Bicycle®

2022
Annual Report

Bicycle®

To Our Shareholders,

The year 2022 was a crucial one for Bicycle, as we continued to announce multiple clinical data milestones across our pipeline that we believe further validate the Company's platform. We have remained focused and encouraged as we continue to advance our pipeline of novel therapeutic candidates based on our proprietary bicyclic peptide, or *Bicycle®* technology. As a result, we believe our team's hard work has brought us closer to actualizing a world where *Bicycles* offer a new treatment paradigm for people living with cancer and other serious diseases.

We made significant progress advancing our pipeline of differentiated therapeutic *Bicycle* candidates, including end of Phase I updates for our Bicycle Toxin Conjugates® (BTCs) BT5528 and BT8009. In addition, our *Bicycle* tumor-targeted immune cell agonist (Bicycle TICA™), BT7480, continued to advance in the clinic. Our collaborations with leading biopharmaceutical companies like Genentech and Ionis made steady pre-clinical progress. These partnerships further demonstrate the broad utility of our platform and science, while we stay committed to creating molecules with the potential to treat some of the most serious diseases and address future public health challenges.

Bicycle is a company founded on Nobel Prize-winning science. *Bicycles* combine the binding characteristics typically associated with biologics with the manufacturing and pharmacokinetic properties of small molecules. We believe the unique features of *Bicycles* make them ideally suited for certain applications across a range of therapeutic areas where patients face high unmet needs.

Our leading BTC candidates include BT5528, a second-generation BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful, and BT8009, a second-generation Nectin-4-targeting BTC with a potentially differentiated profile from an FDA-approved Nectin-4 targeting antibody-drug conjugate.

BT5528 has continued to demonstrate anti-tumor activity in heavily pre-treated patients with EphA2-positive cancers, showing signs of differentiation compared to antibody-based approaches. BT5528 continues in the dose expansion portion of the ongoing Phase I/II clinical trial, and we were pleased to observe anti-tumor activity in heavily pre-treated patients with EphA2-postive ovarian and urothelial cancers. We are also making significant progress advancing BT8009, completing the Phase I dose escalation portion of the trial and establishing the recommended Phase II dose. BT8009 demonstrated clinical activity in bladder, lung, and breast cancers, with a profile demonstrating differentiation compared to antibody-based approaches. We are encouraged that the U.S. Food and Drug Administration granted Fast Track Designation for BT8009 as a monotherapy for previously treated locally advanced or metastatic urothelial cancer, and we look forward to providing updates on the program by the end of this year.

Beyond BTCs, we are excited to provide an update later this year from the Phase I dose escalation portion of the ongoing Phase I/II trial for BT7480, the Company's novel, fully synthetic TICA targeting Nectin-4 and agonizing CD137. Preclinical studies have demonstrated that BT7480 activates CD137 only in the presence of Nectin-4 expressing tumor cells. We believe these *Bicycles* have the potential to represent a new class of immuno-oncology (IO) therapies that could potentially overcome limitations of existing approaches.

We were excited to announce the expansion of our collaboration with Genentech on the discovery and pre-clinical development of novel *Bicycle*-based IO therapies against multiple targets, which was originally signed in February 2020. In July 2022, Genentech exercised its second option to initiate a new program, expanding the exclusive strategic collaboration agreement with us to discover, develop and commercialize novel *Bicycle*-based IO therapies. With the continuation of this partnership, we stand well positioned for potential expansion of our IO pipeline while retaining the value of our wholly owned IO programs. We look forward to providing further updates as we explore the potential of *Bicycles* in IO.

We continue to expand the potential of our bicyclic peptide technology into 2023, as we have utilized non-dilutive funding and collaborations to explore the therapeutic potential of *Bicycles*. We recently signed a strategic collaboration with Novartis to discover, develop and commercialize *Bicycle* radio-conjugates (BRCs) for multiple agreed upon oncology targets. We will utilize our proprietary phage platform to discover *Bicycles* to be developed into BRCs, and Novartis will be responsible for further development, manufacture, and commercialization. We will be eligible to receive milestone payments and tiered royalties on *Bicycle*-based medicines, if any, that are commercialized by Novartis.

The additional capital raised through our collaborations provides us with a strategic advantage amidst challenging macroeconomic conditions and underscores our strength within the industry. We believe our dedicated team of experts, coupled with our strong balance sheet, will position us for continued success.

We intend to continue to carry this momentum throughout 2023, and I am very proud to be working alongside an accomplished team of leaders and scientists dedicated to our mission to pioneer new treatment options designed to address therapeutic needs that cannot be met by existing modalities. I would like to thank the patients who volunteer to participate in our trials, their treating physicians, and the full Bicycle Therapeutics team for their dedication to achieving this mission.

I look forward to keeping shareholders updated on our future progress, and I thank you for your ongoing support.

Sincerely,

Kevin Lee, Ph.D.
Chief Executive Officer

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

OR

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

For the transition period from to

Commission file number 001-38916

BICYCLE THERAPEUTICS PLC

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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

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

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

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

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☒	Smaller reporting company ☒
	Emerging growth company ☐

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

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

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240.10D-1(b). ☐

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

The aggregate market value (approximate) of the registrant's voting and non-voting common equity held by non-affiliates based on the closing price per American Depositary Share, or ADS, of the registrant's ADSs on The Nasdaq Global Select Market on June 30, 2022 (the last business day of the registrant's most recently completed second fiscal quarter) was $489,652,180.

As of February 23, 2023, the registrant had 30,021,071 ordinary shares, nominal value £0.01 per share, outstanding.

Documents Incorporated by Reference:

Portions of the registrant's definitive proxy statement, or Proxy Statement, for its 2023 Annual General Meeting, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2022, are incorporated by reference into Part III of this Annual Report on Form 10-K.

SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS

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

- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- our ability to advance our product candidates into, and successfully complete, clinical trials;
- our reliance on the success of our product candidates in our *Bicycle*® Toxin Conjugate, or BTC™, *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™ and other pipeline programs;
- our ability to utilize our screening platform to identify and advance additional product candidates into clinical development;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- our ability to develop sales and marketing capabilities;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- our ability to operate our business without infringing the intellectual property rights and proprietary technology of third parties;
- costs associated with defending intellectual property infringement, product liability and other claims;
- regulatory developments in the United States, the United Kingdom and other jurisdictions and changes to 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 additional 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;
- future revenue, hiring plans, expenses, capital expenditures, capital requirements and share performance;
- the impact of public health crises (such as COVID-19) and other adverse global economic conditions on our operations and the 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;
- potential business interruptions resulting from geo-political actions, such as war and terrorism or the perception that such hostilities may be imminent;
- our failure or perceived failure to comply with existing or future laws, regulations, contracts, self-regulatory schemes, standards, and other obligations related to data privacy and security (including security incidents) could harm our business, increase the costs of our products or services, limit their use or adoption, and otherwise negatively affect our operating results and business; and
- other risks and uncertainties, including those listed under the caption "Risk Factors."

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

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

TABLE OF CONTENTS

PART I

ITEM 1. BUSINESS.

We are a clinical-stage biopharmaceutical company developing a novel class of medicines, which we refer to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained to form two loops which stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making *Bicycles* attractive candidates for drug development. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic, or PK, properties of a small molecule. The relatively large surface area presented by *Bicycles* allows 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, qualities which we believe explain the molecules' favorable toxicological profile.

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

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

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

The following table summarizes key information about our programs:

Target / Product	Partner / Sponsor	Indication	Modality	Preclinical	IND-enabling	Phase I	Phase II/ Expansion	Phase III
Internal Programs								
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate					
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate					
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™					
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™					
Partnered Programs								
THR-149 (Kallikrein inhibitor)	OXURION	Ophthalmology						
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate					
BT7401 (multivalent CD137 system agonist)	CANCER RESEARCH UK	Immuno-oncology						

We were founded in 2009 based on innovative science conducted by Sir Greg Winter and Professor Christian Heinis. Sir Greg Winter is a pioneer in monoclonal antibodies and, in 2018, was awarded a Nobel Prize in chemistry for the invention of the technology underpinning our proprietary phage display screening platform that we use to identify *Bicycles*. From our founding through December 31, 2022, we have generated substantial intellectual property, including 4 patent families directed to novel scaffolds and linkers, 12 patent families directed to our platform technology, 75 composition of matter patent families directed to bicyclic peptides and related conjugates, and 12 patent families directed to later inventions relating to such bicyclic peptides and related conjugates, such as methods of making or using certain bicyclic peptide conjugates for treating various indications. As of December 31, 2022, our trademark portfolio consisted of 67 trademark registrations across four territories (the United Kingdom, European Union, United States and Japan) as well as a number of pending applications for new trademarks. The work we have conducted in developing *Bicycles* and our proprietary screening platform have created substantial know-how that we believe provides us with a competitive advantage.

Our management team includes veteran executives in drug development from leading biopharmaceutical companies including Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Pfizer and Takeda. Our board of directors and scientific advisory board include industry experts with extensive experience in drug development.

Our Strategy

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

- ***Progress our most advanced internal candidates, BT5528, BT8009, and BT7480 through clinical development.*** We are evaluating BT5528, a second-generation BTC targeting 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* TICA targeting Nectin-4 and agonizing CD137, in a company-sponsored Phase I/II clinical trial. We intend to advance development of these candidates across oncology indications based on target expression.

- ***Continue IND-enabling activities for BT7455.*** BT7455 is a fully synthetic *Bicycle* TICA that contains a *Bicycle* targeting EphA2 and a *Bicycle* targeting the costimulatory receptor CD137. BT7455 has been shown in preclinical models to rapidly penetrate tumors, demonstrate anti-tumor activity, and induce immune memory specific to the implanted tumor. IND-enabling activities are ongoing.

- ***Pursue clinical development of our discovery programs.*** We intend to continue our ongoing discovery activities to screen and select promising candidates for oncology indications. For example, early I-O discovery efforts have resulted in the identification of *Bicycle* TICA candidates targeting natural killer, or NK, cells. We are also developing third generation BTCs. We are currently advancing these programs into lead optimization.

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

- ***Collaborate strategically with leading organizations to access enabling technology and expertise in order to expand the application of our novel* Bicycle *modality to indications beyond oncology.*** We are collaborating with leading biopharmaceutical companies and organizations to apply our novel *Bicycle* modality to other disease areas, including, immune-oncology, or I-O, anti-infective, cardiovascular, ophthalmology, dementia, central nervous system, neuromuscular and respiratory indications. We may

opportunistically enter into additional collaborations in the future to apply our technology to areas of unmet medical need.

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

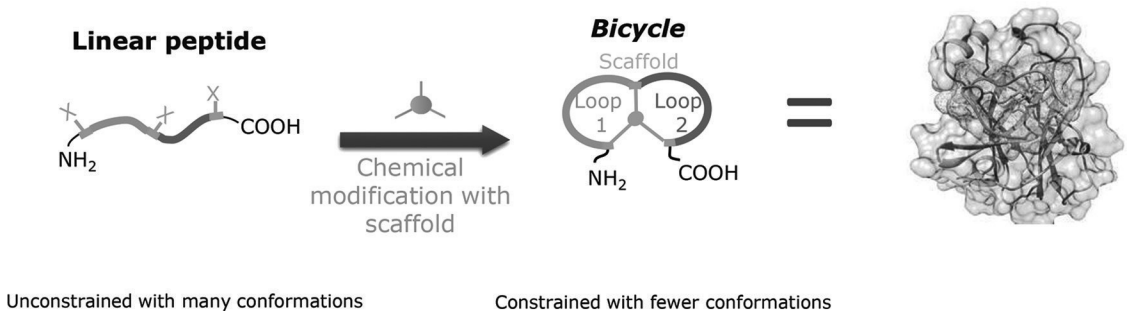
The *Bicycle* Opportunity

Introduction to Bicycles

Bicycles are fully synthetic, short peptides consisting of nine to 20 amino acids constrained to form two loops which stabilize the structural geometry of the peptide and facilitate target binding with high affinity and selectivity. *Bicycles* represent a unique therapeutic class, combining the pharmacological properties normally associated with a biologic with the manufacturing and PK advantages of a small molecule, with no signs of immunogenicity observed to date.

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

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



We have expanded the diversity of the chemical space we can cover from approximately 10^{13} potential molecules in 2009 to in excess of 10^{20} potential molecules today. We have applied our novel *Bicycle* modality to a growing range of targets, from a single target in 2009 to more than 130 today. We can create a wide range of *Bicycles* by varying four parameters:

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

Properties of Bicycles *as Therapeutic Agents*

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

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

Properties of* Bicycles *May Translate into Potential Therapeutic and Other Advantages

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

Comparison of* Bicycles *to Other Common Classes of Therapeutics

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

*Requires use of extension technology

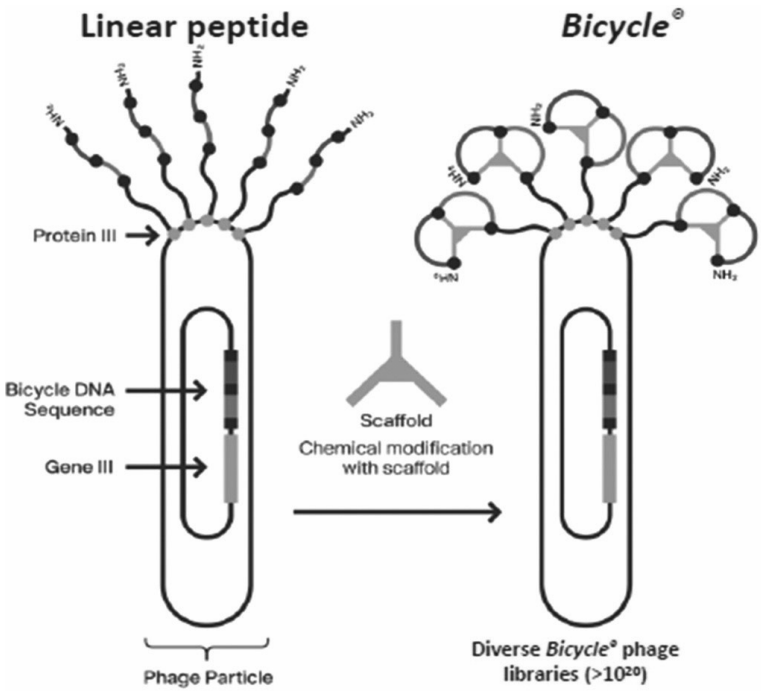
Our Proprietary *Bicycle* Screening Platform

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

Phages are bacteria-infecting viruses consisting of genetic material wrapped in a protein coat. Phages can be harnessed to identify *Bicycles* by splicing DNA into the genome of a phage so that the linear peptides that encode *Bicycles* are presented on the surface of the phage. One of our founders, Sir Greg Winter, a pioneer in phage display, applied this technology and added a cyclization step that forms *Bicycles* from these linear peptides. This technology underpins our novel and proprietary screening platform.

Our screening process self-selects for *Bicycles* that are amenable to attachment, commonly referred to as conjugation, to other molecular payloads such as cytotoxins, innate immune agonists or other *Bicycles*. *Bicycles* can be linked together with synthetic ease to create complex molecules with combinatorial pharmacology. Alternatively, *Bicycles* in the form of multimers can also be used as standalone therapeutics, such as those that we are exploring in our systemic and tumor-targeted immune cell agonist programs. We believe that the flexibility of our *Bicycles* and our powerful screening platform allow new therapeutics to be rapidly conceived and reduced to practice to potentially serve diverse therapeutic applications across a wide range of indications. We can readily identify *Bicycles* that may drug a wide spectrum of targets and target classes, including many that have so far been undruggable with small molecules, such as protein-protein interactions.

Schematic of our Proprietary* Bicycle *Screening Process



We have optimized our proprietary *Bicycle* screening platform, enabling the technique to be applied to a diverse range of over 130 challenging targets to date, successfully identifying *Bicycles* for over 80% of these targets, some of which are intractable to small molecules. During these screens, *Bicycles* with diverse pharmacologies were identified, including enzyme inhibitors, receptor antagonists, agonists (partial, full and supra) and neutral site binders. Neutral site binders often bind to entirely novel sites on target proteins, previously undescribed in the scientific literature. These binders can be useful when conjugated with therapeutic payloads since they allow antigen-targeted payload delivery without impacting target function.

Our Product Candidates

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

Our Programs

The following table summarizes key information about our programs.

Program	Interest	Stage	Status
Internal programs			
BT5528	• High EphA2 expressing tumors (oncology)	• Phase I/II	• Ongoing company-sponsored Phase I/II clinical trial
BT8009	• High Nectin-4 expressing tumors (oncology)	• Phase I/II	• Ongoing company-sponsored Phase I/II clinical trial
BT7480 (Nectin-4/CD137 *Bicycle* TICA)	• Immuno-oncology	• Phase I/II	• Ongoing company-sponsored Phase I/II clinical trial
BT7455 (EphA2/CD137 *Bicycle* TICA)	• Immuno-oncology	• Preclinical	• IND-enabling activities in process
Partnered programs			
THR-149 (Plasma Kallikrein Inhibitor)	• Ophthalmology	• Phase II	• Collaborating with Oxurion
BT1718	• High MT1-MMP expressing tumors (oncology)	• Phase I/IIa	• Ongoing Phase I/lla clinical trial in collaboration with CRUK
BT7401 (multivalent CD137 agonist)	• Immuno-oncology	• Preclinical	• CRUK to fund and sponsor development through a Phase IIa clinical study
Undisclosed	• Immuno-oncology	• Preclinical	• Collaborating with Genentech
Multiple targets	• Cardiovascular, metabolic, respiratory	• Preclinical	• Collaborating with AstraZeneca
Novel anti-infectives	• Anti-infectives	• Preclinical	• Collaborating with Innovate UK and Small Business Research Initiative
Novel CNS targets	• CNS	• Preclinical	• Collaborating with Dementia Discovery Fund and Oxford Drug Discovery Institute and Ionis
Novel neuromuscular targets	• Neuromuscular	• Preclinical	• Collaborating with Ionis

Our Internal Programs

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

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

Bicycle *Toxin Conjugates*®

Within our BTC programs, we are evaluating BT5528, a second-generation BTC that targets EphA2 and carries a monomethyl auristatin E, or MMAE, cytotoxin payload, in an ongoing, company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics, and preliminary clinical activity in patients with solid tumors. In October 2021, we announced interim Phase I results from this clinical trial where we observed preliminary signs of anti-tumor activity and established a recommended Phase II dose range. In June 2022, we announced that the first patient had been dosed in the dose expansion cohorts of the Phase I/II study of BT5528 which include urothelial and ovarian cancers, as well as a basket cohort of other solid tumors, including non-small cell lung cancer, triple-negative breast cancer, head and neck cancer, and esophageal cancer. Enrollment in these cohorts remains ongoing. In September 2022, we announced top-line results from the completed dose escalation portion of the Phase I/II trial.

We are evaluating BT8009, another second-generation BTC that targets Nectin-4 and carries an MMAE cytotoxin payload, in an ongoing company-sponsored Phase I/II clinical trial to assess to assess the safety, pharmacokinetics and preliminary clinical activity in patients with Nectin-4 expressing advanced malignancies. We presented preliminary results from this clinical trial in October 2021 and in April 2022, we presented updated interim results where we presented confirmed signs of anti-tumor activity. In November 2022, we announced updates from the

Phase I/II trial, including that the Phase I dose escalation portion of the trial was complete and that the first patient had been dosed in the Phase II expansion cohorts. Results from the completed dose escalation portion of the trial were presented at the 2023 ASCO Genitourinary (GU) Cancers Symposium in February 2023.

In January 2023, we announced that the U.S. Food and Drug Administration, or FDA, granted Fast Track Designation, or FTD, to our BT8009 monotherapy for the treatment of adult patients with previously treated locally advanced or metastatic urothelial cancer. FTD is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition.

Background

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

Properties of Bicycle *Toxin Conjugates*

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

- ***Extensive and rapid tumor penetration.*** *Bicycles* have been observed in our preclinical studies to penetrate tumors more rapidly and exhibited increased penetration to poorly perfused regions of the tumor when compared to a comparator antibody. Early clinical data from an ongoing clinical trial has shown ten times higher tumor cytotoxin levels than corresponding plasma levels based on clinical tumor biopsies taken 24 hours post-infusion.

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

- ***Short systemic half-life and renal elimination***. *Bicycles* have been observed in clinical and preclinical studies to have a short systemic half-life of approximately 20 to 30 minutes. Due to their small size, *Bicycles* are able to exit the tissue rapidly and are excreted through the kidneys rather than the liver, which we expect will support a favorable toxicity profile.

- ***No requirement for internalization.*** Unlike ADCs, which require cellular internalization for activity, BTCs do not require internalization into the cell, and therefore potentially can target a wider range of tumor antigens.

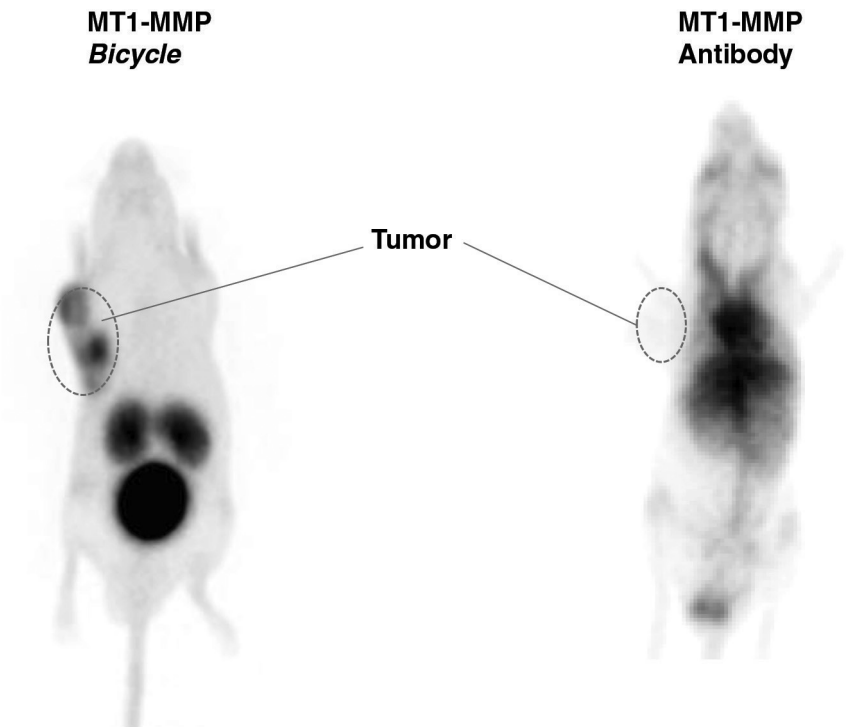
- ***Access to non-expressing tumor cells.*** The toxin in our BTCs is liberated in the extracellular space, enabling cell-killing adjacent cells that do not express the specific target through a toxin bystander effect. In our preclinical studies, we observed activity for BTCs even in tumors that were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

- ***Larger toxin payload.*** Despite the small size of *Bicycles*, they are able to carry a larger dose of toxin per unit mass than a comparator ADC. Therefore, we believe that *Bicycles* can deliver a higher concentration of the linked toxin to increase the probability of tumor killing.

- ***Manufacturing.*** The fully synthetic process by which *Bicycles* are manufactured facilitates ease and consistency of manufacturing and improved formulation compared to ADCs.

