Monia

Name: Brett Monia

Title: Chief Executive Officer

APPENDIX 1

DEFINED TERMS

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity that directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with it. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities, capital stock or share capital (or such lesser percentage that is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the preamble.

"***American Depositary Shares***" shall mean shares issued by the Depositary pursuant to the Deposit Agreement, each representing one Ordinary Share.

"***Applicable Regulatory Authorities***" has the meaning set forth in Section 2.12.

"***BicycleTx***" has the meaning set forth in the recitals.

"***Board***" means the board of directors of the Company.

"***Business Day***" means a day Monday through Friday on which banks are generally open for business in the State of California, the State of New York and London, England.

"***Change of Control Transaction***" has the meaning set forth in Section 5.2.

"***Closing***" has the meaning set forth in Section 1.3(a).

"***Closing Cash***" has the meaning set forth in Section 1.3(a).

"***Closing Date***" means the date on which the Closing actually occurs.

"***Collaboration Agreement***" has the meaning set forth in the recitals.

"***Company Rights***" has the meaning set forth in Section 2.11(c).

"***Company Sale***" has the meaning set forth in Section 4.4.

"***Company Trials***" has the meaning set forth in Section 2.13.

"***Cross-Receipt***" has the meaning set forth in Section 1.3(b)(i)A).

"***Deposit Agreement***" means the Deposit Agreement, dated as May 28, 2019, as amended from time to time, among the Company, the Depositary, and holders from time to time of the American Depositary Shares.

"***Depositary***" means mean Citibank, N.A.

"***Dispute***" has the meaning set forth in Section 8.1.

"***DOJ***" means the U.S. Department of Justice.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC thereunder.

"***Execution Date***" has the meaning set forth in the preamble.

"***Expiration Date***" has the meaning set forth in Section 7.5(c).

"***FDA***" has the meaning set forth in Section 2.12.

"***FTC***" means the U.S. Federal Trade Commission.

"***GAAP***" means generally accepted accounting principles in the United States of America.

"Good Clinical Practices" means the legal, scientific and ethical standards for the performance of clinical research on medicinal products involving humans, including as reflected in the regulations of the FDA at 21 C.F.R. parts 50, 54, 56, and 312.

"Good Laboratory Practices" means the legal, scientific and ethical standards for the performance of nonclinical laboratory studies, including as set out in the regulations of the FDA at 21 C.F.R. part 58.

"***Governmental Authority***" means any federal, state, provincial, local, municipal, foreign or other governmental or quasi-governmental authority, including any arbitrator and applicable securities exchanges, or any department, minister, agency, commission, commissioner, board, subdivision, bureau, agency, instrumentality, court or other tribunal of any of the foregoing.

"***Health Care Laws***" means Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395-1395lll (the Medicare statute); Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396w-5 (the Medicaid statute); the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b); the civil False Claims Act, 31 U.S.C. §§ 3729 et seq.; the criminal False Claims Act 42 U.S.C. 1320a-7b(a); any other criminal laws relating to health care fraud and abuse, including but not limited to 18 U.S.C. Sections 286 and 287 and the health care fraud criminal provisions under the Health Insurance Portability and Accountability Act of 1996, 42 U.S.C. §§ 1320d et seq., ("***HIPAA***"); the Civil Monetary Penalties Law, 42 U.S.C. §§ 1320a-7a; the Physician Payments Sunshine Act, 42 U.S.C. § 1320a-7h; the Exclusion Laws, 42 U.S.C. § 1320a-7; HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, 42 U.S.C. §§ 17921 et seq.; the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 et seq.; the Public Health Service Act, 42 U.S.C. §§ 201 et seq.; the regulations promulgated pursuant to such laws; and any similar federal, state and local laws and regulations, each and all as may be amended from time to time.

"***HIPAA***" has the meaning set forth in the definition of "Health Care Laws."

"***IEC***" has the meaning set forth in Section 2.13.

"***Indemnified Party***" has the meaning set forth in Section 7.4(a).

"***Indemnifying Party***" has the meaning set forth in Section 7.4(a).

"***Intellectual Property***" shall mean trademarks, trade names, trade dress, service marks, copyrights, and similar rights (including registrations and applications to register or renew the registration of any of the foregoing), patents and patent applications, trade secrets, and any other similar intellectual property rights.

"***Intellectual Property License***" shall mean any license, permit, authorization, approval, contract or consent granted, issued by or with any Person relating to the use of Intellectual Property.

"***IRB***" has the meaning set forth in Section 2.13.

"***Law***" means any federal, state, local or foreign constitution, treaty, law, statute, ordinance, rule, regulation, interpretation, directive, policy, order, writ, decree, injunction, judgment, stay or restraining order of any Governmental Authority, the terms of any permit, and any other ruling or decision of, agreement with or by, or any other requirement of, any Governmental Authority.

"***Lien***" means any lien (statutory or otherwise), charge, security interest, pledge, mortgage, restriction on use or transfer, financing statement or similar encumbrance of any kind or nature whatsoever (including any conditional sale or other title retention agreement and any lease having substantially the same effect as any of the foregoing and any assignment or deposit arrangement in the nature of a security device).