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

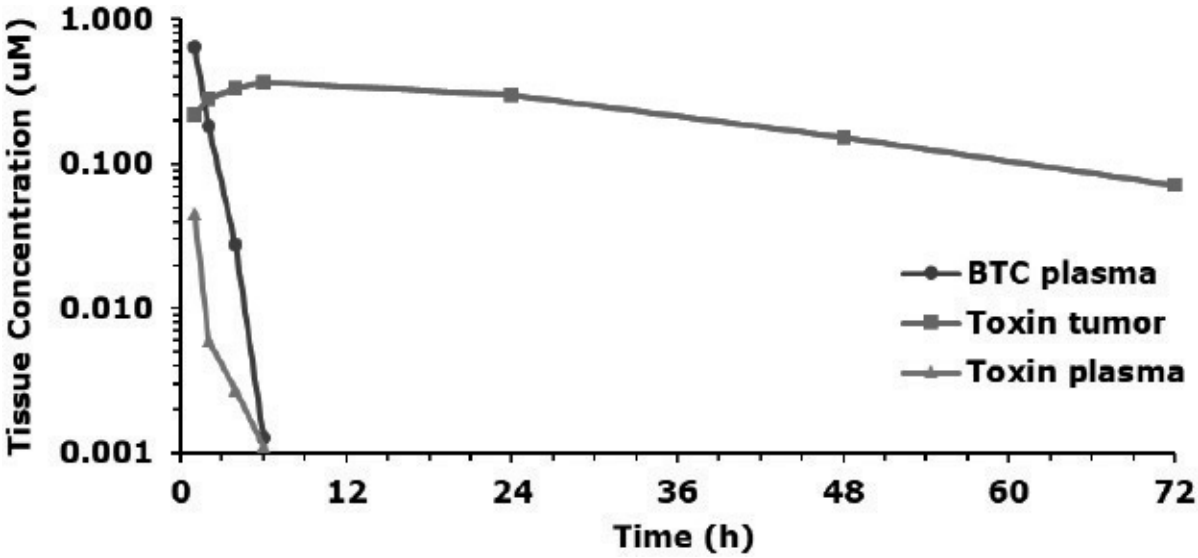
PET Imaging Revealing Payload Delivery in a Mouse Model



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

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

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

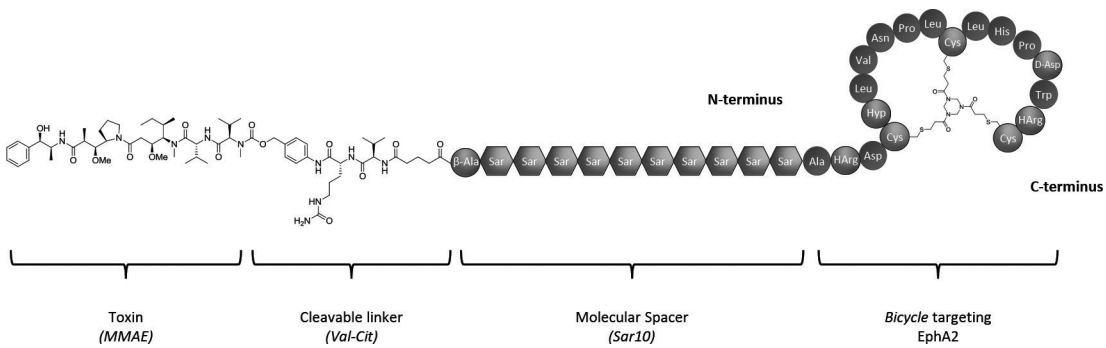


We believe these data demonstrate the potential of BTCs to have long-term sustained activity and to limit the toxicity associated with ADCs.

BT5528

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

Schematic of BT5528



EphA2 is a member of the Ephrin superfamily of receptor tyrosine kinases regulating cell migration, adhesion, proliferation and differentiation. EphA2 is expressed at relatively low levels in normal adult tissues, but is overexpressed in numerous difficult-to-treat tumors including lung, breast, bladder, head and neck, gastric, ovarian, and pancreatic cancer. In both cell-derived and patient-derived preclinical models, we observed anti-tumor activity signals following administration of our EphA2 toxin conjugates, which correlated with EphA2 expression, as determined by FACS studies.

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

We believe EphA2 is an attractive target for our BTCs due to the potential of *Bicycles* to overcome the safety concerns observed with ADCs. In our preclinical PK and toxicokinetic studies, we observed a short systemic half-life and volume of distribution approximately equal to extracellular fluid. We observed that the accumulation of MMAE in the tumor tissue led to mitotic arrest of tumor cells and tumor regression was evident within days of administration. Due to the shorter half-life, improved penetration into solid tumors and kidney elimination, we believe that BT5528 could overcome the challenges faced by ADCs.

BT5528 was evaluated in preclinical studies in multiple species, including rodents and non-human primates. In our preclinical studies, BT5528 was not observed to have a significant effect on clotting parameters and did not exhibit abnormal liver function at tolerated doses. We also observed no bleeding events in primates at toxin equivalent doses over 150-fold higher than the clinical dose of an ADC with the same amino acid sequence and with the same linker-toxin combination and average drug/antibody ratio as MEDI-547 used in patients.

Clinical Development

We are currently evaluating BT5528 in a company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics and preliminary clinical activity in patients with advanced solid tumors associated with EphA2 expression. On October 7, 2021, we announced interim results from our Phase I clinical trial of BT5528. 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, or RP2D, of 6.5-8.5mg/m^2 every other week. On September 7, 2022, we announced Phase I dose escalation top-line results from our Phase I/II trial of BT5528. A total of 45 patients (15 at the RP2D of 6.5mg/m^2 every other week) were dosed with a median of four prior lines of therapy. Expression of EphA2 was evaluated retrospectively using an immunohistochemistry, or IHC, assay. Amongst these patients, anti-tumor activity was observed in urothelial and ovarian cancer patients. A total of 21 ovarian cancer patients were dosed. Of these, nine response evaluable patients were determined to be EphA2-positive based on the IHC assay. The median prior lines of therapy for these nine patients was four. Among these nine late-line ovarian cancer patients, six patients (67%) were observed to have a reduction in target lesions, including one patient with a complete response, or CR, and one with a partial response, or PR, under Response Evaluation Criteria in Solid Tumors, or RECIST, version 1.1, resulting in a disease control rate, or DCR, of 67% and an overall response rate, or ORR, of 22%. A total of eight urothelial patients were dosed. Of these, three response evaluable patients were determined to be EphA2-positive based on the IHC assay and of these three patients, two were observed to have tumor reductions constituting a PR under RECIST version 1.1 (ORR and DCR of 67%).

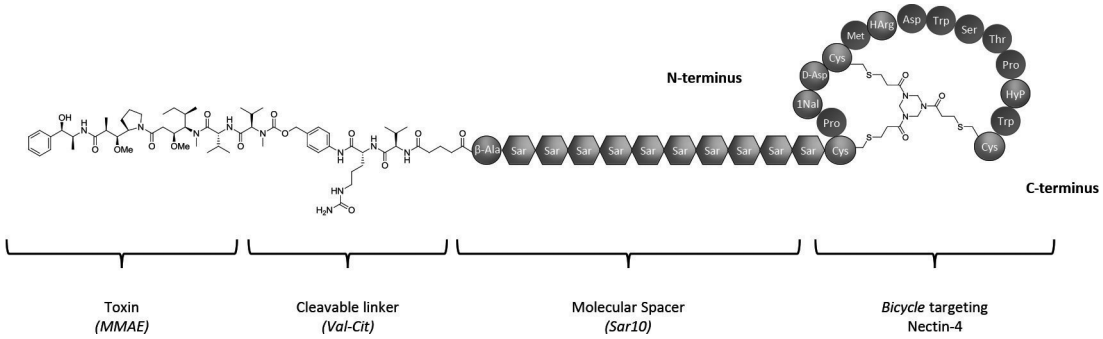
BT5528 was well-tolerated at the RP2D of 6.5mg/m^2 every other week. Low, or no, levels of incidence of neutrophil count decrease, peripheral neuropathy, skin rash and eye disorders were reported. Low-grade GI treatment-related events were those most commonly reported amongst the 15 patients at this dose. There were three treatment-related adverse events that were grade-3 or above at this RP2D: diarrhea (n=1, 7%) and anemia (n=2, 13%). In addition, and in contrast to the toxicities observed with EphA2 ADCs, we have observed no signs of treatment-related coagulopathy to date.

Based on the findings from the Phase I clinical trial, we are advancing in ongoing expansion cohorts 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.

BT8009

BT8009 is a second-generation BTC designed to target Nectin-4, a well-validated tumor antigen. The molecule is composed of our Nectin-4 targeting *Bicycle*, a val-cit cleavable linker, and a cytotoxin MMAE payload.

Schematic of BT8009



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

We are aware of one Nectin-4 ADC program in advanced development stages. This program, enfortumab vedotin, is being developed jointly by Seagen, Inc., or Seagen, and Astellas Pharma, Inc., or Astellas, and received approval from the FDA in December 2019, as a treatment for patients with locally advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor and received approval from the European Commission, or EC, in April 2022, as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. Seagen and Astellas are also pursuing additional indications for enfortumab vedotin.

Clinical Development

We are advancing BT8009 in the Phase I portion of our company-sponsored Phase I/II clinical trial to assess safety, pharmacokinetics and preliminary clinical activity in patients with Nectin-4 expressing advanced malignancies. Early clinical data supports a PK profile that is consistent with both preclinical predictions and data to date from our ongoing Phase I trial of BT5528. On October 7, 2021, we announced preliminary results from an ongoing Phase I clinical trial, on April 11, 2022, we announced updated interim results from an ongoing Phase I clinical trial and in February 2023, we announced results from the completed Phase I clinical trial of BT8009.

Among four urothelial cancer patients dosed at 2.5mg/m^2 weekly, one patient (25%) was observed to have a confirmed tumor reduction that met the criteria of a partial response under RECIST 1.1. Two additional patients were observed to have stable disease, for a disease control rate of 75% at this dose level. Among the eight urothelial patients dosed at 5.0mg/m^2 weekly, four of the eight patients (50%) were observed to have tumor reductions that met the criteria of confirmed RECIST 1.1 partial or complete response including one patient (13%) with a confirmed complete response. Two additional patients were observed to have stable disease, for a disease control rate of 75% at this dose level. Between the two urothelial patients dosed at 7.5mg/m^2 weekly, one (50%) had a confirmed RECIST 1.1 partial response prior to dose reduction. Among non-urothelial patients, we reported one stable disease head and neck cancer patient at the 7.5mg/m^2 biweekly dose and two stable disease non-small cell lung cancer patients: one at 2.5mg/m^2 and the other at 7.5mg/m^2 weekly. Finally, we reported that 5.0mg/m^2 weekly would be a recommended Phase II dose, or RP2D.

On November 8, 2022, we reported that we had dosed our first patient in the Phase II dose expansion portion of the Phase I/II trial and that the Phase I portion was complete. We announced a second RP2D, 7.5mg/m^2 dosed days 1 and 8 on a 21-day cycle, and that a confirmed partial RECIST 1.1 responder with lung cancer was observed at this dose level.

Results from the completed Phase I clinical trial were presented in February 2023. The data showed that the overall response rate among urothelial patients in the 7.5mg/m^2 dosed days 1 and 8 on a 21-day cycle and 10mg/m^2 biweekly cohorts was consistent with that observed among urothelial patients in the 5.0mg/m^2 cohort, with confirmed clinical responses under RECIST 1.1 observed to be one out of two patients (50%) in the 7.5mg/m^2 dosed days 1 and 8 on a 21-day cycle cohort and two out of four patients (50%) in the 10mg/m^2 biweekly cohort. The data from the different dose levels showed that BT8009 continues to exhibit a favorable tolerability profile.

BT8009 was well-tolerated amongst 49 patients in the Phase I clinical trial, with a low incidence of adverse events common to antibody-based approaches. The most common treatment-related adverse events across the study were gastroenterologically related and fatigue. Across all patients at all doses, there was a low incidence of skin rash of any form, eye disorders, neuropathy of any form and no cases of pneumonitis in any patient at any dose. The most common Grade 3 or higher treatment-related adverse event was neutropenia: seven cases or 14%; four of these were at doses above the RP2Ds. There were three subjects with serious adverse events (SAEs) at or above Grade 3 that were drug related (6%). Of these, none was in the 5 mg/m^2 cohort. The incidence of Grade 3 or higher related adverse events at or below the two RP2Ds was low. At the 5 mg/m^2 weekly dose, there were no cases of Grade 3 or higher skin rash, eye disorders, neuropathy or pneumonitis.

On January 4, 2023, we announced that the FDA granted FTD to our BT8009 monotherapy for the treatment of adult patients with previously treated locally advanced or metastatic urothelial cancer. FTD is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition.

Bicycle *Immune Cell Agonist*

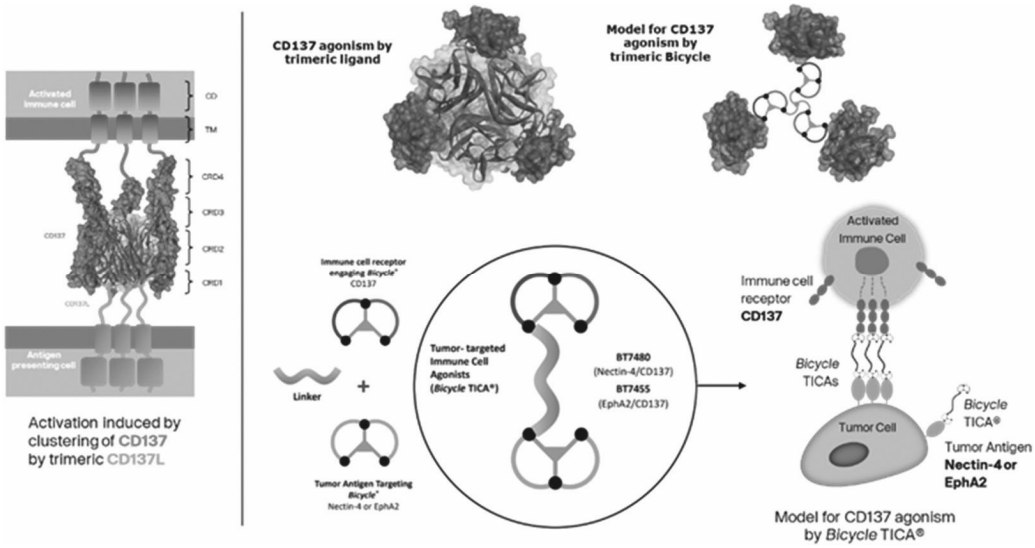
Approaches that activate cytotoxic T-cells and other types of cells used in a body's immune response have been observed to improve outcomes in cancer. However, prolonged immune activation can be toxic and lead to T-cell exhaustion, which is a challenge amplified by the long half-life of antibodies and biologics that are often used in these treatment approaches. We believe the differentiated properties of *Bicycles* may allow us to develop molecules with a pharmacodynamically distinct and improved profile over existing therapies.

We are aware of anti-CD137 antibodies undergoing clinical testing, including urelumab being developed by Bristol-Myers Squibb, which produced single agent responses but also severe liver toxicity, and utomilumab being developed by Pfizer, which exhibited minimal clinical activity with less toxicity. We are developing immune cell agonists, designed to trigger an immune response to tumors. We have identified potent *Bicycle* agonists of CD137, a tumor necrosis factor receptor, or TNFR, family member. We believe that *Bicycles* represent a differentiated approach to target CD137 that may confer several advantages over existing modalities due to the small size and PK characteristics of *Bicycles*. Our *Bicycle* immune cell agonists are designed to circumvent the limitations of antibody and biologic therapies, such as liver toxicity and limited efficacy, and to better enable combination therapy. *Bicycle* immune cell agonists can be formed by conjugating multiple copies of a CD137 *Bicycle* to form multimers or by utilizing a bi-specific format in which CD137 *Bicycles* are linked to *Bicycles* that bind to tumor antigens, inhibit checkpoint proteins or otherwise activate the immune system. We believe we are currently the only company that has fully chemically synthetic multivalent or tumor-targeted CD137 agonists.

Properties of Bicycle *Immune Cell Agonists*

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

Schematic of Proposed CD137* Bicycle *Agonists



These *Bicycle* CD137 agonists feature the following favorable pharmacological characteristics for immuno-oncology therapeutics. We believe these characteristics have the potential to overcome the limitations of antibodies and fusion proteins.

- ***Simplicity and small size.*** Our systemic and tumor-targeted immune cell agonizing *Bicycles* are chemically synthesized and are very small in comparison to other molecules targeting the CD137 receptor. For example, the approximate molecular weight of urelumab is 146 kDa. In contrast, the molecular weight of our multivalent and tumor-targeted *Bicycles* are in the range of approximately 4 kDa to 15 kDa, which is designed to facilitate the rapid penetration of the therapeutic into tumor tissue.

- ***Tunable PK.*** *Bicycles* are amenable to chemical modifications that allow the PK to be fine-tuned. We believe this enables the development of molecules with the optimal balance of prolonged CD137 agonism, but with rapid enough elimination from systemic circulation to avoid the undesired toxicities of CD137, as has been observed with urelumab. In addition, this tunable half-life is expected to enable different sequences of therapeutics to be evaluated in the clinic potentially reducing the risk of overlapping toxicities.

- ***Renal elimination.*** Rapid renal elimination may avoid liver toxicity observed with other CD137 agonists in development.

- ***Modular.*** The modular nature of *Bicycles* permits the presentation of CD137 binders in various orientations and in combination with other *Bicycles* allowing us to design molecules with a range of activities. We believe that we can select the optimal activity profile to avoid the weak efficacy seen with the utomilumab molecule or the overstimulation of CD137 by urelumab that resulted in systemic toxicity.

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

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

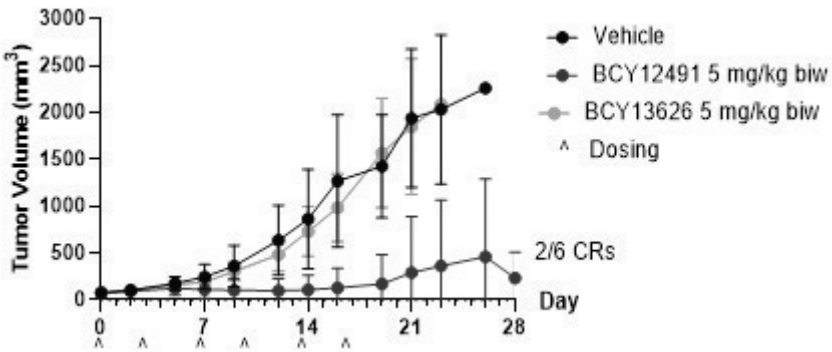
Our product candidate BT7480 is a Bicycle tumor-targeted immune cell agonist, or *Bicycle* TICA. A *Bicycle* TICA links immune cell receptor binding *Bicycles* to tumor antigen binding *Bicycles*. We are evaluating BT7480, a *Bicycle* TICA targeting Nectin-4 and agonizing CD137, in a company-sponsored Phase I/II clinical trial to assess the safety and tolerability of BT7480, and to determine a recommended Phase II dose.

Background

We have linked immune cell receptor binding *Bicycles* to tumor antigen binding *Bicycles* to form *Bicycle* TICAs. We have found this approach to be generalizable across tumor antigen and immune cell receptors. We constructed CD137-targeting *Bicycle* TICA molecules and observed that these bi-specific *Bicycles* agonize the CD137 receptor only in the presence of cells that express the appropriate tumor antigen. Additionally, we have constructed *Bicycle* TICA molecules with *Bicycles* that bind to another member of the TNF family of T-cell costimulatory receptors TNFRSF4, also known as OX40.

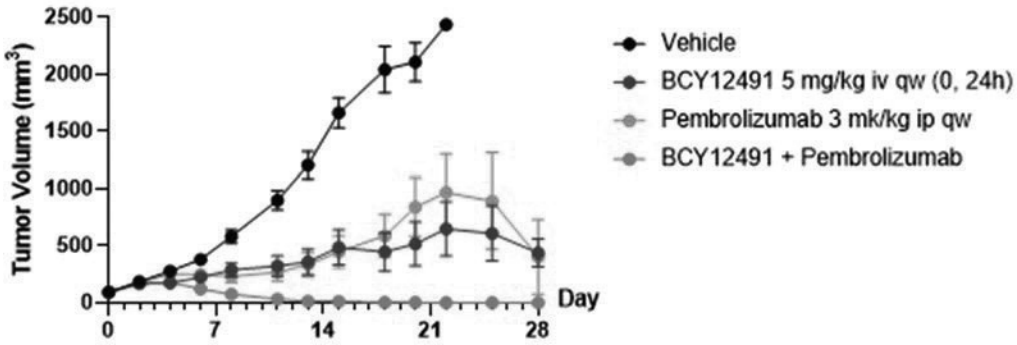
In pre-clinical studies, we have observed that intermittent dosing of BCY12491, an EphA2/CD137 *Bicycle* TICA, leads to a robust anti-tumor activity in syngeneic MC38 mouse model using humanized CD137 (huCD137) C57BL/6 mice. Administration of BCY12491 in six intravenous biweekly doses over a period of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

Activity of EphA2* Bicycle *TICA in vivo



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

Activity of EphA2* Bicycle *TICA and PD1 Inhibitor in vivo

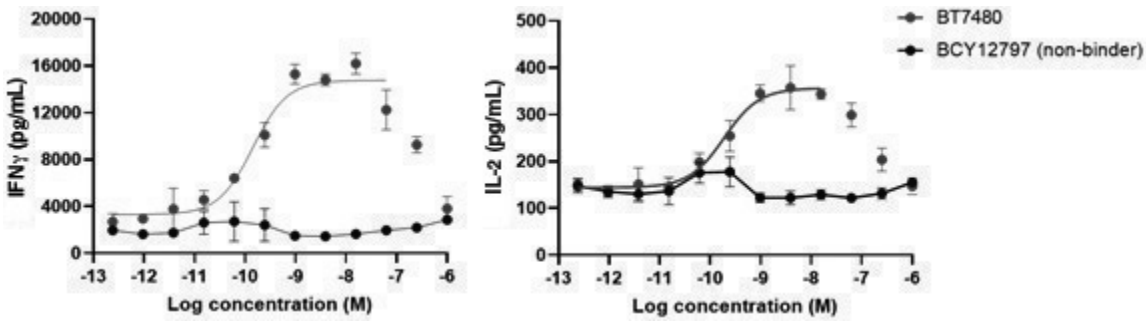


We believe that our ability to rapidly generate and test *Bicycle* TICA molecules and their simple molecular format may form the basis of additional programs in the future. In addition to the immune cell and tumor targets that we have already investigated, we are screening for *Bicycles* that target NK cell receptors as well as additional immune cell and tumor specific antigens. We have identified *Bicycle* TICA candidates that target and activate NK cells. We have observed that treatment of primary human NK cells in co-culture with target-positive tumor cells with NK TICAs results in increased NK cell mediated tumor cell killing and an increase in NK cell secreted pro-inflammatory cytokines.

BT7480

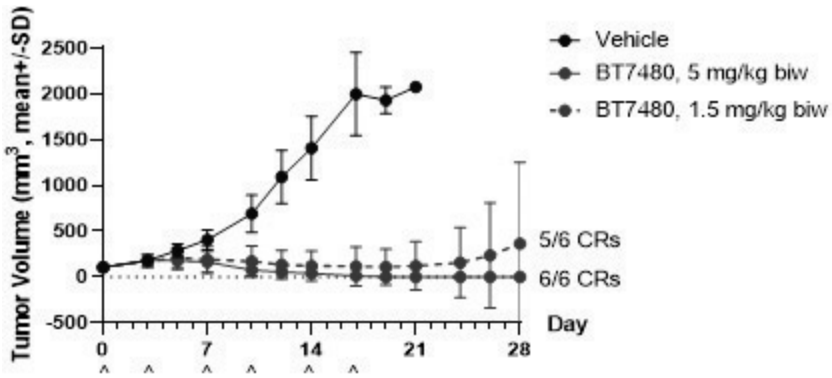
BT7480 is a *Bicycle* TICA that targets CD137 and Nectin-4. BT7480 exhibits potent CD137 agonism in an engineered CD137 reporter assay system that correlates with Nectin-4 surface expression on the co-cultured tumor cells. In addition, BT7480 induces robust production of interleukin-2, or IL-2, and interferon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

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



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

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



Clinical Development

We are evaluating BT7480, in a Company-sponsored Phase I/II clinical trial. In November 2021, we announced that we had dosed the first patient in this trial. The Phase I/II multi-center, open-label trial will evaluate BT7480 administered once weekly. Enrollment is ongoing in the Phase I dose escalation of BT7480 given as a monotherapy, and we may evaluate BT7480 dosed in combination with nivolumab in future Phase I dose escalation cohorts. The Phase I portion of the trial is primarily designed to assess the safety and tolerability of BT7480, and to determine a recommended Phase II dose, or RP2D. Following selection of an RP2D, we expect to initiate a Phase II dose expansion portion with the primary objective of evaluating the clinical activity of BT7480 as monotherapy and in combination with nivolumab in patients with Nectin-4-positive tumors.

BT7455

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

Our Partnered Programs

THR-149

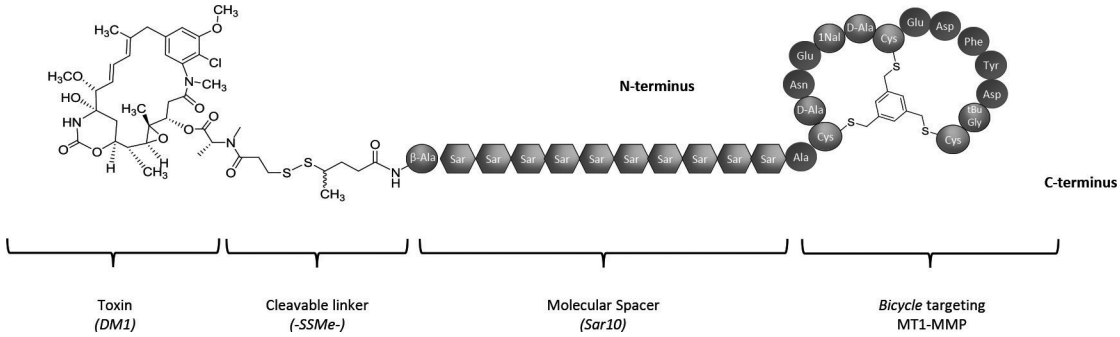
In August 2013, we entered into a research collaboration and license agreement with Oxurion NV, or Oxurion, focused on ophthalmology. The lead molecule of the partnership is THR-149, a novel plasma kallikrein inhibitor, for the treatment of diabetic macular edema, or DME. A Phase I clinical trial of THR-149 was completed in July 2019. The Phase I clinical trial, conducted by Oxurion, was an open-label, multi-center, non-randomized study to evaluate the safety of a single intravitreal injection of THR-149 at three ascending dose levels in 12 subjects with visual impairment due to center-involved DME. The study also investigated changes to patients' best corrected visual acuity (BCVA). A rapid onset of action was observed from Day 1, with an increasing average improvement in BCVA of up to 7.5 letters at Day 14. This activity was maintained with an average improvement in BCVA of 6.5 letters at Day 90 following a single injection of THR-149.

Oxurion is conducting a Phase II clinical trial, consisting of a two-part, randomized, prospective, multi-center study assessing multiple injections of THR-149 in DME patients who have previously shown a suboptimal response to anti-VEGF therapy. In September 2021, Oxurion announced results from Part A of the clinical trial. Part B of the study is ongoing, which will enroll just over 100 patients who have previously shown a suboptimal response to anti-VEGF therapy, and where THR-149 will be evaluated against aflibercept, the current standard of care, as the active comparator.

BT1718

BT1718 is a BTC that we are developing in collaboration with CRUK for oncology indications. The molecule is comprised of our MT1-MMP targeting *Bicycle*, a hindered disulphide cleavable linker and a DM1 cytotoxin payload. We are not aware of any other cytotoxin conjugates in development that target MT1-MMP.

Schematic of BT1718



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

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

Clinical Development

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

The ongoing Phase IIa part of the trial, which commenced in 2020, is evaluating BT1718 in patients with tumors that express MT1-MMP at the RP2D of 20mg/m^2, based on the findings from the Phase I part of the trial. To determine tumor types of interest, a clinically validated MT1-MMP immunohistochemistry, or IHC, assay, developed in collaboration with Cancer Research UK, was used to screen tumor tissue microarrays, or TMA, from multiple tumor types selected based on literature reports of high expression of MT1-MMP, including breast, lung, gastric, ovarian, endometrial, bladder, and esophageal cancers. To date, the percentage of patients determined to be MT1-MMP-positive at the pre-specified cutoff is consistent with previous translational research findings. Patients were enrolled into two solid tumor cohorts, one in squamous non-small cell lung cancer, or NSCLC, and the other in an all-comers “basket” cohort. Each cohort was designed to evaluate 16 patients with a specified tumor type determined using the results of the

MT1-MMP IHC TMA analysis. The endpoints for the Phase IIa part of this clinical trial are safety and preliminary efficacy in patients with tumors expressing MT1-MMP.

Our Collaborations

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

Ionis

On December 31, 2020, we entered into an evaluation and option agreement, or the Evaluation and Option Agreement, with Ionis Pharmaceuticals, Inc., or Ionis, pursuant to which 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 the Company's platform technology. Ionis paid a non-refundable $3.0 million payment that was fully creditable against the upfront payment to be paid upon the execution of a license agreement.

On July 9, 2021, we and Ionis entered into a collaboration and license agreement, or the Ionis Collaboration Agreement, following Ionis' exercise of the Ionis Option on July 9, 2021. 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. 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, we have 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. We 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 we are responsible for performing, we may use the assistance of a contract research organization, or CRO. We have 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, or JSC, with an equal number of representatives from us 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 Evaluation and Option 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 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, or 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, 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.

In December 2021, we and Ionis entered into an amendment to the Ionis Collaboration Agreement, or the Ionis Amendment. Ionis paid us $1.6 million and we agreed to perform additional research services utilizing our proprietary phage screening technology to identify and optimize new product candidates that target the TfR1 receptor. We performed additional research services for an initial six-month period, which was extended in August 2022 for an additional three months, in exchange for consideration of $0.8 million. In October 2022, Ionis exercised an option it had for us to perform additional research services for an additional six months in exchange for the remaining consideration of $0.8 million.

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.

Concurrently with the execution of the Ionis Collaboration Agreement on July 9, 2021, we entered into a share purchase agreement, or the Ionis Share Purchase Agreement, with Ionis, pursuant to which Ionis purchased 282,485 of our ordinary shares, or 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 agreed that until January 9, 2023, it would not, without our prior written consent and subject to certain conditions and exceptions, among other things, directly or indirectly acquire additional shares of our outstanding equity securities, seek or propose a tender or exchange offer, merger or other business combination involving us, solicit proxies or consents with respect to any matter, or undertake other specified actions related to the potential acquisition of additional equity interests in us. The Share Purchase Agreement also provided that, subject to limited exceptions, Ionis could not sell any of the Ionis Shares until July 2022.

Genentech

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

Under the terms of the Genentech Collaboration Agreement, we received a $30.0 million upfront, non-refundable payment. The initial discovery and optimization activities are focused on utilizing our phage screening technology to identify product candidates aimed at two I-O targets, or Genentech Collaboration Programs, which may also include additional discovery and optimization of *Bicycles* as a targeting element for each Genentech Collaboration Program, or each a Targeting Arm. Genentech also had the option to nominate up to two additional I-O targets, or each an Expansion Option, which may also include an additional Targeting Arm for each Expansion Option, as additional Genentech Collaboration Programs. Genentech exercised the Expansion Options in October 2021 and June 2022, respectively. Genentech paid us an expansion fee of $10.0 million for each Expansion Option. Genentech also has rights, under certain limited circumstances, to select an alternative target to be the subject of a Genentech Collaboration Program, in some cases subject to payment of an additional target selection fee.

If Genentech elects for us to perform discovery and optimization services for certain Targeting Arms, we will be entitled to receive an additional advance payment for the additional research services. Genentech exercised its right to select a Targeting Arm for one of the initial Genentech Collaboration Programs at the inception of the arrangement and for the first Expansion Option in October 2021, which entitled us to additional payments of $1.0 million each. If a Targeting Arm achieves specified criteria in accordance with the research plan, Genentech will be required to pay a

further specified amount in the low single digit millions for each such Targeting Arm as consideration for the additional services to be provided.

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

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

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

Dementia Discovery Fund

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

Cancer Research UK

BT1718

In December 2016, we entered into a clinical trial and license agreement with Cancer Research UK and Cancer Research Technology Ltd., a wholly owned subsidiary of Cancer Research UK that Cancer Research UK's commercial activities operate through, or the Cancer Research UK Agreement. Pursuant to the agreement, as amended in March 2017 and June 2018, Cancer Research UK Centre for Drug Development will sponsor and fund a Phase I/IIa clinical trial of our product candidate, BT1718, in patients with advanced solid tumors.

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

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

The Cancer Research UK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity 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 terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met. We were 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, us 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 we are 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, we will reimburse Cancer Research UK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case, Cancer Research UK will not be obliged to grant a license to us in respect of the results of the clinical trial and we will assign or grant to CRTL an exclusive license to develop and commercialize the product without CRTL being required to make any payment to us.

BT7401

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

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

digit percentage on net sales of products developed, and sublicense royalties to the Cancer Research UK in the low double digit percentage of sublicense income depending on the stage of development when the license is granted.

The BT7401 Cancer Research UK agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity generates its revenue from the sale of tobacco products), or upon written notice by either party prior to the last cycle of treatment has been completed under the clinical trial. If the study is terminated by us prior to the filing of a clinical trial authorization, or by Cancer Research UK for an insolvency event or a material breach by us prior to the start of a clinical trial, we will reimburse Cancer Research UK for certain costs paid or committed prior to the start of the clinical trial. In such case where we are acquired by an entity that generates its revenue from the sale of tobacco products, Cancer Research UK will not be obliged to grant a license to us in respect of the results of the clinical trial and we will assign or grant to Cancer Research Technology Limited an exclusive license to develop and commercialize the product without Cancer Research Technology Limited being required to make any payment to us.

AstraZeneca

In November 2016, we entered into a research collaboration agreement with AstraZeneca AB, or the AstraZeneca Collaboration Agreement. The collaboration is focused on the research and development of *Bicycle* peptides that bind to an undisclosed number of biological targets for the treatment of respiratory, cardiovascular and metabolic diseases. After discovery and initial optimization of such *Bicycle* peptides, AstraZeneca is responsible for all research and development, including lead optimization and drug candidate selection. AstraZeneca receives development, commercialization and manufacturing license rights with regard to any selected drug candidate(s).

Under the AstraZeneca Collaboration Agreement, Bicycle performed research activities, under mutually agreed upon research plans. The research plans include two discrete parts, on a research program by research program basis: (i) the Bicycle Research Term, which is focused on the generation of Bicycle peptide libraries using our peptide drug discovery platform, to be screened against selected biological targets, with the goal of identifying compounds that meet agreed criteria set by the parties, and (ii) the AZ Research Term, during which AstraZeneca may continue research activities with the goal of identifying compounds that satisfy the relevant pharmacological and pharmaceutical criteria for clinical testing. Each research program is to continue for an initial period of three years, referred to as the research term, including one year for the Bicycle Research Term and two for the AZ Research Term. AstraZeneca may extend the research term for each research program by twelve months (or fifteen months, if needed to complete certain toxicology studies). The research term for a specific program can be shorter if it is ceased due to a screening failure, a futility determination, or abandonment by AstraZeneca.

Under the terms of the AstraZeneca Collaboration Agreement, we granted to AstraZeneca the right and license (with the right to sublicense) to certain background, foreground and platform intellectual property, for the duration of the agreement, to the extent reasonably necessary or useful for AstraZeneca to conduct the activities that are assigned to it in the applicable research plan or that are reasonably necessary or useful or the purpose of researching, developing or exploiting resulting compounds and products. We have agreed not to, directly or indirectly, by ourselves or in collaboration with others, screen the Bicycle platform for compounds that bind to a target that is the subject of the AstraZeneca collaboration or otherwise perform any work related to or disclose such a target until the earlier of the tenth anniversary of the date on which such target was selected or the dosing of the first patient in the first Phase III clinical trial for a product that modulates such collaboration target.

AstraZeneca receives development and commercialization licenses associated with each designated drug candidate, and owes a milestone fee of $8.0 million for the first drug candidate selected from each research program. In addition, AstraZeneca is required to make certain other milestone payments to us upon the achievement of specified development, regulatory and commercial milestones. For each research program, we are eligible to receive, in addition to the milestone fee described above, up to $162.0 million in development, regulatory and commercial milestones on a research program by research program basis, for a total of up to $170.0 million in milestone payments per research program. In addition, to the extent any of the drug candidates covered by the licenses conveyed to AstraZeneca are commercialized, we would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of

net sales. Royalty payments are subject to certain reductions, including in certain countries where AstraZeneca faces generic competition.

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

Under the AstraZeneca Collaboration Agreement, AstraZeneca was granted an option to nominate additional targets on the same contractual terms as the initial targets. In May 2018, AstraZeneca made an irrevocable election to exercise the additional target option, giving AstraZeneca the option to designate additional targets, for $5.0 million that was paid by AstraZeneca to us in January 2019. In January 2022, AstraZeneca elected to extend the AZ Research Term for the fourth target by 12 months. As of December 31, 2022, the fourth target research program is in the AZ Research Term, and the remainder of the AstraZeneca collaboration programs have been terminated.

Oxurion

In August 2013, we entered into a research collaboration and license agreement, or the Oxurion Collaboration Agreement, with Oxurion NV, or Oxurion, which agreement was amended in November 2017. Under the Oxurion Collaboration Agreement, we were responsible for identifying *Bicycle* peptides related to the collaboration target, human plasma kallikrein, for use in various ophthalmic indications. Oxurion is responsible for further development and product commercialization after the defined research screening is performed by us. THR-149 was selected as a development compound under the Oxurion collaboration agreement. We granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Oxurion collaboration agreement provides for certain milestone payments to us upon the achievement of specified research, development, regulatory and commercial milestones. More specifically, for each collaboration compound, we are eligible to receive up to €8.3 million in research and development milestone payments, from which we have received €3.8 million as of December 31, 2022, in connection with the development of THR-149, and up to €16.5 million in regulatory milestone payments (e.g., €5 million for granting of first regulatory approval in either the United States or the European Union for the first indication). In addition, to the extent any of the collaboration products covered by the licenses granted to Oxurion are commercialized, we would be entitled to receive tiered royalty payments of mid-single digits based on a percentage of net sales. Royalty payments are subject to certain reductions. Also, if Oxurion grants a sublicense to a third party for rights to the program for non-ophthalmic use prior to the filing of an IND, we would be entitled to receive payments in the double digits (no higher than first quartile) based on a percentage of non-royalty sublicensing income. If Oxurion grants a sublicense to a third party for rights to the program for non-opthalmic use after the filing of an IND, we would be entitled to receive payments of mid-single digits to low teen-digits.

Either party may terminate the Oxurion Collaboration Agreement if the other party has breached any of its material obligations and such breach continues after the specified cure period. Either party may terminate the Oxurion Collaboration Agreement in the event of the commencement of any proceeding in or for bankruptcy, insolvency, dissolution or winding up by or against the other party. Oxurion may terminate the Oxurion Collaboration Agreement for convenience. We may terminate the Oxurion Collaboration Agreement if Oxurion challenges the validity of any licensed patents or opposes the grant of a licensed patent.

Founder Royalty Arrangements

We have entered into two royalty agreements with our founders, Christian Heinis, John Tite, and Sir Greg Winter, and our initial investors, Atlas Venture Fund VIII LP, Novartis Bioventures LTD. Pursuant to the first royalty agreement, we are obligated to pay an aggregate royalty percentage in the low single digits on net sales arising from

products licensed under the Oxurion collaboration agreement. Pursuant to the second royalty agreement, we are obligated to pay an aggregate royalty percentage in the low single digits on net sales arising from products licensed under the AstraZeneca collaboration agreement.

Intellectual Property

Overview

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including our *Bicycle* platform. This includes seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties, which are directed to the use of our Bicycle platform, composition of matter of bicyclic peptides identified through use of the platform and further chemical optimization, conjugates comprising such bicyclic peptides, methods of using our product candidates, and other inventions that are important to our business.

As of December 31, 2022, we had 4 patent families directed to novel scaffolds and linkers, 12 patent families directed to our platform technology, 75 composition of matter patent families directed to bicyclic peptides and related conjugates, and 12 patent families directed to later inventions relating to such bicyclic peptides and related conjugates, such as methods of making or using certain bicyclic peptide conjugates for treating various indications.

We own at least four patent families relating to our product candidate BT5528, including patent families directed to its composition of matter, methods of use for treating of cancer and methods of identifying patients suitable to receive BT5528. The issued patents in these families, and the pending patent applications if issued, are expected to expire between 2038 and 2041, not including any patent term extensions and/or patent term adjustments.

We own at least five patent families relating to our product candidate BT8009, including patent families directed to its composition of matter, methods of use for treating cancer, synthetic routes to BT8009 and methods of identifying patients suitable to receive BT8009. The issued patents in these families, and the pending patent applications if issued, are expected to expire between 2039 and 2042, not including any patent term extensions and/or patent term adjustments.

We own at least eight patent families relating to product candidate BT7480, including patent families directed to its composition of matter and the composition of matter of its constituent bicyclic peptides, methods of use for treating cancer, combinations with other active agents, and the methods of identifying patients suitable to receive BT7480. The issued patents from these families, and the pending patent applications, if issued, are expected to expire between 2038 and 2042, not including any patent term extensions and/or patent term adjustments.

We own at least two patent families relating to product candidate THR-149, which is licensed to Oxurion, including patent families directed to its composition of matter and method of treatment of related indications, including ophthalmic disorders. The issued patents from these families, and the pending patent applications if issued, are expected to expire between 2032 and 2034, not including any patent term extensions and/or patent term adjustments.

We own at least six patent families relating to our product candidate BT1718, including patent families directed to its composition of matter, methods of use for treating cancer, the pharmacokinetic profile of BT1718 and its synthesis. The issued patents in these families, and the pending patent applications if issued, are expected to expire between 2035 and 2040, not including any patent term extensions and/or patent term adjustments.

We also rely on trade secrets and know-how that may be important for the development of our business. This includes aspects of our proprietary technology platform and our continuing technological innovation to develop, maintain, and strengthen our position in the field of peptide, peptidomimetic, and small molecule-based therapeutics. We additionally may rely on regulatory protection afforded through data exclusivity, market exclusivity and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for our product candidates, technology and know-how, defend and enforce our patents; prevent others from infringing our proprietary rights, preserve the confidentiality of our trade secrets, and to operate without infringing the proprietary rights of others.

Our ability to stop third parties from making, having made, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable licenses, patents or trade secrets that cover these activities. In some cases, these rights may need to be enforced by third party licensors. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same. For more information, please see "Risk Factors — Risks Related to Our Intellectual Property."

We seek to protect our proprietary position in a variety of ways, including by pursuing patent protection in certain jurisdictions where it is available. For example, we file U.S. and certain foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets and that may be used to identify and develop novel products. We seek protection, in part, through confidentiality and proprietary information agreements. We are a party to various other license agreements that give us rights to use specific technologies in our research and development.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application related to the patent. A U.S. patent also may be accorded a patent term adjustment, or PTA, under certain circumstances to compensate for delays in obtaining the patent caused by the United States Patent and Trademark Office, or USPTO. In some instances, such a PTA may result in a U.S. patent term extending beyond 20 years from the earliest date of filing a non-provisional patent application related to the U.S. patent. In addition, in the United States, the term of a U.S. patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions.

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

Company-Owned Intellectual Property

As of December 31, 2022, our patent portfolio included 4 patent families directed to novel scaffolds and linkers, 12 patent families directed to our platform technology, 75 patent families directed to bicyclic peptides and related conjugates, and 12 patent families directed to later inventions relating to such bicyclic peptides and related conjugates, such as methods of making or using certain bicyclic peptide conjugates for treating various indications.

In total, as of December 31, 2022, we owned about 326 patents in the United States and in foreign jurisdictions, such as Australia, Canada, China, Europe, Hong Kong, Japan, New Zealand, Russia and Singapore. In addition, as of December 31, 2022, we had about 522 patent applications pending in the United States and in foreign jurisdictions, such as Argentina, Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, Korea, New Zealand, Russia, Singapore and Taiwan, as well as pending international applications under the Patent Cooperation Treaty, or PCT. These patents, as well as any patents that may be issued from these patent applications, are generally expected to have terms that will expire at various dates between February 2029 and December 2043, not including any patent term extensions and/or patent term adjustments.

In total, as of December 31, 2022, we owned 67 registered trademarks across four territories (United Kingdom, European Union, United States, and Japan), as well as a number of pending applications for new trademarks.

Trade Secret Protection

Finally, we may rely, in some circumstances, on trade secrets to protect our technology. We anticipate relying on trade secrets to protect the know-how behind our *Bicycle* platform. However, trade secrets can be difficult to protect. We seek to protect our technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For further information, please see "Risk Factors — Risks Related to Our Intellectual Property."

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a number of currently marketed products and product candidates in preclinical research and clinical development by third parties for the various oncology applications that we are targeting. For example, a number of multinational companies as well as large biotechnology companies, are developing programs for the targets that we are exploring for our BTC programs, including Seagen, which has a marketed Nectin-4 antibody-drug conjugate. Furthermore, many companies are pursuing development programs for CD137 or CD137 bi-specific antibodies. In addition, we are aware that technologies for drug discovery, including peptide-based medicines, continue to advance rapidly, which may compete with our own screening technology or render it obsolete.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in discovering product candidates, obtaining approval for drugs and achieving widespread market acceptance. Our competitors' drugs may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

Sales and Marketing

Subject to receiving marketing approval, we intend to pursue the commercialization of our product candidates either by building internal sales and marketing capabilities or through opportunistic collaborations with others.

We plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Manufacturing

Each of our *Bicycles* is entirely synthetic. We believe the synthetic nature of our product candidates allow for a more cost effective and scalable manufacturing process compared to biologics. In addition, this property of *Bicycles* allows for the manufacturing of product candidates of consistent pharmaceutical quality with favorable stability characteristics. Based on our experience, we believe that the manufacturing of *Bicycles* can be made to be well controlled, reproducible and scalable.

We operate an outsourced model for the manufacture of our product candidates, and contract with multiple good manufacturing practice, or GMP, licensed pharmaceutical contract development and manufacturing organizations, both for the synthesis of each drug substance component, and the formulation and packaging of each finished drug product candidates. We selected these organizations based on their experience, capability, capacity and regulatory status. Projects are managed by a specialist team of our internal staff, which is designed to promote compliance with the technical aspects and regulatory requirements of the manufacturing process. We do not own or operate GMP manufacturing facilities, nor do we currently plan to build our own GMP manufacturing capabilities for production of clinical or commercial supply.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs and devices under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities. In addition, an applicant may need to recall a product.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of nonclinical, or preclinical, laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;

- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent IRB representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of a new drug application, or NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA can place an IND on full or partial clinical hold at any point in development, and depending upon the scope of the hold, clinical trial(s) may not restart until resolution of the outstanding concerns to the FDA's satisfaction.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA

regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- ***Phase I.*** The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- ***Phase II.*** The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- ***Phase III.*** The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

- ***Phase IV.*** Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase I, Phase II and Phase III clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the applicant must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to substantial user fees, and the sponsor of an approved NDA is also subject to annual program user fees. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor whether the application is sufficiently complete to permit substantive review. The FDA may request additional

information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are Fast Track designation, Breakthrough Therapy designation and priority review designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's NDA before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing an application under rolling review does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical

evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting adverse reaction, documented enhancement of patient compliance that is expected to lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit and to provide regular updates to the FDA on the progress of such studies. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase IV or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase IV clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the NDA holder and any third-party manufacturers that the NDA holder may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or voluntary product recalls;

- fines, warning letters or holds on post-approval clinical trials;

- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;

- product seizure or detention, or refusal to permit the import or export of products; or

- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs generally may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Drug Supply Chain Security Act, which regulates the distribution of drugs at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states, which additionally limit the distribution of prescription pharmaceutical products and impose requirements to ensure accountability in distribution.

Companion Diagnostics

We may employ companion diagnostics to help us to more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics can identify patients who are most likely to benefit from a particular therapeutic product; identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness. Companion diagnostics are regulated as medical devices by the FDA and, as such, require either clearance or approval prior to commercialization. The level of risk combined with available controls to mitigate risk determines whether a companion diagnostic device requires Premarket Approval Application, or PMA, approval or is cleared through the 510(k) premarket notification process. For a novel therapeutic product for which a companion diagnostic device is essential for the safe and effective use of the product, the companion diagnostic device should be developed and approved or 510(k)-cleared contemporaneously with the therapeutic. The use of the companion diagnostic device will be stipulated in the labeling of the therapeutic product.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug."

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, which states the proposed generic drug will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. An applicant who submits a section 505(b)(2) NDA, which is for new or improved formulations or new uses of previously approved drug products and where at least one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, also must certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV

certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will be receiving orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the

effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Europe/Rest of World Regulation

In addition to regulations in the United States, there are a variety of regulations in other jurisdictions governing, among other things, clinical trials, commercial sales and distribution of medicinal products. Even if FDA approval of a particular product is obtained, it must still obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. Previously, in the European Union, pursuant to the EU Clinical Trials Directive 2001/20/EC, a clinical trial application had to be submitted to each country's national regulatory authority in which the clinical trial was to take place, together with an independent ethics committee, much like the FDA and IRB, respectively. In 2014, a new Clinical Trials Regulation 536/2014, replacing the current Directive, was adopted. The new Regulation is directly applicable in all EU Member States (without national implementation) and entered into application on January 31, 2022. The new Regulation seeks to simplify and streamline the approval of clinical trials in the European Union. Pursuant to the Regulation, the sponsor shall submit a single application for approval of a clinical trial via the EMA's Clinical Trials Information System, or CTIS, which will cover all regulatory and ethics assessments from the member states concerned. Any submissions made from January 31, 2023 onwards must be made through CTIS and all trials authorized pursuant to the Directive that are still ongoing on January 31, 2025 must be made through CTIS. Once the CTA is approved in accordance with a member state's requirements, clinical trial development may proceed. Approval and monitoring of clinical trials in the European Union is, as it was under the Directive, the responsibility of individual member states, but compared to the position prior to the applicability of the Clinical Trials Regulation there is likely to be more collaboration, information-sharing, and decision-making between member states. The new Regulation also aims to streamline and simplify the rules on safety reporting and introduces enhanced transparency requirements, such as mandatory submission of a summary of the clinical trial results to a new EU Database.