"***Losses***" has the meaning set forth in Section 7.1.

"***Material Adverse Effect***" means any change, effect or circumstance, individually or in the aggregate, (a) that is reasonably likely to be materially adverse to the business, operations, assets or financial condition of the Company or Purchaser, as the case may be, taken as a whole, or (b) that materially impairs the ability of the Company or Purchaser to perform its obligations pursuant to the transactions contemplated by this Agreement or the Collaboration Agreement; *provided however*, that, none of the following (alone or when aggregated with any other effects), shall be deemed to be a Material Adverse Effect, and none of the following (alone or when aggregated with any other effects), shall be taken into account for purposes of clause (a) above: (A) (1) general market, economic or political conditions or (2) conditions (or any changes therein) in the industries in which the Company or Purchaser conducts business, in each case, including any acts of terrorism or war, weather conditions, global virus pandemics, epidemics or other force majeure events, in the case of each of clauses (1) and (2), solely to the extent that such effects do not have and are not reasonably likely to have a material disproportionate impact on the Company or Purchaser, as the case may be; (B) this Agreement, the Collaboration Agreement (including any amendments thereto), and the transactions contemplated hereby and thereby; or (C) changes in the trading price or volume of the American Depositary Shares or the Purchaser's ordinary shares, in and of themselves.

"***Nasdaq***" means The Nasdaq Global Select Market.

"***Option Agreement***" has the meaning set forth in the recitals.

"***Ordinary Shares***" has the meaning set forth in the recitals.

"***Purchaser***" has the meaning set forth in the preamble.

"***Permits***" has the meaning set forth in Section 2.10.

"***Person***" means a human being, labor organization, partnership, firm, enterprise, association, joint venture, corporation, limited liability company, cooperative, legal representative, foundation, society, political party, estate, trust, trustee, trustee in bankruptcy, receiver or any other organization or entity whatsoever, including any Governmental Authority.

"***Proprietary Rights***" has the meaning set forth in Section 2.11(c).

"***Purchase Price***" has the meaning set forth in Section 1.1.

"***Regulatory Authorizations***" has the meaning set forth in Section 2.12.

"***Rule 144***" has the meaning set forth in Section 5.1(a).

"***SEC***" means the United States Securities and Exchange Commission or any successor entity.

"***SEC Documents***" has the meaning set forth in Section 2.5(a).

"***Securities Act***" means the Securities Act of 1933, as amended, and the rules and regulations of the SEC thereunder.

"***Share Cap***" means a number of Ordinary Shares equal to 9.99% of the Ordinary Shares issued and outstanding on the Execution Date, rounded down to nearest number of Ordinary Shares.

"***Share Value***" means a price per Share (rounded to the nearest cent) equal to the product of (a) 1.3 and (b) the volume weighted average price per American Depositary Share as displayed under the heading "Bloomberg VWAP" on Bloomberg page "BCYC AQR" (or its equivalent successor if such page is not available) for a twenty (20) Trading Day period, starting with the scheduled opening of trading on the twentieth (20th) Trading Day prior to the date of the Purchaser's exercise of its option under the Option Agreement and ending with the scheduled close of trading of the primary trading session on the Trading Day prior to date of Purchaser's exercise of its option under the Option Agreement, as reported on Nasdaq.com, without regard to after-hours trading or any other trading outside of the regular trading session trading hours; *provided* that the Share Value shall in no event be lower than the Minimum Price (as defined in accordance with the rules and regulations of Nasdaq) on the Execution Date.

"***Shares***" has the meaning set forth in Section 1.1.

"***Standstill Period***" has the meaning set forth in Section 4.4.

"***Standstill Provisions***" has the meaning set forth in Section 4.4.

"***Tax***" means any federal, state, local, or foreign income, gross receipts, license, payroll, employment, excise, severance, stamp, occupation, premium, windfall profits, environmental (including taxes under Section 59A of the Internal Revenue Code of 1986, as amended), customs duties, capital stock, share capital, franchise, profits, withholding, social security (or similar), unemployment, disability, real property, personal property, sales, use, transfer, registration, value added, alternative or add-on minimum, estimated, or other tax of any kind whatsoever, including any interest, penalty, or addition thereto, whether disputed or not.

"***Termination Date***" has the meaning set forth in Section 9.1(d).

"Third Party" means any entity other than BicycleTx, the Company, the Purchaser or an Affiliate of BicycleTx, the Company, or the Purchaser.

"***Trading Day***" means a day on which Nasdaq is open for trading.

"***The Company***" has the meaning set forth in the preamble.

Exhibit 31.1

CERTIFICATION

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: November 4, 2021

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

Exhibit 31.2

CERTIFICATION

I, Lee Kalowski, certify that:

1. I have reviewed this 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: November 4, 2021

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

Exhibit 32.1

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

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Kevin Lee, Chief Executive Officer of Bicycle Therapeutics plc (the "Company"), and Lee Kalowski, Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2021, 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: November 4, 2021

IN WITNESS WHEREOF, the undersigned have set their hands hereto as of the 4th day of November, 2021.

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."