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

- The centralized MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, and which is valid throughout the entirety of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing an active substance not authorized in the EEA before May 20, 2004, for products that constitute a significant therapeutic, scientific or technical innovation or for which a centralized authorization would be in the interest of patients.

- National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. Products receiving orphan designation, can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product's market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the criteria for orphan drug designation are no longer met, in other words, when it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply sufficient quantities of the orphan medicinal product.

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

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

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, no uniform policy for coverage and reimbursement exists in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. Therefore, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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

Outside the United States, ensuring adequate coverage and payment for our product candidates will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control

company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Other Healthcare Laws and Regulations

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Such restrictions under applicable federal and state healthcare laws and regulations, include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, health information privacy and security, price reporting and physician sunshine laws. Some of our pre-commercial activities are subject to some of these laws.

The federal Health Care Program Anti-Kickback Statute, or Anti-Kickback Statute, prohibits any person or entity, including a prescription drug manufacturer or a party acting on its behalf, from, among other things, knowingly and willfully, directly or indirectly, soliciting, receiving, offering, or providing any remuneration that is intended to induce the referral of business, including the purchase, order or recommendation or arranging of, any good or service for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the Anti-Kickback Statute has been violated. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Moreover, a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

The federal civil False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, for payment to, or approval by, federal programs, including Medicare and Medicaid, claims for items or services, including drugs, that are false or fraudulent or not provided as claimed. Persons and entities can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, any of our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and other third-party payor reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for federal civil False Claims Act violations may include up to three times the actual damages sustained by the government, plus significant mandatory civil penalties for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, False Claims Act violations may also implicate various federal criminal statutes.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false,

fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Like the Anti-Kickback Statute a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Also, many states have similar fraud and abuse statutes or regulations that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, to the extent that any of our product candidates, if approved, are sold in a foreign country, we may be subject to similar foreign laws.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, including the final omnibus rule published on January 25, 2013, mandates, among other things, the adoption of uniform standards for the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy and security of individually identifiable health information, which require the adoption of administrative, physical and technical safeguards to protect such information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, defined as independent contractors or agents of certain healthcare providers, healthcare clearinghouses and health plans, known as covered entities, that create, receive or obtain protected health information in connection with providing a service for or on behalf of a covered entity or another business associate. HITECH also increased the civil and criminal penalties that may be imposed against covered entities and business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, certain state and foreign laws govern the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. For further information concerning the data privacy and security laws we may be subject to and our processing of personal data, see the risk factor titled "*We are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation, fines and penalties, disruptions of our business operations, reputational harm, loss of revenue or profits, and other adverse business consequences.*"

The U.S. federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, ACA, including the provision commonly referred to as the Physician Payments Sunshine Act imposed, among other things, annual reporting requirements for covered manufacturers for certain payments and other transfers of value provided to physicians, as defined by such law, other healthcare professionals (such as physician assistant and nurse practitioners), and teaching hospitals, as well as certain ownership and investment interests held by physicians and their immediate family members.

In addition, we may be subject to certain analogous state and foreign laws of each of the above federal healthcare laws. In some instances, such laws may be broader in scope than its federal counterpart, such as certain state anti-kickback and false claims laws, which may apply to claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers. In addition, certain states and local jurisdictions also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices or require the tracking and reporting of gifts, compensation or other remuneration to physicians and other healthcare professionals.

Because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs, we intend to develop a comprehensive compliance program that establishes internal control to facilitate adherence to the rules and program requirements to which we will or may become subject. Although the development and implementation of compliance programs designed to establish internal control and facilitate compliance can mitigate the risk of investigation, prosecution, and penalties assessed for violations of these laws, the risks cannot be entirely eliminated.

If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, significant administrative, civil and criminal penalties, damages, fines, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state

healthcare programs, including Medicare and Medicaid, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Healthcare Reform

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress passed the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;

- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

- expansion of the types of entities eligible for the 340B drug discount program;

- establishment of the Medicare Part D coverage gap discount program by requiring manufacturers to now provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- establishment of a Center for Medicare and Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

There have been judicial, executive branch and Congressional challenges to certain aspects of the ACA. President Trump signed several Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing or delaying penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance, eliminating the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. On 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. Prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. On August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost through a newly established manufacturer discount program. It is unclear how any additional healthcare reform measures of the Biden administration or future legal challenges will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to legislative amendments, will remain in effect through 2031 unless additional Congressional action is taken. However, certain COVID-19 relief legislation suspended the Medicare sequester from May 1, 2020 through March 31, 2022. Following the termination of the sequester, under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Also, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries, Presidential executive orders and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the former Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. In July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to President Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles.

In addition, the IRA will, among other things, (i) allow HHS to negotiate the price of certain drugs and biologics covered under Medicare, and subject drug manufacturers to civil monetary penalties and a potential excise tax by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law, and (ii) impose rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. It is currently unclear how the IRA will be effectuated but is likely to have a significant impact on the pharmaceutical industry.

At the state level, individual states in the United States are increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient

reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Further, it is possible that additional governmental action is taken in response to the ongoing COVID-19 pandemic. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit, and the United Kingdom officially withdrew from the European Union on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom was subject to a transition period until December 31, 2020, or the Transition Period, during which European Union rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, which outlines the future trading relationship between the United Kingdom and the European Union, was agreed upon in December 2020 and formally entered into force on May 1, 2021.

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

Orphan designation in Great Britain following Brexit is, unlike in the European Union, not available pre-marketing authorization. Applications for orphan designation are made at the same time as an application for a marketing authorization. The criteria to be granted an orphan drug designation are essentially identical to those in the European Union but based on the prevalence of the condition in Great Britain. It is therefore possible that conditions that were or would have been designated as orphan conditions in Great Britain prior to the end of the Transition Period are or would no longer be and that conditions that were not or would not have been designated as orphan conditions in the European Union will be designated as such in Great Britain.

The European Union's regulatory environment for clinical trials has been harmonized as part of the Clinical Trials Regulation, which entered into application on January 31, 2022. It is currently unclear as to what extent the United Kingdom will seek to align its regulations with the European Union.

Employees and Human Capital

As of December 31, 2022, we had 236 full-time or part-time employees, including 86 with M.D. or Ph.D. degrees. Of these employees, 187 employees are engaged in research and development activities and 49 employees are engaged in general and administrative activities. Our employees are primarily based at the locations of our office and laboratory facilities: 156 are located in the United Kingdom and 80 are located in the United States. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider the relationship with our employees to be good.

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

Compensation and Benefits

We believe our employees are our most valuable assets and are key to achieving our goals. We focus our efforts on attracting and retaining a diverse, high-performing workforce through offering competitive and fair compensation packages that are based on robust industry market data. Our total compensation package includes competitive base pay, annual bonus, equity participation, and a broad range of benefits, including retirement planning, healthcare and insurance benefits, paid time off, paid family and medical leave, flexible working, and various health and wellness programs. We also run recognition programs that highlight employees who exhibit exceptional performance and demonstrate our company values.

We ensure that our compensation programs are designed to be equitable and fair, and routinely analyze data to ensure that our programs are administered on a fair and equitable basis.

Diversity, Equity and Inclusion (DEI)

We believe a diverse workforce is critical to our success and we are fundamentally committed to creating and maintaining a work environment in which employees are treated fairly, with dignity, decency, respect and in accordance with all applicable laws. We understand that varied perspectives lead to the best ideas and outcomes. We believe that by creating a workplace where every individual can feel welcome and valued, we will be better able to achieve our corporate objectives. All employees must adhere to a code of business conduct and ethics and our employee handbook, which combined, define standards for appropriate behavior and are annually trained to help prevent, identify, report, and stop any type of discrimination and harassment. Our recruitment, hiring, development, training, compensation, and advancement is based on qualifications, performance, skills, and experience without regard to gender, race, or ethnicity.

We have formed a cross-functional DEI network that continues to develop the DEI strategy.

Career Development

We invest heavily in our employees' personal and professional development. We offer a vast array of learning and development opportunities including online and classroom training and learning, mentoring and coaching programs, training academies and management and leadership development programs.

We are committed to developing the next generation of talent and providing our employees with opportunity, and have active internship partnerships with local universities in both the United States and United Kingdom.

Corporate Information

In 2009, we were incorporated as a limited liability company under the laws of England and Wales. In 2017, we effected a reorganization to create a new holding company which, in connection with our IPO, was re-registered as a public limited company named Bicycle Therapeutics plc. Bicycle Therapeutics plc is the parent company of three wholly owned subsidiaries, two of which are based in Cambridge, United Kingdom and one of which is based in Massachusetts, United States, that carry on our business.

The U.K. subsidiaries are BicycleTx Limited and BicycleRD Limited, and the U.S. subsidiary is Bicycle Therapeutics Inc. Our principal executive offices are located at Blocks A & B, Portway Building, Granta Park, Great Abington, Cambridge, CB21 6GS, United Kingdom, and our phone number is +44 1223 261503.

Available Information

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

Item 1A. Risk Factors.

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

Summary of Selected Risk Factors

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

- We have a history of significant operating losses and expect to incur significant and increasing losses for the foreseeable future, and we may never achieve or maintain profitability.
- We may need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product discovery and development programs or commercialization efforts.
- 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.
- Our failure to comply with the covenants or payment obligations under our existing term loan facility with Hercules Capital, Inc., or Hercules, could result in an event of default, which may result in increased interest charges, acceleration of our repayment obligations or other actions by Hercules, any of which could negatively impact our business, financial condition and results of operations.
- We are substantially dependent on the success of our internal development programs and of our product candidates from our *Bicycle* Toxin Conjugate, or BTC, and *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™, programs, which may not successfully complete clinical trials, receive regulatory approval or be successfully commercialized.
- We are at an early stage in our development efforts, and our product candidates and those of our collaborators represent a new category of medicines and may be subject to heightened regulatory scrutiny until they are established as a therapeutic modality.

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

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

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

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

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

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

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

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

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

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

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

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

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

- We are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation, fines and penalties, disruptions of our business operations, reputational harm, loss of revenue or profits, and other adverse business consequences.

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

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

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

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

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

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

Risks Related to Our Financial Position and Need for Additional Capital

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

We do not expect to generate revenue or profitability that is necessary to finance our operations in the short term. Since inception, we have incurred recurring losses, including net losses of $112.7 million, $66.8 million and $51.0 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, the Company had an accumulated deficit of $331.1 million. To date, we have not commercialized any products or generated any revenues from the sale of products, and absent the realization of sufficient revenues from product sales, we may never attain profitability in the future. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical trials. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our shareholders' equity and working capital.

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

- continue to develop and conduct clinical trials with respect to our BTC™ and *Bicycle* TICA™ programs and our other pipeline programs;

- initiate and continue research, preclinical and clinical development efforts for any future product candidates;

- seek to discover and develop additional product candidates and further expand our clinical product pipeline;

- seek marketing and regulatory approvals for any product candidates that successfully complete clinical trials;

- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;

- maintain, expand and protect our intellectual property portfolio;

- expand our research and development infrastructure, including hiring and retaining additional personnel, such as clinical, quality control and scientific personnel;

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

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

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

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

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

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

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

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

companies in the early stages of development, especially clinical-stage biopharmaceutical companies such as ours. Any predictions made about our future success or viability may not be as accurate as they would be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

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

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

We may need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate 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 ongoing costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

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

We believe that our existing cash and cash equivalents of $339.2 million as of December 31, 2022, will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Annual Report. Our estimate may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of, and research and preclinical development efforts for, our current and future product candidates;
- our ability to enter into, and the terms and timing of, any collaborations, licensing or other arrangements;
- our ability to identify one or more future product candidates for our pipeline;
- the number of future product candidates that we pursue and their development requirements;

- the outcome, timing and costs of seeking regulatory approvals;

- the costs of commercialization activities for any of our product candidates that receive marketing approval to the extent such costs are not the responsibility of any collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;

- subject to receipt of marketing approval, revenue, if any, received from commercial sales of our current and future product candidates;

- our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure;

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

- the costs of operating as a public company.

While the long-term economic impact of either the COVID-19 pandemic or the conflict between Russia and Ukraine is difficult to assess or predict, each of these events has caused significant disruptions to the global financial markets and contributed to a general global economic slowdown. Furthermore, inflation rates, particularly in the United States and the United Kingdom, have increased recently to levels not seen in decades. Increased inflation may result in increased operating costs (including labor costs) and may affect our operating budgets. In addition, the U.S. Federal Reserve has raised, and is expected to further raise, interest rates in response to concerns about inflation. Increases in interest rates, especially if coupled with reduced government spending and volatility in financial markets, may further increase economic uncertainty and heighten these risks. If the disruptions and slowdown deepen or persist, we may not be able to access additional capital on favorable terms, or at all, which could in the future negatively affect our financial condition and our ability to pursue our business strategy.

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

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

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

We are party to a secured term loan facility with Hercules. As of December 31, 2022, our outstanding borrowings under this facility totaled $30.0 million. In connection with the Loan and Security Agreement, as amended, with Hercules, or the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control (as defined by the Loan Agreement), financial reporting obligations, and certain limitations on indebtedness, liens (including a negative pledge on intellectual property and other assets), investments, distributions (including dividends), collateral, investments, transfers, mergers or acquisitions, taxes, corporate changes, and deposit accounts. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, the occurrence of certain events that could reasonably be expected to have a material adverse effect as set forth in the Loan Agreement, cross acceleration to third-party indebtedness and certain events relating to bankruptcy or insolvency. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal and interest payments due, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement, including proceeding against the collateral securing such indebtedness. Such increased interest charges, accelerated repayment, proceedings against the collateral or other actions may have a negative impact on our business, financial condition and results of operations.

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

As of December 31, 2022, we had $30.0 million of borrowings outstanding under the Loan Agreement with Hercules with an interest rate that is capped at 9.05%. 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 that targets 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 FDA in the United States, or the European Commission, whose decision is based on a recommendation from the European Medicines Agency, or EMA, in Europe or similar regulatory authorities will approve our BTCs or any of our other product candidates for any given indication for several potential reasons, including the failure to follow Good Clinical Practice, or GCP, a negative assessment of the risks and benefits, insufficient product quality control and standardization, failure to have Good Manufacturing Practices, or GMP, compliant manufacturing facilities, or the failure to agree with regulatory authorities on clinical endpoints.

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

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

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

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

- obtain and enforce sufficient intellectual property rights for any approved products and product candidates and maintain freedom to operate for such products with respect to the intellectual property rights of third parties.

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

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

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

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

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

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

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

Preclinical studies and clinical trials are long, expensive and unpredictable processes that can be subject to extensive delays. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. It may take several years and require significant expenditures to complete the preclinical studies and clinical trials necessary to commercialize a product candidate, and delays or failure are inherently unpredictable and can occur at any stage. New or ongoing public health crises, such as the ongoing COVID-19 pandemic, 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. Interruptions resulting from such crises may reduce our, or our collaboration partners', abilities to administer the investigational product to enrolled patients, present difficulties for enrolled patients to adhere to protocol-mandated visits and laboratory/diagnostic testing, increase the possibility of patient dropouts, or impact our, and our suppliers', abilities to provide investigational product to trial sites, all of which could negatively impact the data we are able to obtain from our clinical trials and complicate regulatory review.

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

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

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

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

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

receive certain contractual payments, which could have a material adverse effect on our business, financial position, results of operations and future growth prospects.

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

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

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

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

In addition, clinical testing of BT5528, BT8009 and BT1718 is currently taking place outside of the United States. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

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

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

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

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

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

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

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

We may employ companion diagnostics to help us more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are

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

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

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

Four of our product candidates are currently undergoing safety testing in the form of Phase I/IIa or Phase I/II clinical trials. None of our products have completed this testing to date. While our current and future product candidates will undergo safety testing to the extent possible and, where applicable, under such conditions discussed with regulatory authorities, not all adverse effects of drugs can be predicted or anticipated. Unforeseen side effects could arise either during clinical development or, if such side effects are rarer, after our products have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. So far, we have not demonstrated, and we cannot predict if ongoing or future clinical trials will demonstrate, that BT5528, BT8009, BT7480, BT1718 or any other of our product candidates are safe in humans.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify

undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following consequences could occur:

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

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

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

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

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

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

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for

specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

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

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

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

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

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

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

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

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

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

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

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

to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

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

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

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

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

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

The potential impact on our results of operations and liquidity resulting from Brexit remains unclear. The actual effects of Brexit will depend upon many factors and significant uncertainty remains. By way of example, the Retained EU Law (Revocation and Reform) Bill 2022, which is currently progressing through UK Parliament seeks to allow the UK government to repeal or replace certain EU Law that was incorporated into UK law effective as of the end of the Transition Period to provide for certainty. The outcome of such process is unclear, but has the potential to cause further Brexit-related uncertainty.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit has had, and will continue to have, a material impact on the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, Great Britain is no longer covered by the centralized procedures for obtaining European Union-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in Great Britain. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and

restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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

Brexit may influence the attractiveness of the United Kingdom as a place to conduct clinical trials. The European Union's regulatory environment for clinical trials has been harmonized as part of the Clinical Trials Regulation, which entered into application on January 31, 2022. The MHRA has conducted a consultation on proposed revisions to U.K. clinical trials legislation, but it is currently unclear as to what extent the United Kingdom will seek to align its regulations with the European Union. Failure of the United Kingdom to closely align its regulations with the European Union may have an effect on the cost of conducting clinical trials in the United Kingdom as opposed to other countries and/or make it harder to seek a marketing authorization for our product candidates on the basis of clinical trials conducted in the United Kingdom. Pursuant to the Regulation, clinical trial data arising from a clinical trial site in a country outside of the EEA that is used in applications for clinical trial approval in the European Union must adhere to standards that are equivalent to those found in the Regulation. In the short term, there will be few changes to clinical trials that only have sites in the United Kingdom. The MHRA has confirmed that the sponsor of a clinical trial can be based in the EEA for an initial period following Brexit. Further investigational medicinal products can be supplied directly from the European Union/EEA to either a trial site or a distribution hub in Great Britain. Such products will require oversight by the holder of a U.K. Manufacturing and Import Authorisation but do not currently require recertification. The United Kingdom is now a "third country" for the purpose of clinical trials that have sites in the EEA. For such trials the sponsor/legal representative must be based in the EEA, and the trial must be registered on the EU Clinical Trials Register (including data on sites outside of the EEA).

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

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

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

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

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

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

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

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

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

Recruiting and training an internal commercial organization is expensive and time consuming and could delay any product launch. Some or all of these costs may be incurred in advance of any approval of any of our product candidates. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing

capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire a sales force in the United States or other target market that is sufficient in size or has adequate expertise in the medical markets that we intend to target.

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

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

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

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

Cancer therapies are sometimes characterized as first-line, second-line, third-line or later-line therapies, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy, immunotherapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We may initially seek approval of BT5528, BT8009, BT7480, BT1718 and any other product candidates we develop as a therapy for patients who have received one or more prior treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval potentially as a first-line therapy, but there is no guarantee that product candidates we develop, even if approved, would be approved for first-line therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

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

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

Any marketing approvals that we receive for any current or future product candidate may be subject to limitations on the approved indicated uses for which the product may be marketed or the conditions of approval, or contain requirements for potentially costly post-market testing and surveillance to monitor the safety and efficacy of the

product candidate. The FDA may also require a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval of any product candidate, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. If the FDA or a comparable foreign regulatory authority approves a product candidate, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import and export and record keeping for the product candidate will be subject to extensive and ongoing regulatory requirements. These requirements include, among others, submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current Good Manufacturing Practice, or cGMP, and Good Clinical Practice, or GCP, for any clinical trials that we conduct post-approval, and prohibitions on the promotion of an approved product for uses not included in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products.

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

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

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

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

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

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

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

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

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

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

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

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

- the potential efficacy and potential advantages over alternative treatments;

- the frequency and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;

- the frequency and severity of any side effects resulting from follow-up requirements for the administration of our product candidates;

- the relative convenience and ease of administration;

- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

- the strength of marketing and distribution support and timing of market introduction of competitive products;

- publicity concerning our products or competing products and treatments; and

- sufficient third-party insurance coverage and adequate reimbursement.

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

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

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

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

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

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

We expect the cost of our product candidates to be substantial, when and if they achieve market approval. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of our product candidates will depend substantially, both domestically and abroad, on

the extent to which the costs of our product candidates will be paid by private payors, such as private health coverage insurers, health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health care programs, such as Medicare and Medicaid. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, even if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

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

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

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

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

that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

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

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

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

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

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

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

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

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

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

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

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

- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the Anti-

Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

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

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

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

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

Additionally, we are subject to U.S. state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the Anti-Kickback Statute and FCA, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. Certain states and local jurisdictions also require the registration of pharmaceutical sales representatives. There are ambiguities as to what is required to comply with these state requirements, and if we fail to comply with an applicable state law requirement we could be subject to significant penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. For further information concerning the data privacy and security laws we may be subject to and our processing of personal data, see the risk factor titled "*We are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation, fines and penalties, disruptions of our business operations, reputational harm, loss of revenues or profits, and other adverse business consequences.*"

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, 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. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. On August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or the IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket costs through a newly established manufacturer discount program. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013, and due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2031 unless additional Congressional action is taken. However, pursuant to certain COVID-19 relief legislation these Medicare sequester reductions were suspended from May 1, 2020 through March 31, 2022. Following the resumption of the sequester, under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries, Presidential executive orders and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. In addition, the IRA, among other things, (i) allows HHS to negotiate the price of certain drugs and biologics covered under Medicare, and subjects drug manufacturers to civil monetary penalties and a potential excise tax by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law, and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. It is currently unclear how the IRA will be effectuated but it is likely to have a significant impact on the pharmaceutical industry. Similarly, individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures.

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

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

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

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

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

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

We are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation, fines and penalties, disruptions of our business operations, reputational harm, loss of revenue or profits, and other adverse business consequences.

In the ordinary course of business, we collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, processing) personal data and other sensitive information, including proprietary and confidential business data, trade secrets, intellectual property, data we collect about trial participants in connection with clinical trials, and sensitive third-party data. Our data processing activities may subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contractual requirements, and other obligations relating to data privacy and security.

In the United States, federal, state, and local governments have enacted numerous data privacy and security laws, including data breach notification laws, personal data privacy laws, consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), and other similar laws. For example, the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, imposes specific requirements relating to the privacy, security, and transmission of individually identifiable health information. Additionally, various U.S. states, including California, Virginia and Colorado, have passed comprehensive privacy laws, and similar laws are being considered in several other states, as well as at the federal and local levels. These developments may further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties upon whom we rely.

Outside of the U.S., an increasing number of laws, regulations, and industry standards may govern data privacy and security. For example, the European Union's General Data Protection Regulation, or EU GDPR, and the United Kingdom's GDPR, or UK GDPR, impose strict requirements for processing personal data. For example, under the EU GDPR, companies may face temporary or definitive bans on data processing and other corrective actions; fines of up to 20 million Euros or 4% of annual global revenue, whichever is greater; or private litigation related to processing of personal data brought by classes of data subjects or consumer protection organizations authorized at law to represent their interests.

In the ordinary course of business, we transfer personal data from the United Kingdom (UK) to the United States or other countries. The UK has enacted laws requiring data to be localized or limiting the transfer of personal data to the United States and other countries whose privacy laws it believes are inadequate. Although there are currently various mechanisms that may be used to transfer personal data from the UK to the United States in compliance with law, such as the UK data transfer agreement, these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal data to the United States. If there is no lawful manner for us to transfer personal data from the UK to the United States, or if the requirements for a legally-compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors, and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Additionally, companies that transfer personal data out of the UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators, individual litigants, and activist groups.

In addition to data privacy and security laws, we are also bound by other contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful.

We may publish privacy policies, marketing materials, and other statements, regarding data privacy and security. If these policies, materials, or statements are found to be deficient, lacking in transparency, deceptive, unfair, or misrepresentative of our practices, we may be subject to investigation, enforcement actions by regulators, or other adverse consequences.

Obligations related to data privacy and security are quickly changing, becoming increasingly stringent, and creating regulatory uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflicting among jurisdictions. Preparing for and complying with these obligations requires us to devote significant resources and may necessitate changes to our services, information technologies, systems, and practices and to those of any third parties that process personal data on our behalf.

We may at times fail (or be perceived to have failed) in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties on whom we rely may fail to comply with such obligations, which could negatively impact our business operations. If we or the third parties on which we rely fail, or are perceived to have failed, to address or comply with applicable data privacy or security obligations, we could face significant consequences, including but not limited to: government enforcement actions (e.g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class-action claims); additional reporting requirements and/or oversight; bans on processing personal data; and orders to destroy or not use personal data. Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: loss of customers; inability to process personal data or operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or substantial changes to our business model or operations.

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

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, including, without limitation, restrictive regulations such as the EU GDPR and UK GDPR governing the use, processing, and cross-border transfer of personal data;
- 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.

Any or all of these factors could have a material adverse impact on our business, financial condition and results of operations. Moreover, global instability increased after Russia invaded Ukraine in February 2022. In response to the invasion, North Atlantic Treaty Organization, or NATO, has deployed additional military forces to Eastern Europe, including to Lithuania, and the United Kingdom, the European Union and the United States implemented certain sanctions against Russia. The invasion of Ukraine and the retaliatory measures that have been taken, or could be taken in the future, by the United States, NATO, and other countries have created global security concerns that could result in a regional conflict and otherwise have a lasting impact on regional and global economies, any or all of which could disrupt

our supply chain and increase the costs associated with or otherwise adversely affect our ability to conduct ongoing and future clinical trials of our product candidates. In addition, the conflict has had significant ramifications on global financial markets, which may adversely impact our ability to raise capital in the future on favorable terms or at all.

Cyber-attacks or other failures in telecommunications or information technology systems and deficiency in our, or those of third parties upon which we rely, cybersecurity could result in information theft, data corruption and significant disruption of our business operations

In the ordinary course of business, we and the third parties upon which we rely, may collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, processing) proprietary, confidential, and sensitive data, including personal data (such as health-related data), intellectual property, and trade secrets (collectively, sensitive information). Cyber-attacks, malicious internet-based activity, online and offline fraud, and other similar activities threaten the confidentiality, integrity, and availability of our sensitive information and information technology systems, and those of the third parties upon which we rely. Such threats are prevalent and continue to rise, are increasingly difficult to detect, and come from a variety of sources, including traditional computer "hackers," threat actors, "hacktivists," organized criminal threat actors, personnel (such as through theft or misuse), sophisticated nation states, and nation-state-supported actors.

Some actors now engage and are expected to continue to engage in cyber-attacks, including without limitation nation-state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and the third parties upon which we rely may be vulnerable to a heightened risk of these attacks, including retaliatory cyber-attacks, that could materially disrupt our systems and operations, supply chain, and ability conduct our research and development programs and our clinical trials. We and the third parties upon which we rely may be subject to a variety of evolving threats, including but not limited to social-engineering attacks (including through phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks (such as credential stuffing), credential harvesting, personnel misconduct or error, ransomware attacks, supply-chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, and other similar threats. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, loss of sensitive data and income, reputational harm, and diversion of funds. Remote work has become more common and has increased risks to our information technology systems and data, as more of our employees utilize network connections, computers, and devices outside of our premises or network, including working at home, while in transit and in public locations. Future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Furthermore, we may discover security issues that were not found during due diligence of such acquired or integrated entities, and it may be difficult to integrate companies into our information technology environment and security program.

In addition, our reliance on third-party service providers could introduce new cybersecurity risks and vulnerabilities, including supply-chain attacks, and other threats to our business operations. We may rely on third-party service providers and technologies to operate critical business systems to process sensitive information in a variety of contexts, including, without limitation, encryption and authentication technology, employee email, content delivery to customers, CROs for managing clinical trial data, and other functions. We may also rely on third-party service providers to provide other products, services, parts, or otherwise operate our business. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, the liability of such third party may be limited such that any award may be insufficient to cover our damages, or we may be unable to recover any such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

Any of the previously identified or similar threats could cause a security incident or other interruption that could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption,

disclosure of, or access to our sensitive information or our information technology systems, or those of the third parties upon whom we rely. A security incident or other interruption could disrupt our ability (and that of third parties upon whom we rely) to provide our services. We may expend significant resources or modify our business activities (including our clinical trial activities) to try to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures or industry-standard or reasonable security measures to protect our information technology systems and sensitive information.

Applicable data privacy and security obligations may require us to notify relevant stakeholders of security incidents. Such disclosures are costly, and the disclosure or the failure to comply with such requirements could lead to adverse consequences. If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences. These consequences may include: government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing sensitive information (including personal data); litigation (including class-action claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant consequences may cause customers to stop using our services, deter new customers from using our services, and negatively impact our ability to grow and operate our business. Our contracts may not contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts are sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, that such coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future claims.

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

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

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

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

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

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

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

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

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

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

For example, we were previously involved in litigation with Pepscan Systems B.V., and its affiliates, or Pepscan, related to a non-exclusive patent license agreement that our subsidiary, BicycleRD Limited, or BicycleRD, entered into with Pepscan in 2009. 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, paid €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 impacts due to the ongoing COVID-19 pandemic or the Russia-Ukraine war. If our third-party manufacturers are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed or infeasible, and regulatory approval or commercial launch of that product candidate may be delayed or not obtained, which could significantly harm our business.

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

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

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

- reliance on third parties for manufacturing process development, regulatory compliance and quality assurance;

- limitations on supply availability resulting from capacity and scheduling constraints of third parties;

- the possible breach of manufacturing agreements by third parties because of factors beyond our control; and

- the possible termination or non-renewal of the manufacturing agreements by the third party, at a time that is costly or inconvenient to us.

Third-party manufacturers may not be able to comply with cGMP requirements or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and/or criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. In addition, some of the product candidates we intend to develop, including BT5528, BT8009, and BT1718 use toxins or other substances that can be produced only in specialized facilities with specific authorizations and permits, and there can be no guarantee that we or our manufacturers can maintain such authorizations and permits. These specialized requirements may also limit the number of potential manufacturers that we can engage to produce our product candidates, and impair any efforts to transition to replacement manufacturers.

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

If the third parties that we engage to supply any materials or manufacture product for our preclinical tests and clinical trials should cease to continue to do so for any reason, including as a result of the impacts of new or ongoing public health crises, such as COVID-19, on the global workforce and manufacturing operations, we likely would experience delays in advancing these tests and trials while we identify and qualify replacement suppliers or manufacturers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our product candidates or the substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively.

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

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

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

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

secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

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

Risks Related to Our Intellectual Property

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on research, manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. As of December 31, 2022, our patent portfolio included 4 patent families directed to novel scaffolds and linkers, 12 patent families directed to our platform technology, 75 composition of matter patent families directed to bicyclic peptides and related conjugates, and 12 patent families directed to later inventions relating to such bicyclic peptides and related conjugates, such as methods of making or using certain bicyclic peptide conjugates for treating various indications. As of December 31, 2022, our trademark portfolio consisted of 67 trademark registrations across 4 territories (the United Kingdom, European Union, United States and Japan) as well as a number of pending applications for new trademarks.

In certain situations and as considered appropriate, we have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, or whether the claims of any resulting patents will provide us with a competitive advantage or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection. It is possible that defects of form in the preparation or filing of patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If there are material defects in the form, preparation, prosecution or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents.

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

with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected.

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

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

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

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

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

If we initiate legal proceedings against a third-party to enforce a patent covering one of our products or product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product or product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the United States Patent and Trademark Office (USPTO), or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

products. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Employee Matters and Managing Growth

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 our hybrid work environment, information that is normally protected, including company confidential information, may be less secure. We have adopted a code of conduct and business ethics to which all of our employees must adhere, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and

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

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

We have recently experienced significant growth in the number of our employees and the scope of our operations and expect to continue to expand, 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 Cambridge, 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 February 23, 2023, the trading price of our ADSs has ranged from $6.24 to $62.08. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, holders of our ADSs may not be able to sell their ADSs at or above price at which they purchased their ADSs. The market price for our ADSs may be influenced by many factors, including:

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

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

The global economy, including credit and financial markets, has experienced extreme volatility and disruptions, including, among other things, severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, supply chain shortages, increases in inflation rates, higher interest rates and uncertainty about economic stability. For example, the COVID-19 pandemic resulted in widespread unemployment, economic slowdown and extreme volatility in the capital markets. Similarly, the ongoing war between Russia and Ukraine has created extreme volatility in the global capital markets and is expected to have further global economic consequences, including disruptions of the global supply chain and energy markets. Any such volatility and disruptions may have adverse consequences on us or the third parties on whom we rely. If the equity and credit markets continue to deteriorate, it may make any necessary debt or equity financings more difficult to obtain in a timely manner or on favorable terms, more costly or more dilutive. Increased inflation rates can adversely affect us by increasing our costs, including labor and employee benefit costs. In addition, higher inflation and macro turmoil and uncertainty could also adversely affect our buyers and sellers, which could reduce demand for our products. These factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

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

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

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

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

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

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

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

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

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

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

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

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

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to report annually and include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income," "global intangible low-taxed income," and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. 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. An individual that is a Ten Percent Shareholder with respect to a CFC generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a U.S. corporate that is a Ten Percent Shareholder with respect to a CFC. Failure to comply with these reporting and tax paying obligations may subject a Ten Percent Shareholder to significant monetary penalties and may prevent the statute of limitations from starting with respect to such shareholder's U.S. federal income tax return for the year for which reporting was due. 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 (directly, indirectly or constructively through the application of attribution rules) 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 a 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. United States persons should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC.

If we are a 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, including cash. 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 United States person holds our shares, such U.S. shareholder 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 2022 taxable year. However, no assurances can be provided that we will not be a PFIC for the current or any future taxable year or that we have not been a PFIC in any prior taxable years. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. As a result, there can be no assurance regarding if we will be PFIC or will not be a PFIC in the future. In addition, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into and our corporate structure.

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

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

As a group that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Relief program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, under the SME Program, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carry them forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these SME Program tax credit cash rebate claims. We may not be able to continue to claim payable research and development tax credits in the future if we cease to qualify as a small or medium-sized enterprise under the SME Program, based on size criteria concerning employee headcount, turnover and gross assets.

The United Kingdom research and development tax credit regime has in recent years been, and continues to be, subject to review and amendment. The U.K. Finance Act 2021 introduced a cap on payable credit claims under the SME Program in excess of £20,000 with effect from April 2021 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception which prevents the cap from applying. That exception requires the company to be creating, taking steps to create or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. If such exception does not apply, this could restrict the amount of payable credit that we claim. Additionally, for qualifying research and development expenditure incurred on or after April 1, 2023, under the SME Program, the additional deduction that may be claimed in respect of such expenditure will decrease from 130% to 86%, and the cash rebate rate will decrease from 14.5% to 10%. The U.K. government announced its intention to introduce further restrictions to the U.K. research and development relief programs, refocusing such programs towards innovation in the United Kingdom. On July 21, 2022, draft legislation was published setting out, among other things, details of such proposed restrictions which (if enacted) would, in particular, limit our ability (except in limited circumstances) to make claims under the existing relief programs in respect of accounting periods beginning on or after April 1, 2023 for (i) research and development subcontracted to a third party (and, in the case of the RDEC Program, in respect of contributions made to a qualifying body) where such third party (or qualifying body) performs the work outside of the United Kingdom, and (ii) expenditure incurred on externally provided workers that are not paid through United Kingdom payroll. Most recently, on January 13, 2023, the U.K. government launched a consultation on its proposal to merge the SME Program and the RDEC Program into a single scheme; if such proposal is implemented, it is expected that the SME Program will be discontinued in its current form with effect from April 1, 2024. These and other potential future changes to the U.K. research and development tax relief programs may be made which mean we may no longer qualify or may impact the extent to which we can make claims.

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

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

The tax treatment of the company is, and our ADSs and ordinary shares are, subject to changes in tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, as well as tax policy initiatives and reforms related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project (including "BEPS 2.0"), the European Commission's state aid investigations and other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid, or the stamp duty or stamp duty reserve tax treatment of our ADSs or ordinary shares. The Retained EU Law (Revocation and Reform) Bill is currently proceeding through the United Kingdom parliament, or the Bill, which provides for the revocation of EU laws and rights which, notwithstanding Brexit, currently remain effective in the United Kingdom, except where the U.K. government and/or parliament take active steps to preserve the EU law position within United Kingdom law. Certain aspects of the stamp duty and stamp duty reserve tax treatment of our ordinary shares and ADSs are based on EU law which could be affected by this Bill. Accordingly, if this Bill is enacted, and steps are not taken by the U.K. government and/or parliament to preserve the current position, this could, in particular, result in a charge to stamp duty reserve tax on the issuance of new ADSs, at the rate of 1.5% of the issue price, potentially with effect from December 31, 2023, which would represent an additional cost if we seek to raise further capital in this way.

In the United States on August 16, 2022, President Biden signed into law the IRA, which includes a minimum tax equal to 15% of the adjusted financial statement income of certain corporations, as well as a 1% excise tax on share buybacks. In addition, beginning in 2022, the Tax Cuts and Jobs Act of 2017 eliminates the option to deduct research and development expenditures and requires taxpayers to amortize them over five years pursuant to IRC Section 174, 15 years for expenditures attributable to research and development conducted outside the United States. Although Congress is considering legislation that would defer the amortization requirement to later years, we have no assurance that the provision will be repealed or otherwise modified. If the requirement is not modified or deferred, it may materially reduce our cash flows. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

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

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, while we believe that we operate in compliance with applicable transfer pricing laws and intend to continue to do so, our transfer pricing procedures are not binding on applicable tax authorities. HMRC, the Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that

we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties and, such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

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

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

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

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

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

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

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

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

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

- in the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, if we were to be subject to the Takeover Code, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a "squeeze out" to obtain 100% control of us. Accordingly, acceptances of

90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting, as well as the sanction of the U.K. court;

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

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

General Risks

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

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

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

As a public company we will continue to incur significant legal, accounting, and other expenses that we did not incur as a private company, including costs resulting from public company reporting obligations under the Securities Act, or the Securities Exchange Act of 1934, as amended, or the Exchange Act, and regulations regarding corporate governance practices. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the results of the SEC, the Nasdaq listing requirements, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We have hired, and may continue to hire, additional accounting, finance and other personnel in connection with our becoming, and our efforts to comply with the requirements of being, a public company, and our management and other personnel devote a substantial amount of time towards maintaining compliance with these requirements. These requirements have increased our legal and financial compliance costs and have made and will make some activities more time-consuming and costly. We continuously evaluate the rules and regulations applicable to us as a public company and cannot predict or estimate the amount of additional costs we may incur or the

timing of such costs. These reporting requirements, rules and regulations, coupled with the increase in potential litigation exposure associated with being a public company, could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees or to serve as executive officers, or to obtain certain types of insurance, or including directors' and officers' insurance, on acceptable terms.

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

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

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

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. Our management is required to assess the effectiveness of our controls over financial reporting annually. Pursuant to Section 404, we are also required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm at such time when we are no longer a smaller reporting company. Any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

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

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

We could be subject to securities class action litigation.

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

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

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

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

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

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

ITEM 1B. UNRESOLVED STAFF COMMENTS.

Not applicable.

ITEM 2. PROPERTIES.

We occupy approximately 13,500 rentable square feet of office and laboratory space in Cambridge, United Kingdom under a lease that expires in December 2026, and approximately 45,000 rentable square feet of office and laboratory space in Cambridge, United Kingdom under another lease that expires in December 2031, which may be cancelled after December 2026, and may be renewed for 10 years, also cancelable in the fifth year of the extension. We also lease an additional 11,000 rentable square feet of office and laboratory space in Lexington, Massachusetts under a lease that expires in December 2027. In January 2023, we entered into a lease agreement for approximately 23,000 rentable square feet of office and laboratory space in Cambridge, Massachusetts that has a contractual period of approximately three years, which, subject to certain conditions, may be extended for an additional two years at our option. We believe that our office and laboratory spaces are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

ITEM 3. LEGAL PROCEEDINGS.

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

European Patent Opposition Proceedings

In May 2017, we and Oxurion NV 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. The hearing of this appeal took place on November 15, 2022. The decision of the EPO Technical Board of Appeal was to revoke European patent 1 854 477. This decision cannot be appealed.

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.

In light of the European Patent Office's findings with respect to Dyax Corp's patents, we are no longer a party to any active European Patent Opposition proceedings.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

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

Market Information

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

Holders of Ordinary Shares

As of February 23, 2023, there were approximately 59 holders of record of our ordinary shares and one holder of record of our ADSs. The number of beneficial owners of the ADSs in the United States is likely to be much larger than the number of record holders of our ordinary shares in the United States.

Recent Sales of Unregistered Equity Securities

None.

Use of Proceeds from Registered Securities

Not applicable.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. [Reserved]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

You should read this discussion and analysis of our financial condition and consolidated results of operations together with the consolidated financial statements, related notes and other financial information included in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including statements of our plans, objectives, expectations and intentions, contain forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Please also see the section titled "Forward-Looking Statements."

For the discussion of the financial condition and results of operations for the year ended December 31, 2021 compared to the year ended December 31, 2020, refer to "Management's Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations" and "—Liquidity and Capital Resources" included in the Company's Annual Report on Form 10-K for the year ended December 31, 2021, which was filed with the Securities and Exchange Commission, or the SEC, on March 1, 2022.

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* allows 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, qualities which we believe explain the molecules' favorable toxicological profile.

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

Our product candidates BT5528, BT8009, and BT1718 are each a *Bicycle*® Toxin Conjugate, or BTC™. These *Bicycles* are chemically attached to a toxin that when administered is cleaved from the *Bicycle* and kills the tumor cells. We are evaluating BT5528, a second-generation BTC targeting Ephrin type A receptor 2, or EphA2, in a company-sponsored Phase I/II clinical trial and BT8009, a second-generation BTC targeting Nectin-4, in a company-sponsored Phase I/II clinical trial. In addition, BT1718 is being developed to target tumors that express Membrane Type 1 matrix metalloproteinase, or MT1 MMP, and is being investigated for safety, tolerability and efficacy in an ongoing Phase I/IIa clinical trial sponsored and fully funded by the Cancer Research UK Centre for Drug Development, or Cancer Research UK. In addition, our product candidates BT7480 and BT7455, are each a *Bicycle* tumor-targeted immune cell agonist®, or *Bicycle* TICA™. A *Bicycle* TICA links immune cell receptor binding *Bicycles* to tumor antigen binding *Bicycles*. We are evaluating BT7480, a *Bicycle* TICA targeting Nectin-4 and agonizing CD137, in a company-sponsored Phase I/II clinical trial, and IND-enabling studies for BT7455, an EphA2/CD137 Bicycle TICA, are ongoing. 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 I clinical trial of BT8009. We observed signs of anti-tumor activity in our clinical trial of BT5528 and established a recommended Phase II dose range. On June 8, 2022, we announced that the first patient had

been dosed in the dose expansion cohorts of the Phase I/II study of BT5528 which include urothelial and ovarian cancers, as well as in a basket cohort of other solid tumors, including non-small cell lung cancer, triple-negative breast cancer, head and neck cancer, and esophageal cancer. Enrollment in these cohorts remains ongoing. On September 7, 2022, we announced top-line results from the completed dose escalation portion of the Phase I/II trial of BT5528.

In our ongoing Phase I/II clinical trial of BT8009, we have observed signs of anti-tumor activity. On November 8, 2022, we announced updates from the Phase I/II trial of BT8009, including that the Phase I dose escalation portion of the trial was complete and that the first patient had been dosed in the Phase II expansion cohorts. Results from the completed dose escalation portion of the trial were presented at the 2023 ASCO Genitourinary (GU) Cancers Symposium in February 2023.

On January 4, 2023, we announced that the FDA has granted Fast Track Designation, or FTD, to our BT8009 monotherapy for the treatment of adult patients with previously treated locally advanced or metastatic urothelial cancer. FTD is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition.

The Phase IIa portion of a Phase I/IIa clinical trial of BT1718 that is sponsored and fully funded by Cancer Research UK is ongoing. Enrollment in the BT7480 Phase I trial is ongoing and is progressing on schedule during the dose escalation portion of the clinical trial.

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

Financial Overview

Since our inception, we have devoted substantially all of our resources to developing our *Bicycle* platform and our product candidates, BT5528, BT8009, BT1718, BT7480, BT7455 and BT7401, conducting research and development of our product candidates and preclinical programs, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of our American Depositary Shares, or ADSs, ordinary shares, and convertible preferred shares; proceeds received from upfront payments, research and development payments, and development milestone payments from our collaboration agreements with Ionis Pharmaceuticals, Inc, or Ionis, Genentech Inc., or Genentech, the Dementia Discovery Fund, or DDF, Sanofi (formerly Bioverativ Inc.), AstraZeneca AB, or AstraZeneca and Oxurion NV, or Oxurion; and borrowings pursuant to our debt facility with Hercules Capital, Inc., or Hercules. From our inception in 2009 through December 31, 2022, we have received gross proceeds of $564.4 million from the sale of ADSs, ordinary shares and convertible preferred shares, including the proceeds from our initial public offering, follow-on offering and at-the-market, or ATM, offering program; and $135.2 million of cash payments under our collaboration revenue arrangements, including $46.6 million from Ionis, $54.0 million from Genentech, $10.3 million from AstraZeneca, and $6.6 million from Oxurion; and borrowings of $30.0 million pursuant to our Loan and Security Agreement, as amended, or the 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 $112.7 million, $66.8 million and $51.0 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $331.1 million. These losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

We anticipate that our expenses and capital requirements will increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and, if any product candidates are approved, pursue the commercialization of such product candidates by building internal sales and marketing capabilities. We expect that our expenses and capital requirements will increase substantially if and as we:

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

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

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances, charitable and governmental grants, monetization transactions or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back, or discontinue the development and commercialization of one or more of our product candidates. Both the ongoing COVID-19 pandemic and the Russia-Ukraine war have resulted in a significant disruption of global financial markets and contributed to a general global economic slowdown. If the disruption persists and deepens, whether as a result of these events or otherwise, we could experience an inability to access additional capital.

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

As of December 31, 2022, we had cash and cash equivalents of $339.2 million. We believe that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Annual Report on Form 10-K. We have based this estimate on assumptions that may prove to be wrong, and we could deplete our available capital resources sooner than we expect. See "— Liquidity and Capital Resources."

Components of Our Results of Operations

Collaboration Revenues

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

Expenses

Research and Development Expenses

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

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

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

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

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

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

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as a result of our expanded portfolio of product candidates and as we: (i) continue the clinical development and seek to obtain marketing approval for our product candidates, including BT5528, BT8009, BT7480 and BT1718; (ii) initiate clinical trials for our product candidates, including BT7455; and (iii) build our in-house process development and analytical capabilities and continue to discover and develop additional product candidates.

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

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

- progressing the preclinical and clinical development of BT7455 and BT7401;
- establishing an appropriate safety profile with IND-enabling studies to advance our preclinical programs into clinical development;
- identifying new product candidates to add to our development pipeline;
- successful enrollment in, and the initiation and completion of clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with others;
- establishing commercial manufacturing capabilities or making arrangements with third party manufacturers;
- the development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials;
- addressing any competing technological and market developments, as well as any changes in governmental regulations;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how, as well as obtaining and maintaining regulatory exclusivity for our product candidates;
- continued acceptable safety profile of the drugs following approval; and
- attracting, hiring and retaining qualified personnel.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, the FDA, EMA or another regulatory authority may require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or we may experience significant trial delays due to patient enrollment or other reasons, including the impacts of the ongoing COVID-19 pandemic, in which case we would be required to expend significant additional financial resources and time on the completion of clinical development. 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 applicable functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the remeasurement at period-end exchange rates in foreign currencies are recorded in general and administrative expense in the statement of operations and comprehensive loss. As such, our operating expenses may be impacted by future changes in exchange rates. See "*Quantitative and Qualitative Disclosures About Market Risks*" for further discussion.

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

Other Income (Expense)

Interest Income

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

Interest Expense

Interest expense consists primarily of interest expense for financing arrangements. As of December 31, 2022, we have borrowings of $30.0 million outstanding pursuant to our Loan Agreement with Hercules.

Benefit From Income Taxes

We are subject to corporate taxation in the United States and the United Kingdom. We have generated losses since inception and have therefore not paid United Kingdom corporation tax. The benefit from income taxes presented in our consolidated statements of operations and comprehensive loss is mainly the result of deferred tax assets benefited in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement.

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

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

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

SME Program for the year ended December 31, 2021. For the year ended December 31, 2022, the payable credit claims under the SME Program in excess of £20,000 are subject to a cap of approximately three times the total PAYE and NIC liability paid by the Company, unless an exception applies. That exception requires the Company to be creating, taking steps to create, or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total amount claimed. We expect the portion of qualifying research and development expenditures that are subject to the research and development tax credit will decrease in future periods.

Unsurrendered U.K. losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of U.K. taxable profits. After accounting for our tax credits receivable, we had accumulated tax losses for carry forward in the United Kingdom of $181.8 million and $120.3 million as of December 31, 2022 and 2021, respectively.

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

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Collaboration revenues	$ 14,463	$ 11,697	$ 10,390
Operating expenses:			
Research and development	81,609	44,880	33,149
General and administrative	49,507	32,435	29,201
Total operating expenses	131,116	77,315	62,350
Loss from operations	(116,653)	(65,618)	(51,960)
Other income (expense):			
Interest income	5,756	120	683
Interest expense	(3,344)	(2,984)	(457)
Total other income (expense), net	2,412	(2,864)	226
Net loss before income tax provision	(114,241)	(68,482)	(51,734)
Benefit from income taxes	(1,524)	(1,663)	(724)
Net loss	$ (112,717)	$ (66,819)	$ (51,010)

Comparison of the Years Ended December 31, 2022 and 2021

	Year Ended December 31,		
	2022	2021	Change
		(in thousands)	
Collaboration revenues	$ 14,463	11,697	$ 2,766
Operating expenses:			
Research and development	81,609	44,880	36,729
General and administrative	49,507	32,435	17,072
Total operating expenses	131,116	77,315	53,801
Loss from operations	(116,653)	(65,618)	(51,035)
Other income (expense):			
Interest income	5,756	120	5,636
Interest expense	(3,344)	(2,984)	(360)
Total other income (expense), net	2,412	(2,864)	5,276
Net loss before income tax provision	(114,241)	(68,482)	(45,759)
Benefit from income taxes	(1,524)	(1,663)	139
Net loss	$ (112,717)	(66,819)	$ (45,898)

Collaboration Revenues

Collaboration revenues increased by $2.8 million in the year ended December 31, 2022, compared to the year ended December 31, 2021, primarily due to an increase of $5.1 million from our collaboration with Ionis entered into in July 2021, offset by a $2.1 million decrease from our collaboration with Genentech due primarily to lower revenue recognized for research services, as well as revenue recognized upon the expiration of material rights in the year ended December 31, 2021 that did not recur in the year ended December 31, 2022.

Research and Development Expenses

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

	December 31,		
	2022	2021	Change
	(in thousands)		
BT5528 (EphA2)	$ 10,702	$ 5,380	$ 5,322
BT8009 (Nectin-4)	11,054	7,656	3,398
BT1718 (MT1)	692	760	(68)
Bicycle tumor-targeted immune cell agonists	11,268	6,008	5,260
Other discovery and platform related expense	21,811	15,519	6,292
Employee and contractor related expenses	31,346	17,133	14,213
Share-based compensation	10,394	4,974	5,420
Facility expenses	5,155	1,443	3,712
Research and development incentives and government grants	(20,813)	(13,993)	(6,820)
Total research and development expenses	$ 81,609	$ 44,880	$ 36,729

Research and development expenses increased by $36.7 million in the year ended December 31, 2022 compared to the year ended December 31, 2021, primarily due to an increase of $20.2 million in direct program spend, primarily associated with increased clinical program expenses for BT5528 and BT8009, *Bicycle* TICA program development expenses, and increased other discovery and platform-related expenses, including costs of our collaboration agreements, as well as increases of $14.2 million in employee and contractor-related expenses attributable to increased headcount, $5.4 million of incremental share-based compensation expense primarily associated with equity grants issued since the prior year, and $3.7 million in facilities-related expenses primarily associated with our U.K. lease entered into in December 2021. These increases were offset by $6.8 million of incremental research and development incentives, including U.K. research and development tax credit reimbursements due to the corresponding increase in research and development spending.

We begin to separately track program expenses at candidate nomination, at which point we accumulate all direct external program costs incurred to support that program to date. Through December 31, 2022, we have incurred approximately $30.4 million, $29.8 million, and $15.0 million of direct external expenses for the development of BT5528, BT8009, and BT1718, respectively, since their candidate nominations, and an aggregate of $22.6 million of direct external expenses for the development of the two named *Bicycle* TICA candidates since their nominations.

General and Administrative Expenses

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

	Year Ended December 31,		
	2022	2021	Change
	(in thousands)		
Personnel-related costs	$ 13,948	$ 9,783	$ 4,165
Professional and consulting fees	9,836	9,606	230
Other general and administration costs	8,783	6,295	2,488
Share-based compensation	16,385	7,109	9,276
Effect of foreign exchange rates	555	(358)	913
Total general and administrative expenses	$ 49,507	$ 32,435	$ 17,072

General and administrative expenses increased by $17.1 million in the year ended December 31, 2022 compared to the year ended December 31, 2021. This increase is primarily due to a $9.3 million increase in share-based compensation expense primarily associated with equity grants issued since the prior year, an increase of $4.2 million in personnel-related costs due to increased headcount, an increase of $2.5 million in other general and administrative costs,

including insurance expenses, to support operations as a public company, and an unfavorable impact of $0.9 million due to the effect of foreign exchange rates.

Other Income (Expense), net

Other income (expense), net increased by $5.3 million in the year ended December 31, 2022 compared to the year ended December 31, 2021, primarily due to an increase of $5.6 million in interest income related to higher interest rates as well as increases in our cash equivalents held in 30-day deposit accounts offset by an increase of $0.4 million in interest expense related to the borrowings under the Loan Agreement with Hercules.

Liquidity and Capital Resources

Liquidity

From our inception in 2009 through December 31, 2022, we have not generated any revenue from product sales and have incurred significant operating losses and negative cash flows from our operations. We do not expect to generate significant revenue from sales of any products for several years, if at all.

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

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2022, 2021 and 2020:

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Net cash used in operating activities	$ (86,111)	$ (14,794)	$ (17,789)
Net cash used in investing activities	(18,987)	(2,030)	(1,200)
Net cash provided by financing activities	6,692	320,725	62,843
Effect of exchange rate changes on cash	(1,120)	(1,211)	19
Net (decrease) increase in cash and cash equivalents	$ (99,526)	$ 302,690	$ 43,873

Operating Activities

Net cash used in operating activities for the year ended December 31, 2022, was $86.1 million as compared to $14.8 million for the year ended December 31, 2021. The increase in cash used in operations of $71.3 million is primarily due to an increase in net loss of $45.9 million as described in the Results of Operations above, offset by an increase in non-cash expenses, including $14.7 million of share-based compensation expense, $2.3 million of depreciation expense, $3.3 million of deferred income tax benefit, and a decrease in cash flows from changes in our operating assets and liabilities of $39.1 million. The decrease in cash flows from changes in our operating assets and liabilities was primarily driven by decreases resulting from changes in deferred revenue of $39.3 million due to the Ionis collaboration upfront payment received in the third quarter of 2021 and the Genentech Expansion Option payment received in the fourth quarter of 2021, research and development incentives receivable of $7.8 million, and accounts receivable of $6.2 million, offset by increases resulting from changes in accrued expenses and other liabilities of $11.1 million, accounts payable of $1.4 million, and prepaid expenses and other assets of $1.0 million.

Investing Activities

During the years ended December 31, 2022 and 2021, we used $19.0 million and $2.0 million, respectively, of cash in investing activities. The increase for the year ended December 31, 2022 as compared to the year ended December

31, 2021 is associated with purchases of property and equipment, consisting primarily of leasehold improvements and laboratory equipment related to our U.K. lease entered into in December 2021.

Financing Activities

During the year ended December 31, 2022, net cash provided by financing activities was $6.7 million, primarily consisting of net proceeds from the exercise of share options of $1.0 million and net proceeds from our ATM program of $5.7 million.

During the year ended December 31, 2021, net cash provided by financing activities was $320.7 million, primarily consisting of net proceeds from our October 2021 follow-on offering of $188.4 million, net proceeds from our ATM program of $102.6 million, borrowing of $15.0 million under our Loan Agreement with Hercules, proceeds of $7.6 million from the issuance of ordinary shares under the share purchase agreement with Ionis and $7.2 million from the exercise of share options.

Loan Agreement

Our Loan Agreement, as amended from time to time, with Hercules as agent, consists of (i) outstanding term loans of $30.0 million and (ii) subject customary conditions, additional term loans of up to an aggregate of $45.0 million, which are available through December 31, 2024, but have not yet been drawn. Borrowings under the Loan Agreement bear interest at an annual rate equal to the prime rate as reported in the Wall Street Journal plus 4.55%, with a minimum annual rate of at least 8.05%, capped at a rate no greater than 9.05%. The interest-only period ends on April 1, 2025. We may prepay all or any portion greater than $5.0 million of the outstanding borrowings, subject to a prepayment premium equal to 1.5% prior to December 31, 2023. The Loan Agreement also provides for an end of term charge, payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. In connection with the Loan Agreement, we granted Hercules a security interest in substantially all of our personal property and other assets, other than our intellectual property. In addition, the Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, as well as customary events of default. For additional information on the Loan Agreement, see Note 6. Long-term debt, to our consolidated financial statements.

Capital Resources and Funding Requirements

Our material cash requirements include expenses associated with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and as we:

- continue our development of our product candidates, including continuing current trials and conducting future clinical trials of BT5528, BT8009, BT7480 and BT1718;
- progress the preclinical and clinical development of BT7455 and BT7401;
- seek to identify and develop additional product candidates;
- develop the necessary processes, controls and manufacturing data to seek to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop, maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, commercial and scientific personnel;

- acquire or in-license other products and technologies;

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

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

If we obtain marketing approval for any product candidate that we identify and develop, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing, and distribution to the extent that such sales, marketing, and distribution are not the responsibility of our collaboration partners.

In addition, the following table summarizes our contractual obligations as of December 31, 2022 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods. For additional information, see Note 11. Commitments and continencies of our consolidated financial statements.

	Payments due by period			
	Total	Less than 1 year	1 to 3 years	3 years to 5 years
	(in thousands)			
Operating lease commitments (1)	$ 16,039	$ 3,972	$ 8,010	$ 4,057
Debt obligations (2)	38,037	2,519	35,518	—
Total	$ 54,076	$ 6,491	$ 43,528	$ 4,057

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

(2) Amounts in the table reflect the contractually required principal, interest and the final payments under the Loan Agreement with Hercules as of December 31, 2022.

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

Our arrangements with Cancer Research UK provide for additional future milestone payments upon the achievement of development, regulatory and commercial milestones, payable in cash and shares, with an aggregate total value of $111.2 million, as well as royalty payments based on a single digit percentage on net sales of products developed. In addition, in November 2020, we entered into a settlement and license agreement with Pepscan Systems B.V. regarding our use of Pepscan's CLIPS peptide technology, which agreement provides for additional future milestone payments by us upon the achievement of development, regulatory and commercial milestones, with an aggregate total value of $92.4 million. We have not included future payments under this agreement in the table above since these obligations are contingent upon future events. As of December 31, 2022, we were unable to estimate the timing or likelihood of achieving these milestones.

As of December 31, 2022, we had cash and cash equivalents of $339.2 million. We expect that our existing cash will enable us to fund our operating expenses and capital expenditure requirements for at least 12 months from the date of filing of this Annual Report.

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 unfavorable global economic and political conditions;
- the scope, progress, results, and costs of drug discovery, preclinical development, laboratory testing, and clinical trials for the product candidates we may develop;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, and distribution, for any product candidates for which we receive marketing approval;
- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.
- the success of our collaborations with Ionis, Genentech, DDF, AstraZeneca, Oxurion and other partners;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the costs of operating as a public company.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, monetization transactions, government contracts or other strategic transactions. To the extent that we raise additional capital through the sale of equity, ownership interests of existing holders of our ADSs and ordinary shares will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of holders of our ADSs or ordinary shares. If we raise additional funds through collaboration agreements, strategic alliances, licensing arrangements, monetization transactions, or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves. Future debt financing, if available, may involve covenants restricting our operations or our ability to incur additional debt. Any debt or equity financing that we raise may contain terms that are not favorable to us or our shareholders.

Both the ongoing COVID-19 pandemic and the evolving conflict between Russia and Ukraine have resulted in significant disruptions to global financial markets and contributed to a general global economic slowdown. The resulting

high inflation rates may materially affect our business and corresponding financial position and cash flows. Inflationary factors, such as increases in the cost of our clinical trial materials and supplies, interest rates and overhead costs may adversely affect our operating results. Rising interest rates also present a recent challenge impacting the U.S. economy and could make it more difficult for us to obtain traditional financing on acceptable terms, if at all, in the future. Additionally, the general consensus among economists suggests that we should expect a higher recession risk to continue over the next year, which, together with the foregoing, could result in further economic uncertainty and volatility in the capital markets in the near term, and could negatively affect our operations. Furthermore, such economic conditions have produced downward pressure on share prices. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may experience increases in the near future (especially if inflation rates remain high or begin to rise again) on our operating costs, including our labor costs and research and development costs, due to supply chain constraints, consequences associated with COVID-19 and the global geopolitical tension as a result of the ongoing conflict between Russia and Ukraine, worsening global macroeconomic conditions, and employee availability and wage increases, which may result in additional stress on our working capital resources. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce, or eliminate our research and development programs or future commercialization efforts.

Critical Accounting Estimates

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

While our significant accounting policies are described in greater detail in Note 2 to our consolidated financial statements appearing elsewhere in the Annual Report on Form 10-K, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Collaboration Revenues

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

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

We recognize revenue in accordance with Accounting Standards Codification Topic 606, *Revenue from Contracts with Customers,* or ASC 606. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, and financial instruments.

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

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

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

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

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

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

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

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

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

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

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

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

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a

pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

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

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs, research institutions and vendors that supply, conduct and manage preclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and actual results could differ from our estimates. As of December 31, 2022, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

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

Interest Rate Sensitivity

As of December 31, 2022, we had cash and cash equivalents of $339.2 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in interest-bearing savings accounts and a 30-day term deposit. 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 December 31, 2022. Our outstanding indebtedness with Hercules bears interest at an annual rate equal to the *Wall Street Journal* prime rate plus 4.55%, with a minimum annual rate of at least 8.05%, capped at a rate no greater than 9.05%. As of December 31, 2022, our outstanding indebtedness with Hercules bears interest at 9.05%. We currently do not engage in any interest rate hedging activity, and we have no intention to do so in the foreseeable future. Based on the current interest rate of the term loan and the scheduled payments thereunder, we do not believe a 1.0% increase in interest rates would have a material impact on our financial condition or results of operations.

Foreign Currency Exchange Risk

The functional currency is the currency of the primary economic environment in which an entity's operations are conducted. The functional currency of Bicycle Therapeutics plc and Bicycle Therapeutics Inc. is the United States Dollar, or USD. 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 consolidated financial statements are presented in USD. The functional currency of our subsidiaries is the same as the local currency.

Monetary assets and liabilities denominated in currencies other than the functional currency are remeasured into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. Adjustments that arise from exchange rate changes on transactions denominated in a currency other than the local currency are included in general and administrative expense in the consolidated statements of operations and comprehensive loss as incurred. We recorded a foreign exchange loss of $0.6 million for the year ended December 31, 2022, and foreign exchange gains of $0.4 million and $0.6 million for the years ended December 31, 2021 and 2020, respectively.

For financial reporting purposes, our consolidated financial statements have been translated into U.S. dollars. We translate the assets and liabilities of BicycleTx Limited and BicycleRD Limited into USD at the exchange rate in effect on the balance sheet date. Revenues and expenses are translated at the average exchange rate in effect during the period and shareholders' equity (deficit) amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net loss but are included in our foreign exchange adjustment included in the consolidated statements of 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 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

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

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

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures.

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

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. Based on the evaluation

of our disclosure controls and procedures as of December 31, 2022, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective.

Management's Report on Internal Control Over Financial Reporting.

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

Our management conducted an assessment of our internal control over financial reporting based on the framework established in 2013 by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013). Based on the assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Attestation Report of the Registered Public Accounting Firm

This report does not include an attestation report of our registered public accounting firm regarding our internal control over financial reporting, in accordance with applicable SEC rules that permit us to provide only Management's report in this Annual Report.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS.

Not Applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

The information required by this Item 10 will be included in the sections titled "Board of Directors and Corporate Governance," "Executive Officers of the Company" and "Delinquent Section 16(a) Reports," if applicable, in our Proxy Statement, which information is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION.

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

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

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

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

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

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

The information required by this Item 14 will be included in the sections titled "Independent Registered Public Accounting Firm Fees" and "Pre-Approval Policies and Procedures" in our Proxy Statement, which information is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES.

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

(a)(1) Financial Statements

(a)(2) Financial Statement Schedules

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

(a)(3) Exhibits

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

Number	Description
3.1	Articles of Association (incorporated by reference to Exhibit 3.2 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.1	Form of Deposit Agreement (incorporated by reference to Exhibit 4.1 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.2	Form of American Depositary Receipt (included in Exhibit 4.1) (incorporated by reference to Exhibit 4.2 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
4.3	Letter Agreement, dated July 1, 2020, between Bicycle Therapeutics plc and Citibank, N.A. (incorporated by reference to Exhibit 4.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on November 5, 2020).
4.4	Amendment to Letter Agreement, dated October 27, 2020, between Bicycle Therapeutics plc and Citibank, N.A. (incorporated by reference to Exhibit 4.4 to Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021).

Number	Description
4.5	Amendment to Letter Agreement, dated May 24, 2021, between Bicycle Therapeutics plc and Citibank, N.A. (incorporated by reference to Exhibit 4.1 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on August 5, 2021).
4.6	Registration Rights Agreement by and among Bicycle Therapeutics Limited and the Investors listed therein, dated December 21, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
4.7	Description of Securities (incorporated by reference to Exhibit 4.4 to the Registrant's Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.1+	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in England (incorporated by reference to Exhibit 10.2 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.2+	Form of Share Option Contract of Bicycle Therapeutics Limited for employees in the United States (incorporated by reference to Exhibit 10.3 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.3+	Rules of the Bicycle Therapeutics Share Option Plan, as amended on September 12, 2019 (incorporated by reference to Exhibit 10.3 to the Quarterly Report on Form 10-Q (File No. 001-38916) filed with the Securities and Exchange Commission on November 7, 2019).
10.4+	Forms of award agreements under the Bicycle Therapeutics Share Option Plan, as amended (incorporated by reference to Exhibit 10.4 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.5+	2019 Employee Share Purchase Plan (incorporated by reference to Exhibit 10.5 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
10.6+	Amended and Restated Bicycle Therapeutics plc 2020 Equity Incentive Plan and forms of award thereunder.
10.7+	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.4 to Amendment No. 1 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on May 13, 2019).
10.8+	Service Agreement, dated September 26, 2019, by and between BicycleTx Ltd. and Kevin Lee (Incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on September 30, 2019).
10.9+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between Bicycle Therapeutics Inc. and Lee Kalowski (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on September 30, 2019).
10.10+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between BicycleTx Ltd. and Michael Skynner, Ph.D. (incorporated by reference to Exhibit 10.9 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.11+	Amendment to Amended and Restated Employment Agreement, dated January 6, 2022, by and between BicycleTx Ltd. and Michael Skynner, Ph.D. (incorporated by reference to Exhibit 10.11 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 1, 2022).

Number	Description
10.12+	Amended and Restated Employment Agreement, dated September 26, 2019, by and between Bicycle Therapeutics Inc. and Nicholas Keen, Ph.D. (incorporated by reference to Exhibit 10.10 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.13+	Service Agreement, dated September 26, 2019, by and between BicycleTx Ltd and Nigel Crockett, Ph.D. (incorporated by reference to Exhibit 10.11 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.14+	Form of letter agreement to amend Service Agreement by and between the BicycleTx Ltd. and its executive officers in the United Kingdom, effective January 1, 2020 (incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on May 7, 2020).
10.15+	Service Agreement, dated July 9, 2020, by and between BicycleTx Ltd. and Dominic Smethurst, MA, MBChB, MRCP, MFPM (incorporated by reference to Exhibit 10.14 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021).
10.16+	Form of letter agreement to amend Service Agreement by and between the BicycleTx Ltd. and its executive officers in the United Kingdom, effective January 1, 2021 (incorporated by reference to Exhibit 10.27 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021).
10.17+	Service Agreement, dated January 5, 2022, by and between BicycleTx Ltd. and Alistair Milnes (incorporated by reference to Exhibit 10.17 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 1, 2022).
10.18+	Form of Deed of Indemnity between the Company and each of its directors (incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on November 12, 2019).
10.19+	Form of Deed of Indemnity between the registrant and each of its executive officers (incorporated by reference to Exhibit 10.2 to Current Report on Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on November 12, 2019).
10.20+	Non-employee Director Compensation Policy, as amended as of December 8, 2022.
10.21	Clinical Trial and License Agreement, by and between Bicycle Therapeutics Limited, Cancer Research Technology Limited, and Cancer Research UK, dated December 13, 2016, as amended and restated by the Deed of Amendment on March 31, 2017, as further amended by the Second Deed of Amendment on June 29, 2018 (incorporated by reference to Exhibit 10.15 to the Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
10.22††	Discovery Collaboration and License Agreement between BicycleTx Limited and Genentech, Inc., dated February 21, 2020 (incorporated by reference to Exhibit 10.18 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 10, 2020).
10.23††	First Amendment to the Discovery Collaboration and License Agreement, dated November 5, 2021, by and between Genentech, Inc. and BicycleTx Limited (incorporated by reference to Exhibit 10.1 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on August 4, 2022).
10.24††	Second Amendment to the Discovery Collaboration and License Agreement, dated June 27, 2022, by and between Genentech, Inc. and BicycleTx Limited (incorporated by reference to Exhibit 10.2 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on August 4, 2022).

Number	Description
10.25††	Third Amendment to the Discovery Collaboration and License Agreement, dated October 26, 2022, by and between Genentech, Inc. and BicycleTx Limited.
10.26††	Collaboration and License Agreement, dated as of July 9, 2021, between BicycleTx Limited and Ionis Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.1 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on November 4, 2021).
10.27††	Amendment No. 1 to Collaboration and License Agreement, dated December 17, 2021, between BicycleTx Limited and Ionis Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.25 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 1, 2022).
10.28††	Amendment No. 2 to Collaboration and License Agreement, dated August 1, 2022, between BicycleTx Limited and Ionis Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.1 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on November 3, 2022).
10.29	Share Purchase Agreement, dated as of July 9, 2021, between Bicycle Therapeutics plc and Ionis Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.2 to Form 10-Q (File No. 001-38916), filed with the Securities and Exchange Commission on November 4, 2021).

Number	Description
10.30††	Settlement and Licence Agreement, dated November 20, 2020, by and among Bicycle Therapeutics plc, Bicycle Therapeutics Inc., BicycleRD Limited, BicycleTx Limited and Pepscan Systems BV, Pepscan Presto BV, Pepscan Therapeutics BV, Pepscan Holding NV, Pepmab BV (incorporated by reference to Exhibit 10.23 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021).
10.31††	Settlement Agreement, dated November 20, 2020, by and among Bicycle Therapeutics plc, Bicycle Therapeutics Inc., BicycleRD Limited, BicycleTx Limited and Pepscan Systems BV, Pepscan Presto BV, Pepscan Therapeutics BV, Pepscan Holding NV, Pepmab BV (incorporated by reference to Exhibit 10.24 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021).
10.32	Loan and Security Agreement, dated September 30, 2020, by and among Bicycle Therapeutics plc, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics, Inc., the lenders party thereto, and Hercules Capital, Inc., as administrative and collateral agent (incorporated by reference to Exhibit 10.1 to Form 8-K (File No. 001-38916), filed with the Securities and Exchange Commission on October 1, 2020).
10.33	First Amendment to Loan and Security Agreement, dated March 10, 2021, by and among Bicycle Therapeutics plc, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics, Inc., the lenders party thereto, and Hercules Capital, Inc., as administrative and collateral agent (incorporated by reference to Exhibit 10.28 to the Annual Report on Form 10-K (File No. 001-38916), filed with the Securities and Exchange Commission on March 11, 2021.
10.34	Second Amendment to Loan and Security Agreement, dated as of July 15, 2022, by and among Bicycle Therapeutics plc and each of its Subsidiaries, the Lenders, and Hercules Capital, Inc., as Agent (incorporated by reference to Exhibit 10.1 to the Form 8-K (File No. 001-38916) filed with the Securities and Exchange Commission on July 15, 2022).
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Company's Registration Statement on Form S-1 (File No. 333-231076), filed with the Securities and Exchange Commission on April 26, 2019).
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney (included on the signature page of this report).
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document.
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.

Number	Description
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover page interactive data file (formatted as Inline XBRL and contained in Exhibit 101)

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

\+ Indicates a management contract or compensatory plan.

†† 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.

ITEM 16. FORM 10-K SUMMARY

None.

Index to Consolidated Financial Statements of
Bicycle Therapeutics plc

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Bicycle Therapeutics plc

Opinion on the Financial Statements

We have audited the accompanying Consolidated Balance Sheets of Bicycle Therapeutics plc and its subsidiaries (the "Company") as of December 31, 2022 and December 31, 2021, and the related Consolidated Statements of Operations and Comprehensive Loss, Consolidated Statements of Shareholders' Equity and Consolidated Statements of Cash Flows for each of the three years in the period ended December 31, 2022, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and December 31, 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinions.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Revenue recognition - Accounting treatment for the exercise of an Expansion Option under the Genentech Collaboration Agreement

As disclosed in Note 9 to the consolidated financial statements, on February 21, 2020, the Company entered into a Discovery Collaboration and License Agreement, as amended from time to time (as amended, the "Genentech Collaboration Agreement") with Genentech, Inc. ("Genentech"). For the years ended December 31, 2022 and 2021, the

Company recognized revenue of $3.6 million and $5.7 million, respectively, and as of December 31, 2022 and 2021, the Company recorded deferred revenue of $39.3 million and $34.4 million, respectively, in connection with the Genentech Collaboration Agreement. In June 2022, Genentech exercised the second Expansion Option to add an additional Genentech Collaboration Program, which triggered a $10.0 million payment to the Company under the Genentech Collaboration Agreement. The Company exercised judgment and concluded that the exercise of the second Expansion Option is accounted for as a continuation of an existing contract as the customer decided to purchase additional goods and services contemplated in the original contract, and as such, the additional arrangement consideration of $10.0 million received pursuant to the option exercise together with the amount originally allocated to the Expansion Option material right of $3.5 million is allocated to the underlying goods and services associated with the Expansion Option. The arrangement consideration was allocated to the separate performance obligations on the same basis as the initial allocation of the Genentech Collaboration Agreement.

The principal considerations for our determination that performing procedures relating to the accounting for the exercise of this Expansion Option under the Genentech Collaboration Agreement as a critical audit matter is i) the significant judgment exercised by management in evaluating the accounting treatment for the exercise of the Expansion Option as a continuation of the existing contract and in allocating the arrangement consideration to the separate performance obligations on the same basis as the initial allocation and ii) the high degree of auditor judgment and audit effort in performing procedures, as well as complexity in evaluating the audit evidence related to management's judgment.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming an overall opinion on the consolidated financial statements. These procedures included, among others, i) evaluating management's assessment of the appropriate accounting treatment for the exercise of the Expansion Option under the Genentech Collaboration Agreement; and ii) testing the completeness, accuracy, and relevance of the data used by management in determining the accounting for such exercise including the information extracted from the original collaboration agreement.

/s/ PricewaterhouseCoopers LLP
Cambridge, United Kingdom
February 28, 2023

We have served as the Company's auditor since 2010.

Bicycle Therapeutics plc
Consolidated Balance Sheets
(amounts in thousands, except share and per share data)

	December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 339,154	$ 438,680
Accounts receivable	2,045	1,000
Prepaid expenses and other current assets	9,022	7,965
Research and development incentives receivable	19,162	10,910
Total current assets	369,383	458,555
Property and equipment, net	19,110	3,123
Operating lease right-of-use assets	13,658	14,666
Other assets	8,458	3,448
Total assets	$ 410,609	$ 479,792
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 6,472	$ 2,721
Accrued expenses and other current liabilities	26,452	14,244
Deferred revenue, current portion	20,418	19,273
Total current liabilities	53,342	36,238
Long-term debt, net of discount	30,315	29,873
Operating lease liabilities, net of current portion	10,885	12,081
Deferred revenue, net of current portion	41,455	52,067
Other long-term liabilities	3,829	3,279
Total liabilities	139,826	133,538
Commitments and contingencies (Note 11)		
Shareholders' equity:		
Ordinary shares, £0.01 nominal value; 57,820,181 and 55,295,420 shares authorized at December 31, 2022 and December 31, 2021, respectively; 29,873,893 and 29,579,364 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	387	384
Additional paid-in capital	601,105	567,637
Accumulated other comprehensive income (loss)	387	(3,388)
Accumulated deficit	(331,096)	(218,379)
Total shareholders' equity	270,783	346,254
Total liabilities and shareholders' equity	$ 410,609	$ 479,792

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

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

	Year Ended December 31,		
	2022	2021	2020
Collaboration revenues	$ 14,463	$ 11,697	$ 10,390
Operating expenses:			
Research and development	81,609	44,880	33,149
General and administrative	49,507	32,435	29,201
Total operating expenses	131,116	77,315	62,350
Loss from operations	(116,653)	(65,618)	(51,960)
Other income (expense):			
Interest income	5,756	120	683
Interest expense	(3,344)	(2,984)	(457)
Total other income (expense), net	2,412	(2,864)	226
Net loss before income tax provision	(114,241)	(68,482)	(51,734)
Benefit from income taxes	(1,524)	(1,663)	(724)
Net loss	$ (112,717)	$ (66,819)	$ (51,010)
Net loss per share, basic and diluted	$ (3.80)	$ (2.67)	$ (2.66)
Weighted average ordinary shares outstanding, basic and diluted	29,660,659	25,061,734	19,145,938
Comprehensives loss:			
Net loss	$ (112,717)	$ (66,819)	$ (51,010)
Other comprehensive income (loss):			
Foreign currency translation adjustment	3,775	(195)	(1,658)
Total comprehensive loss	$ (108,942)	$ (67,014)	$ (52,668)

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

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

	Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (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 ordinary shares upon exercise of warrants	92,885	1	—	—	—	1
Issuance of ADSs upon exercise of share options	79,158	1	270	—	—	271
Issuance of ADSs, net of commissions and offering expenses of $1.9 million	2,928,813	37	48,107	—	—	48,144
Share-based compensation expense	—	—	6,514	—	—	6,514
Foreign currency translation adjustment	—	—	—	(1,658)	—	(1,658)
Net loss	—	—	—	—	(51,010)	(51,010)
Balance at December 31, 2020	21,094,557	266	249,947	(3,193)	(151,560)	95,460
Issuance of ADSs upon exercise of share options	703,786	10	7,173	—	—	7,183
Issuance of ADSs, net of commissions and offering expenses of $16.1 million	7,498,536	104	290,880	—	—	290,984
Issuance of ordinary shares pursuant to the Ionis share purchase agreement	282,485	4	7,554	—	—	7,558
Share-based compensation expense	—	—	12,083	—	—	12,083
Foreign currency translation adjustment	—	—	—	(195)	—	(195)
Net loss	—	—	—	—	(66,819)	(66,819)
Balance at December 31, 2021	29,579,364	384	567,637	(3,388)	(218,379)	346,254
Issuance of ADSs upon exercise of share options	78,074	1	988	—	—	989
Issuance of ADSs, net of commissions and offering expenses of $0.2 million	181,455	2	5,701	—	—	5,703
Issuance of ADSs upon vesting of restricted share units	35,000	—	—	—	—	—
Share-based compensation expense	—	—	26,779	—	—	26,779
Foreign currency translation adjustment	—	—	—	3,775	—	3,775
Net loss	—	—	—	—	(112,717)	(112,717)
Balance at December 31, 2022	29,873,893	$ 387	$ 601,105	$ 387	$ (331,096)	$ 270,783

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

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

	Year Ended December 31,		
	2022	**2021**	**2020**
Cash flows from operating activities:			
Net loss	$ (112,717)	$ (66,819)	$ (51,010)
Adjustments to reconcile net loss to net cash used in operating activities:			
Share-based compensation expense	26,779	12,083	6,514
Depreciation and amortization	3,689	1,409	1,277
Non-cash interest	442	468	78
Deferred income tax benefit	(4,976)	(1,668)	(673)
Changes in operating assets and liabilities:			
Accounts receivable	(1,641)	4,543	(2,149)
Research and development incentives receivable	(9,707)	(1,866)	(1,786)
Prepaid expenses and other assets	(2,020)	(2,974)	502
Operating lease right-of-use assets	2,698	404	771
Accounts payable	2,561	1,196	(663)
Accrued expenses and other current liabilities	12,362	1,185	4,832
Operating lease liabilities	(2,114)	(582)	(621)
Deferred revenue	(2,135)	37,117	24,622
Other long-term liabilities	668	710	517
Net cash used in operating activities	(86,111)	(14,794)	(17,789)
Cash used in investing activities:			
Purchases of property and equipment	(18,987)	(2,030)	(1,200)
Net cash used in investing activities	(18,987)	(2,030)	(1,200)
Cash flows from financing activities:			
Proceeds from the issuance of ADSs, net of issuance costs	5,703	290,984	48,144
Issuance of ordinary shares pursuant to the Ionis share purchase agreement	—	7,558	—
Proceeds from the exercise of share options and sale of ordinary shares	989	7,183	271
Proceeds from the exercise of warrants	—	—	1
Proceeds from issuance of debt	—	15,000	15,000
Payments of debt issuance costs	—	—	(573)
Net cash provided by financing activities	6,692	320,725	62,843
Effect of exchange rate changes on cash and cash equivalents	(1,120)	(1,211)	19
Net (decrease) increase in cash and cash equivalents	(99,526)	302,690	43,873
Cash and cash equivalents at beginning of period	438,680	135,990	92,117
Cash and cash equivalents at end of period	$ 339,154	$ 438,680	$ 135,990
Supplemental disclosure of cash flow information			
Cash paid for interest	$ 2,793	$ 2,515	$ 378
Cash paid for income taxes	$ 2,228	$ 73	$ 124
Cash paid for amounts included in the measurement of operating lease liabilities	$ 3,154	$ 911	$ 961
Purchases of property and equipment included in accounts payable and accrued expenses	$ 1,564	$ 324	$ 109
Advance billings on deferred revenue included in accounts receivable	$ —	$ —	$ 3,000
Non-cash impact right-of-use asset and operating lease liabilities	$ 3,120	$ 13,846	$ —

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

Bicycle Therapeutics plc
Notes to Consolidated Financial Statements

1. Nature of the business and basis of presentation

Bicycle Therapeutics plc (collectively with its subsidiaries, the "Company") is a clinical-stage biopharmaceutical company developing a novel class of medicines, which the Company refers to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are a unique therapeutic modality combining the pharmacology usually associated with a biologic with the manufacturing and pharmacokinetic properties of a small molecule. The Company's initial internal programs are focused on oncology indications with high unmet medical need. The Company 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 consolidated financial statements include the accounts of Bicycle Therapeutics plc and its wholly owned subsidiaries, BicycleTx Limited, BicycleRD Limited and Bicycle Therapeutics Inc. All intercompany balances and transactions have been eliminated on consolidation.

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). The Company has reclassified the deferred income tax benefit within its consolidated statements of cash flows in prior periods to conform to current period presentation.

Liquidity

As of December 31, 2022, the Company had cash and cash equivalents of $339.2 million.

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Since inception, the Company has devoted substantially all of its efforts to business planning, research and development, recruiting management and technical staff and raising capital. The Company has funded its operations with proceeds from the sale of its ordinary shares and American Depositary Shares ("ADSs"), including in its initial public offering ("IPO") completed in May 2019 and follow-on offering completed in October 2021 (Note 7), offerings pursuant to its at-the-market offering program ("ATM") program, prior to its IPO convertible preferred shares, proceeds received from its collaboration arrangements (Note 9) and proceeds from the Loan Agreement with Hercules Capital, Inc. ("Hercules") (Note 6). The Company has incurred recurring losses since inception, including net losses of $112.7 million for the year ended December 31, 2022, $66.8 million for the year ended December 31, 2021 and $51.0 million for the year ended December 31, 2020. As of December 31, 2022, the Company had an accumulated deficit of $331.1 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 annual consolidated financial statements.

The Company expects its expenses to increase substantially in connection with ongoing activities, particularly as the Company advances its preclinical activities and clinical trials for its product candidates in development. Accordingly, the Company will need to obtain additional funding in connection with continuing operations. If the Company is unable to raise funding 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. There is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

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

2. Summary of significant accounting policies

Use of estimates

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

Significant risks and uncertainties

The Company currently operates in a period of economic uncertainty which has been significantly impacted by the ongoing COVID-19 pandemic, domestic and global monetary and fiscal policy, geopolitical instability, the ongoing war in Ukraine, rising inflation and interest rates, and fluctuations in monetary exchange rates. While the Company has experienced limited financial impacts at this time, the Company continues to monitor these factors and events and the potential effects each may have on the Company's business, financial condition, results of operations and growth prospects.

Foreign currency and currency translation

The reporting currency of the Company is the U.S. Dollar ("USD"). The functional currency of Bicycle Therapeutics plc's wholly owned non-U.S. subsidiaries, BicycleTx Limited and BicycleRD Limited, is the British Pound Sterling, and the functional currency of its U.S. subsidiary, Bicycle Therapeutics Inc., is the USD. The functional currency of the Company's subsidiaries is the same as the local currency. Monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. Adjustments that arise from exchange rate changes on transactions denominated in a currency other than the local currency are included in general and administrative expense in the consolidated statements of operations and comprehensive loss as incurred. The Company recorded a foreign exchange loss of $0.6 million for the year ended December 31, 2022, and foreign exchange gains of $0.4 million and $0.6 million for the years ended December 31, 2021 and 2020, respectively.

The Company translates the assets and liabilities of its non-U.S. subsidiaries into USD at the exchange rate in effect on the balance sheet date. Revenues and expenses are translated at the average exchange rate in effect during the period. Unrealized translation gains and losses are recorded as a cumulative translation adjustment, which is included in the consolidated statements of shareholders' equity as a component of accumulated other comprehensive loss.

Concentrations of credit risk and of significant suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents and accounts receivable. The Company deposits its cash in financial institutions in amounts that may exceed federally insured limits and has not experienced any losses on such accounts. The Company does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

As of December 31, 2022 and 2021, accounts receivable consists of amounts due under the Company's collaboration agreements with Ionis Pharmaceuticals, Inc. ("Ionis") and Genentech, Inc. ("Genentech") for which the Company does not obtain collateral. For the years ended December 31, 2022, 2021, and 2020, the Company's revenue has primarily been generated from collaboration agreements with Ionis, Genentech, AstraZeneca AB ("AstraZeneca"), and Oxurion (Note 9).

The Company relies, and expects to continue to rely, on a small number of vendors to manufacture supplies and raw materials for its development programs. These programs could be adversely affected by a significant interruption in these manufacturing services or the availability of raw materials.

Cash and cash equivalents

The Company considers all highly liquid investments that are readily convertible to known amounts of cash with original maturities of three months or less at date of purchase to be cash equivalents. The Company had cash equivalents of $276.1 million and $100.0 million at December 31, 2022 and 2021, respectively.

Accounts receivable

The Company makes judgments as to its ability to collect outstanding receivables and estimates credit losses at the reporting date resulting from the inability of its customers to make required payments. Provisions are made based upon a specific review of all significant outstanding invoices and the overall quality and age of those invoices. To date, the Company has not had any write-offs of bad debt, and the Company did not have an allowance for credit losses as of December 31, 2022 and 2021.

Deferred offering costs

The Company capitalizes certain legal, professional accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in shareholders' equity as a reduction of proceeds generated as a result of the offering. Should an in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the consolidated statements of operations and comprehensive loss.

Property and equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization expense is recognized using the straight-line method over the estimated useful lives of the respective assets as follows:

	Estimated Useful Life
Laboratory equipment	3 to 5 years
Leasehold improvements	Lesser of lease term or useful life
Computer equipment and software	3 years
Furniture and office equipment	3 to 5 years

Costs for property and equipment not yet placed into service are capitalized as construction-in-progress and depreciated in accordance with the above guidelines once placed into service. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in loss from operations. To date, there have been no significant asset retirements. Expenditures for repairs and maintenance are charged to expense as incurred.

Impairment of long-lived assets

Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. To date, the Company has not recorded any material impairment losses on long-lived assets.

Fair value measurements

Certain of the Company's assets and liabilities are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1 — Quoted prices in active markets for identical assets or liabilities.

- Level 2 — Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.

- Level 3 — Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The carrying values of accounts receivable, research and development incentives receivable, prepaid expenses and 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 December 31, 2022 and 2021, the carrying value of the

long-term debt approximates its fair value, which was determined using unobservable Level 3 inputs, including quoted interest rates from a lender for borrowings with similar terms. As of December 31, 2022 and 2021, there were no assets or liabilities measured at fair value on a recurring basis.

Debt issuance costs

Debt issuance costs consist of certain third-party legal expenses and payments made to secure commitments under certain debt financing arrangements. These amounts are recognized as interest expense over the period of the financing arrangement.

Segment and geographic information

Operating segments are defined as components of a business for which separate discrete financial information is available for evaluation by the chief operating decision maker in deciding how to allocate resources and assess performance. The Company and its chief operating decision maker, the Company's Chief Executive Officer, view the Company's operations and manages its business as a single operating segment, which is developing a unique class of chemically synthesized medicines based on its proprietary platform.

The Company operates in two geographic regions: the United Kingdom and the United States.

Leases

Leases are accounted for in accordance with Accounting Standards Codification ("ASC") Topic 842, *Leases* ("ASC 842"). The Company determines if an arrangement is a lease at inception. Assets and liabilities related to operating leases are included in operating lease right of use ("ROU") assets, other current liabilities, and operating lease liabilities in the Company's consolidated balance sheet. The Company has not entered into any finance leases.

ROU assets represent the Company's right to use and control an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. ROU assets and liabilities are recognized on the lease commencement date based on the present value of lease payments over the lease term. The ROU asset also includes lease payments made before the lease commencement date and excludes any lease incentives. The Company identifies and assesses the following significant assumptions in recognizing the ROUA assets and corresponding lease liabilities:

- *Expected lease term* – The expected lease term includes both contractual lease periods and, when applicable, periods covered by an option to extend the lease when it is reasonably certain that the Company will exercise the extension option, or cancelable option periods when it is reasonably certain that the Company would not exercise such cancelation option.

- *Incremental borrowing rate* – As the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available on the commencement date in determining the present value of lease payments. As the Company does not have any external borrowings for comparable terms of its leases, the Company estimates the incremental borrowing rate by comparing interest rates available in the market for similar borrowings and third-party quotations.

- *Lease and non-lease components* – The components of a lease shall be split into three categories, if applicable: lease components (e.g., land, building, etc.), non-lease components (e.g., common area maintenance, maintenance, consumables, etc.) and non-components (e.g., property taxes, insurance, etc.). The fixed and in-substance fixed contract consideration (including any related to non-components) must then be allocated based on fair values to the lease components and non-lease components. The Company's facilities operating leases may have both lease components and non-lease components for which the Company has elected to apply the

practical expedient to account for each lease component and related non-lease component as one single component. The lease component results in a ROU asset being recorded on the balance sheet.

Lease expense for lease payments is considered operating lease cost and is recognized on a straight-line basis over the lease term. Variable payments for other operating costs, which may be billed based on both usage and as a percentage of the Company's share of total square footage, are considered variable lease cost and are recognized in the period in which the costs are incurred. Operating and variable lease cost are recorded as a component of research and development expenses and general and administrative expenses in the consolidated statements of operations and comprehensive loss.

Revenue recognition

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

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

The Company recognizes revenue in accordance with ASC Topic 606, *Revenue from Contracts with Customers* ("ASC 606"). This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, and financial instruments.

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

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

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

Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer. The promised goods or services in the Company's contracts with customers primarily consist of license rights to the Company's intellectual property, research and development services, options to acquire additional research and development services, and options to obtain additional licenses, such as a commercialization license for a potential product candidate. Promised goods or services are considered distinct when: (i) the customer can benefit from the good or service on its own or together with other readily available resources, and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct,

the Company considers factors such as the stage of development of the underlying intellectual property, the capabilities of the collaboration partner to develop the intellectual property on their own and whether the required expertise is readily available. In addition, the Company considers whether the customer can benefit from a promise for its intended purpose without the receipt of the remaining promises, whether the value of the promise is dependent on the unsatisfied promises, whether there are other vendors that could provide the remaining promises, and whether it is separately identifiable from the remaining promises.

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

After the transaction price is determined, it is allocated to the identified performance obligations based on the estimated standalone selling price. The Company must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the standalone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction, probabilities of technical and regulatory success and the estimated costs. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amounts the Company would expect to receive for each performance obligation.

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

Licenses of intellectual property: If a license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the contract, the Company recognizes revenue from portion of the transaction price allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are combined with other promises, such as research and development services and a research license, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the arrangement.

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

Customer options: A customer's rights to choose, at its discretion, to make a payment for additional goods or services is generally considered an option. If the Company is not presently obligated to provide, and does not have a right to consideration for delivering additional goods or services, the item is considered an option. The Company evaluates the customer options for material rights, such as the ability to acquire additional goods or services for free or at

a discount. Optional future services that reflect their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations and are accounted for as separate contracts. If optional future services include a material right, they are accounted for as performance obligations. The Company determines an estimated standalone selling price of any material rights for the purpose of allocating the transaction price. The Company considers factors such as the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised or expires.

Milestone payments: The Company's collaboration agreements may include development and regulatory milestones. The Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such milestones and any related constraint, and if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue and net loss in the period of adjustment. Milestone payments that may only be achieved after the exercise of a customer option are excluded from the initial determination of the transaction price.

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

The Company receives payments from customers based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional, such as when the Company has a contractual right to payment per the terms of the contract.

For a complete discussion of accounting for collaboration revenues, see Note 9, "Significant agreements."

Government grants

From time to time, the Company may enter into arrangements with governmental entities for the purposes of obtaining funding for research and development activities. The Company is reimbursed for costs incurred that are associated with specified research and development activities included in the grant application approved by the government authority. The Company recognizes government grant funding in the consolidated statements of operations and comprehensive loss as the related expenses being funded are incurred. The Company classifies government grants received under these arrangements as a reduction to the related research and development expense incurred, and accrued but unpaid grant income is included in other current assets. The Company analyzes each arrangement on a case-by-case basis, and income is recognized when the Company concludes that it has reasonable assurance that it will comply with the conditions attached to the grant and the expenses have been incurred. There are no significant performance criteria other than to maintain satisfactory progress on the specified project, and there are no significant acceptance or recapture provisions associated with the government grants for the years ended December 31, 2022, 2021 and 2020, respectively. For the years ended December 31, 2022, 2021 and 2020, the Company recognized $1.5 million, $3.0 million, and $0.7 million, respectively, as a reduction of research and development expense related to government grant arrangements. As of December 31, 2022, the Company has approximately $1.1 million of government grant funding remaining for future cost reimbursement through February of 2024.

Research and development costs

Research and development costs are expensed as incurred. Research and development costs consist of costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, travel, facilities costs, depreciation, materials and laboratory supplies, and external costs of outside vendors engaged to conduct preclinical development and clinical development activities, as well as to manufacture clinical trial materials. Facilities costs primarily include the allocation of rent and utilities.

Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized until the related goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered.

Research and manufacturing contract costs and accruals

The Company has entered into various research and development and manufacturing contracts, including contracts with respect to preclinical studies and clinical trials, with companies both inside and outside of the United States. These agreements are generally cancelable with 90 days or less notice, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the research and development and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Research and development incentives and receivable

The Company, through its subsidiaries in the United Kingdom, receives reimbursements of certain research and development expenditures as part of a United Kingdom government's research and development tax reliefs program. Under the program, the Company is able to surrender trading losses that arise from qualifying research and development expenses incurred by the Company's subsidiaries in the United Kingdom for a tax credit of up to 14.5% of the surrenderable losses, subject to certain limitations.

Management has assessed the Company's research and development activities and expenditures to determine which activities and expenditures are likely to be eligible under the research and development incentive program described above. At each period end, management estimates the reimbursement available to the Company based on available information at the time.

The Company recognizes income from the research and development incentives when the relevant expenditure has been incurred, the associated conditions have been satisfied and there is reasonable assurance that the reimbursement will be received. The Company records these research and development incentives as a reduction to research and development expenses in the statements of operations and comprehensive loss, as the research and development tax credits are not dependent on us generating future taxable income, the Company's ongoing tax status, or tax position. The research and development incentives receivable represent an amount due in connection with the above program. The Company recorded a reduction to research and development expense of $19.3 million, $10.8 million and $8.4 million during the years ended December 31, 2022, 2021 and 2020, respectively.

Patent costs

All patent-related costs incurred in connection with preparing, filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the consolidated statements of operations and comprehensive loss.

Share-based compensation

The Company measures all equity awards granted to employees and directors based on the fair value on the date of grant. Compensation expense of those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company records the expense for awards with only service-based vesting conditions using the straight-line method. The Company accounts for forfeitures as they occur.

For share-based awards granted to non-employee consultants, the measurement date is the date of grant. The compensation expense is then recognized over the requisite service period, which is the vesting period of the respective award, without subsequent changes in the fair value of the award.

The fair value of each restricted share award is based on the fair value of the Company's shares, less any applicable purchase price. The fair value of each share option is estimated using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the fair value of shares, the expected share price volatility, the expected term of the award, the risk-free interest rate and expected dividends.

Previously, due to a lack of company-specific historical volatility data, the Company's expected volatility was calculated based on reported volatility data for a representative group of publicly traded companies for which historical information was available. The historical volatility was calculated based on a period of time commensurate with the assumption used for the expected term. During 2022, the Company began to estimate its volatility by using a blend of its stock price history for the length of time it has market data for its stock and the historical volatility of similar public companies for the expected term of each grant. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption. The Company uses the simplified method, under which the expected term is presumed to be the midpoint between the vesting date and the end of the contractual term. The Company utilizes this method due to the lack of historical exercise data and the plain nature of its share-based awards. The Company uses the remaining contractual term for the expected life of non-employee awards. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on ordinary shares.

The Company classifies share-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll or service costs are classified.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' equity that result from transactions and economic events other than those with shareholders. The Company records unrealized gains and losses related to foreign currency translation as a component of other comprehensive loss in the consolidated statements of operations and comprehensive loss.

Contingencies

Liabilities for loss contingencies arising from claims, assessments, litigation, fines, penalties and other sources are recorded when it is probable that a liability has been incurred and the amount can be reasonably estimated. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential loss range is probable and reasonably estimable under the provisions of ASC Topic 450, *Contingencies*. The Company expenses costs as incurred in relation to such legal proceedings as general and administrative expense within the consolidated statements of operations and comprehensive loss.

Income taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on

the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

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

Net loss per share

Basic net loss per share is computed by dividing the net loss by the weighted average number of ordinary shares outstanding for the period. Diluted net loss is computed by adjusting net loss to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net loss per share is computed by dividing the diluted net loss by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares assuming the dilutive effect of ordinary share equivalents. In periods in which the Company reported a net loss, diluted net loss per share is the same as basic net loss per share, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive.

Recently adopted accounting pronouncements

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

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

3. Fair value of financial assets and liabilities

At December 31, 2022 and 2021, the Company had cash equivalents of $276.1 million and $100.0 million, respectively, consisting of a 30-day term deposit, which is considered a Level 1 asset.

4. Property and equipment, net

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

	December 31,	
	2022	2021
Laboratory equipment	$ 14,872	$ 6,746
Leasehold improvements	10,736	809
Computer equipment and software	441	143
Furniture and office equipment	924	225
	26,973	7,923
Less: Accumulated depreciation and amortization	(7,863)	(4,800)
	$ 19,110	$ 3,123

As of December 31, 2022, approximately $2.3 million of laboratory equipment was not yet placed in service. Depreciation expense was $3.7 million, $1.4 million and $1.3 million for the years ended December 31, 2022, 2021 and 2020, respectively.

5. Accrued expenses and other current liabilities

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

	December 31,	
	2022	2021
Accrued employee compensation and benefits	$ 9,928	$ 6,429
Accrued external research and development expenses	10,859	3,980
Accrued professional fees	1,068	882
Current portion of operating lease liabilities	3,125	2,383
Other	1,472	570
	$ 26,452	$ 14,244

6. Long-term debt

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

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

During 2020 and 2021, borrowings under the Loan Agreement bore 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 July 15, 2022, the Borrowers entered into the Second Amendment to the Loan and Security Agreement (the "Second Amendment to LSA") with Hercules. Pursuant to the Second Amendment to LSA, the rate at which the borrowings under the Loan Agreement bear interest was decreased and capped. Under the Second Amendment, interest is paid at an annual rate of the *Wall Street Journal* prime rate plus 4.55%, with a minimum annual rate of at least 8.05%, capped at a rate no greater than 9.05%. In addition, among other amendments, the Second Amendment extended the interest-only period to April 1, 2025, extended the Maturity Date to July 1, 2025, and provided the Borrowers, at their request, the potential for additional term loans, subject to satisfaction of customary conditions, in an aggregate principal amount of up to $45.0 million, and as such the aggregate maximum borrowings under the Loan Agreement increased to $75.0 million.

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) 1.5% of the principal amount outstanding if the prepayment occurs after the first anniversary of the Closing Date but on or prior to December 31, 2023, and (ii) 1.0% of the principal amount outstanding if the prepayment occurs thereafter but prior to the Maturity Date. The Loan Agreement also provides for an end of term charge (the "End of Term Charge"), payable upon maturity or the repayment of obligations under the Loan Agreement, equal to 5.0% of the principal amount repaid. Borrowings under the Loan Agreement are collateralized by substantially all of the Borrower's personal property and other assets, other than their intellectual property. Hercules has a perfected first-priority security interest in certain cash accounts. The Loan Agreement contains customary affirmative and restrictive covenants and representations and warranties, including a covenant against the occurrence of a change in control, as defined in the agreement. There are no financial covenants. The Loan Agreement also includes customary events of default, including payment defaults, breaches of covenants following any applicable cure period, cross acceleration to third-party indebtedness, certain events relating to bankruptcy or insolvency, and the occurrence of certain events that could reasonably be expected to have a material adverse effect. Upon the occurrence of an event of default, a default interest rate of an additional 5.0% may be applied to the outstanding principal and interest payments due, and Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement. The Company has determined that the risk of subjective acceleration under the material adverse events clause is not probable and therefore has classified the outstanding principal in long-term liabilities based on scheduled principal payments.

The Company incurred fees and transaction costs totaling $0.6 million associated with the initial term loan, which are recorded as a reduction to the carrying value of the long-term debt in the consolidated balance sheets. The fees, transaction costs, and the End of Term Charge are amortized to interest expense through the Maturity Date using the effective interest method. The Company evaluated the First Amendment to LSA and the Second Amendment to LSA and concluded that these amendments represent modifications to the Loan Agreement, and as such, the fees and transaction costs associated with the term loan will continue to be amortized to interest expense through the Maturity Date. The effective interest rate of the Hercules borrowings was 10.8% at December 31, 2022.

The Company assessed all terms and features of the Loan Agreement in order to identify any potential embedded features that would require bifurcation. As part of this analysis, the Company assessed the economic characteristics and risks of the debt. The Company determined that all features of the Loan Agreement are clearly and closely associated with a debt host and, as such, do not require separate accounting as a derivative liability. Interest expense associated with the Loan Agreement for the years ended December 31, 2022, 2021 and 2020 was $3.2 million, $2.9 million and $0.4 million, respectively.

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

	December 31, 2022	December 31, 2021
Term loan payable	$ 30,000	$ 30,000
End of term charge	682	376
Unamortized debt issuance costs	(367)	(503)
Carrying value of term loan	$ 30,315	$ 29,873

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

Year Ending December 31,		
2023	$	—
2024		—
2025		31,500
Total	$	31,500

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

7. Ordinary shares

Each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. Holders of ADSs are not treated as holders of the Company's ordinary shares, unless they withdraw the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of the Company's ordinary shares, other than the rights that they have pursuant to the deposit agreement with the depositary. As of December 31, 2022 and 2021, the Company had not declared any dividends.

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

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 ATM program 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. During the year ended December 31, 2022, the Company issued and sold 181,455 ADSs, representing the same number of ordinary shares for gross proceeds of $5.9 million, resulting in net proceeds of $5.7 million after deducting sales commissions and offering expenses of $0.2 million. During the year ended December 31, 2021, the Company issued and sold 3,771,684 ADSs, representing the same number of ordinary shares for gross proceeds of $105.8 million, resulting in net proceeds of $102.6 million after deducting sales commissions and offering expenses of $3.2 million. During the year ended December 31, 2020, the Company issued and sold 2,928,813 ADSs, representing the same number of ordinary shares for gross proceeds of $50.0 million, resulting in net proceeds of $48.1 million after deducting sales commissions and offering expenses of $1.9 million.

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

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, for net proceeds for $188.4 million.

8. Share-based compensation

Employee incentive pool

2020 Equity Incentive 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 ("RSUs"), performance RSUs and other share-based awards to the Company's employees. The Company's non-employee directors and consultants are eligible to receive awards under the 2020 Non-Employee Sub-Plan to the 2020 Plan. All awards under the 2020 Plan, including the 2020 Non-Employee Sub-Plan, will be set forth in award agreements, which will detail the terms and conditions of awards, including any applicable vesting and payment terms, change of control provisions and post-termination exercise limitations. In the event of a change of control of the Company, as defined in the 2020 Plan, any outstanding awards under the 2020 Plan will vest in full immediately prior to such change of control.

The Company initially reserved up to 4,773,557 ordinary shares for future issuance under the 2020 Plan, representing 574,679 new shares, 544,866 shares that remained available for future issuance under the Company's 2019 Share Option Plan (the "2019 Plan") immediately prior to the effectiveness of the 2020 Plan and up to 3,654,012 shares subject to options that were granted under the 2019 Plan and that were granted pursuant to option contracts granted prior to the Company's IPO, in each case that expire, terminate, are forfeited or otherwise not issued from time to time, if any. On June 27, 2022, the Company's shareholders approved an amendment to the 2020 Plan (the "Amendment") which increased the number of ordinary shares reserved for future issuance by 750,000 shares. Additionally, the number of ordinary shares reserved for issuance pursuant to the 2020 Plan will automatically increase on the first day of January of each year, commencing on January 1, 2021, in an amount equal to 5% of the total number of the Company's ordinary shares outstanding on the last day of the preceding year, or a lesser number of shares determined by the Company's board of directors. Pursuant to this evergreen provision, on January 1, 2022, the number of shares reserved for issuance under the 2020 Plan was increased by 1,478,968 shares. The Amendment extended the final date upon which an "evergreen" increase may occur under this provision from January 1, 2030, to January 1, 2032. As of December 31, 2022, there were 1,082,274 shares available for issuance under the 2020 Plan. The number of shares reserved for issuance under the 2020 Plan was increased by 1,493,694 shares effective January 1, 2023.

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.

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

As of December 31, 2022, there were options to purchase 3,172,533 shares and RSUs for 187,725 shares outstanding under the 2020 Plan.

2019 Share Option Plan

In May 2019, the Company adopted the 2019 Plan, which became effective in conjunction with the IPO. As of December 31, 2022, there were 2,133,437 options to purchase ordinary shares outstanding under the 2019 Plan. In conjunction with the adoption of the 2020 Plan, all shares available for future issuance under the 2019 Plan as of June 29, 2020 became available for issuance under the 2020 Plan and the Company ceased making awards under the 2019 Plan. The 2020 Plan is the successor of the 2019 Plan.

Share options previously issued under the 2019 Plan have a 10-year contractual life, and generally either vest monthly over a three-year service period, or over a four-year service period with 25% of the award vesting on the first anniversary of the 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 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 the Company's capitalization. As of December 31, 2022, the total number of shares available for issuance under the ESPP was 901,675 shares. The number of shares reserved for issuance under the ESPP was increased by 298,738 shares effective January 1, 2023. As of December 31, 2022, there have been no offering periods to employees under ESPP.

Share-based compensation

The Company recorded share-based compensation expense in the following expense categories of its consolidated statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Research and development expenses	$ 10,394	$ 4,974	$ 2,603
General and administrative expenses	16,385	7,109	3,911
	$ 26,779	$ 12,083	$ 6,514

Share options

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

	Number of Shares Underlying Share Options	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2021	4,603,486	$ 14.97	8.13	$ 207,009
Granted	1,548,167	44.83	—	—
Exercised	(78,074)	12.67	—	—
Forfeited	(174,691)	27.92	—	—
Outstanding as of December 31, 2022	5,898,888	$ 22.45	7.64	$ 71,002
Vested and expected to vest as of December 31, 2022	5,898,888	$ 22.45	7.64	$ 71,002
Options exercisable as of December 31, 2022	3,352,315	$ 13.93	6.87	$ 55,749

The weighted average grant-date fair value of share options granted during the years ended December 31, 2022, 2021 and 2020 was $31.45 per share, $15.66 per share and $7.87 per share, respectively.

The aggregate intrinsic value of share options is calculated as the difference between the exercise price of the share options and the fair value of the Company's ordinary shares. The aggregate intrinsic value of share options exercised during the years ended December 31, 2022, 2021 and 2020 was $1.5 million, $22.0 million and $1.3 million, respectively.

For the years ended December 31, 2022, 2021 and 2020, the Company recorded share-based compensation expense for share options granted of $21.9 million, $12.1 million and $6.5 million, respectively. Expense for non-employee consultants for each of the years ended December 31, 2022, 2021 and 2020, was immaterial.

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of share options granted to employees and directors:

	Year Ended December 31,		
	2022	2021	2020
Risk-free interest rate	2.2 %	0.6 %	1.3 %
Expected volatility	82.5 %	79.8 %	74.8 %
Expected dividend yield	—	—	—
Expected term (in years)	6.02	5.98	5.98

As of December 31, 2022, total unrecognized compensation expense related to the unvested employee and director share options was $50.1 million, which is expected to be recognized over a weighted average period of 2.8 years.

Restricted share units

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

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

The fair value of RSUs that vested during the years ended December 31, 2022, 2021 and 2020 was $2.1 million, zero and zero, respectively.

Total share-based compensation expense for RSUs granted for the years ended December 31, 2022, 2021 and 2022 was $4.9 million, zero and zero, respectively. As of December 31, 2022, the total unrecognized compensation expense related to unvested RSUs was $8.6 million, which is expected to be recognized over a weighted-average period of 3.0 years.

9. Significant agreements

For the years ended December 31, 2022, 2021 and 2020, the Company recognized revenue for its collaborations with Ionis, Genentech, DDF, AstraZeneca, and Oxurion. The following table summarizes the revenue recognized in the Company's consolidated statements of operations and comprehensive loss from these arrangements (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Collaboration revenues			
Ionis	$ 9,347	$ 4,242	$ —
Genentech	3,565	5,660	4,896
Dementia Discovery Fund	386	391	436
AstraZeneca	1,165	1,404	2,696
Oxurion	—	—	2,362
Total collaboration revenues	$ 14,463	$ 11,697	$ 10,390

Ionis Agreements

Ionis Evaluation and Option Agreement

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

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

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

Ionis Collaboration Agreement

Following the exercise by Ionis of the Ionis Option granted pursuant to the Evaluation and Option Agreement, on July 9, 2021, the Company and Ionis entered into a collaboration and license agreement (the "Ionis Collaboration

Agreement"). Pursuant to the Ionis Collaboration Agreement, the Company granted to Ionis a worldwide exclusive license under the Company's relevant technology to research, develop, manufacture and commercialize products incorporating *Bicycle* peptides directed to the protein coded by the gene TFRC1 (transferrin receptor) ("TfR1 Bicycles") intended for the delivery of oligonucleotide compounds directed to targets selected by Ionis for diagnostic, therapeutic, prophylactic and preventative uses in humans. Ionis will maintain exclusivity to all available targets unless it fails to achieve specified development diligence milestone deadlines. If Ionis fails to achieve one or more development diligence milestone deadlines, the Company has the right to limit exclusivity to certain specific collaboration targets, subject to the payment by Ionis of a low-single-digit million dollar amount per target as specified in the Ionis Collaboration Agreement. Each party will be responsible for optimization of such TfR1 *Bicycles* and other research and discovery activities related to TfR1 *Bicycles*, as specified by a research plan, and thereafter Ionis will be responsible for all future research, development, manufacture and commercialization activities. The Company will perform research and discovery activities including a baseline level of effort for a period of three years for no additional consideration. The parties will negotiate a commercially reasonable rate if additional research activities are agreed to be performed. For certain research and discovery activities that the Company is responsible for performing, the Company may use the assistance of a contract research organization ("CRO"). The Company has retained certain rights, including the right to use TfR1 *Bicycles* for all non-oligonucleotide therapeutic purposes.

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

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

In December 2021, the Company and Ionis entered into an amendment to the Ionis Collaboration Agreement (the "Ionis Amendment"). Ionis paid the Company $1.6 million and the Company agreed to perform additional research services utilizing its proprietary phage screening technology to identify and optimize new product candidates that target the TfR1 receptor. The Company performed the additional research services for an initial six-month period, which was extended in August 2022 for an additional three months, in exchange for consideration of $0.8 million. In October 2022, Ionis exercised an option it had for the Company to perform additional research services for an additional six months in exchange for the remaining consideration of $0.8 million.

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 agreed that until January 9, 2023, it would not, without our prior written consent and subject to certain conditions and exceptions, among other things, directly or indirectly acquire additional shares of our outstanding equity securities, seek or propose a tender or exchange offer, merger or other business combination involving us, solicit proxies or consents with respect to any matter, or undertake other specified actions related to the potential acquisition of additional equity interests in us. The Share Purchase Agreement also provided that, subject to limited exceptions, Ionis could not sell any of the Ionis Shares until July 2022.

The Company determined the fair value of the Ionis Shares to be $7.6 million, based on the closing price of the Company's ADSs of $31.11 per ADS on the date of the Ionis Share Purchase Agreement, less a discount for lack of marketability associated with resale restrictions applicable to the Ionis Shares. 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 discovery services as Ionis cannot obtain the intended benefit of the license without the Company performing the agreed upon research and discovery services, including the optimization of such TfR1 *Bicycles*. The services incorporate proprietary technology, unique skills and specialized expertise to optimize *Bicycles* that are not available in the marketplace. As a result, the exclusive license to research, develop, manufacture and commercialize products has been combined with the research and discovery activities into a single performance obligation. The Company concluded that the low-single-digit million dollar payments upon acceptance of an IND (and payment to extend the exclusive license to research, develop, manufacture and commercialize a product candidate for certain specific collaboration targets if Ionis fails to achieve specified development diligence milestone deadlines) is a customer option, as Ionis has the contractual right to choose to make the payment in exchange for the continued exclusive right to research, develop, manufacture and commercialize the product candidate, and the Company is not presently obligated to provide, and does not have a right to consideration, for the additional goods or services prior to Ionis's exercise of the option. In assessing whether the options under the Ionis Collaboration Agreement represent material rights, the Company considered the additional consideration the Company would be entitled to upon the option exercise and the standalone selling price of the underlying goods and services. For the material rights identified as performance obligations 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 to the separate performance obligations is as follows (in thousands):

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

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

The Company concluded that the Ionis Amendment will be accounted for as a separate contract, as the services are distinct from the Ionis Collaboration Agreement, and the price of the contract increased by an amount of consideration that reflects the Company's standalone selling price. The Company concluded that the option does not contain a material right. The Company recognized the $0.8 million associated with the services in the initial six-month period as revenue as the underlying services were performed using a proportional performance model over the period of service using input based measurements of total full time equivalent efforts and external costs incurred to date as a percentage of total expected full time equivalent efforts and expected external costs, which best reflects the progress towards satisfaction of the performance obligation. As the option to perform additional research services for an additional six months does not contain a material right, the Company accounted for Ionis' exercise of the option in October 2022 as a separate contract. The Company is recognizing the $0.8 million associated with the services for the additional six-month period as revenue as the underlying services are performed using a proportional performance model over the period of service using input based measurements of total full time equivalent efforts and external costs incurred to date as a percentage of total expected full time equivalent efforts and expected external costs, which best reflects the progress towards satisfaction of the performance obligation.

For the years ended December 31, 2022, 2021 and 2020, the Company recognized $9.3 million, $4.2 million and no revenue, respectively, and as of December 31, 2022 and 2021, the Company recorded deferred revenue of $21.5 million and $34.1 million, respectively, in connection with the Ionis Collaboration Agreement, Ionis Amendment, and Ionis Evaluation and Option Agreement.

Genentech Collaboration Agreement

On February 21, 2020, the Company entered into a Discovery Collaboration and License Agreement, as amended from time to time (as amended, 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, the Company received a $30.0 million upfront, non-refundable payment. The initial discovery and optimization activities are focused on utilizing the Company's phage screening technology to identify product candidates aimed at two immuno-oncology targets ("Genentech Collaboration Programs"), which may also include additional discovery and optimization of *Bicycles* as a targeting element for each Genentech Collaboration Program (each a "Targeting Arm"). Genentech also had the option to nominate up to two additional immuno-oncology targets (each, an "Expansion Option") as additional Genentech Collaboration Programs, which may also include an additional Targeting Arm for each Expansion Option. Genentech exercised the Expansion Options in October 2021 and June 2022, respectively. Genentech paid to the Company an expansion fee of $10.0 million for each Expansion Option. Genentech also has rights, under certain limited circumstances, to select an alternative target to be the subject of a Genentech Collaboration Program, in some cases subject to payment of an additional target selection fee.

If Genentech elects for the Company to perform discovery and optimization services for certain Targeting Arms, the Company will be entitled to receive an additional advance payment for the additional research services. Genentech exercised its right to select a Targeting Arm for one of the initial Genentech Collaboration Programs at the inception of the arrangement, and for the first Expansion Option in October 2021, which entitled the Company to additional payments of $1.0 million each. If a Targeting Arm achieves specified criteria in accordance with the research plan, Genentech will be required to pay a further specified amount in the low single digit millions for each such Targeting Arm as consideration for the additional services to be provided.

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

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

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

Accounting Analysis

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

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

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

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

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

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

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

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

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

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

In October 2021, Genentech exercised the first Expansion Option to add an additional Genentech Collaboration Program (Genentech Collaboration Program #3) and paid to the Company an expansion fee of $10.0 million in November 2021. Genentech also elected for Bicycle to perform discovery and optimization services for a Targeting Arm, and the Company received an additional payment of $1.0 million for additional research services. The Company exercised judgment and concluded that the exercise of the first Expansion Option and the option to a specified Targeting Arm is accounted for as a continuation of an existing contract as the customer decided to purchase additional goods and services contemplated in the original contract, as such, the additional arrangement consideration of $11.0 million received upon the option exercises together with the amount originally allocated to the Expansion Option material right of $3.5 million is allocated to the underlying goods and services associated with the Expansion Option. The arrangement consideration was allocated to the separate performance obligations on the same basis as the initial allocation of the Genentech Collaboration Agreement. In December 2022, the Targeting Arm achieved specified criteria in accordance with the research plan under the Genentech Collaboration Agreement and therefore the Company updated its estimate of variable consideration to include an additional $2.0 million, that is no longer constrained. The Company allocated the additional $2.0 million entirely to the Genentech Collaboration Program #3 and Targeting Arm services as the terms of the variable consideration relate specifically to the Company's efforts in satisfying the performance obligation and allocating the variable consideration entirely to the performance obligation is consistent with the allocation objective in ASC 606. The Company is recognizing $8.4 million allocated to Genentech Collaboration Program #3 and Targeting Arm services as the underlying services are performed using a proportional performance model over the period of service of approximately two to three years using input-based measurements of total full-time equivalent efforts and

external costs incurred to date as a percentage of total full-time equivalent efforts and external costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amount allocated to the material right associated with an LSR Go Option for Collaboration Program #3 of $7.4 million and limited substitution material rights of $0.7 million are recorded as deferred revenue and the Company will commence revenue recognition upon exercise of or upon expiry of the respective option. Other variable consideration for development milestones not subject to option exercises was fully constrained, as a result of the uncertainty regarding whether any of the milestones will be achieved.

In June 2022, Genentech exercised the second Expansion Option to add an additional Genentech Collaboration Program ("Genentech Collaboration Program #4"), which triggered a $10.0 million payment to the Company under the Genentech Collaboration Agreement. The Company exercised judgment and concluded that the exercise of the second Expansion Option is accounted for as a continuation of an existing contract as the customer decided to purchase additional goods and services contemplated in the original contract, and as such, the additional arrangement consideration of $10.0 million received pursuant to the option exercise together with the amount originally allocated to the Expansion Option material right of $3.5 million is allocated to the underlying goods and services associated with the Expansion Option. The arrangement consideration was allocated to the separate performance obligations on the same basis as the initial allocation of the Genentech Collaboration Agreement. The Company will recognize $5.3 million allocated to the Genentech Collaboration Program #4 services as the underlying services are performed using a proportional performance model over the period of service of approximately two to three years using input-based measurements of total full-time equivalent efforts and external costs incurred to date as a percentage of total full-time equivalent efforts and external costs expected, which best reflects the progress towards satisfaction of the performance obligation. The amounts allocated to the material right associated with an LSR Go Option for Genentech Collaboration Target #4 of $7.4 million, limited substitution material rights of $0.7 million, and the material right associated with the option to select a Targeting Arm for Genentech Collaboration Program #4 of $0.1 million, were recorded as deferred revenue and the Company will commence revenue recognition upon exercise or expiry of the respective option. Other variable consideration for development milestones not subject to option exercises was fully constrained as a result of the uncertainty regarding whether any of the milestones will be achieved.

For the years ended December 31, 2022, 2021 and 2020, the Company recognized revenue of $3.6 million, $5.7 million and $4.9 million, respectively, and as of December 31, 2022 and 2021, the Company recorded deferred revenue of $39.3 million and $34.4 million, respectively, in connection with the Genentech Collaboration Agreement.

Dementia Discovery Fund Agreement

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

The Company received an upfront payment of $1.1 million in May 2019. The DDF arrangement provided the Company could receive up to an additional $0.7 million, of which $0.6 million has been received as of December 31, 2022, 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 Company's participation in the Research Advisory Panel and the DDF Option are immaterial in the context of the contract, and that neither the DDF Option nor the option for NewCo to obtain additional peptide screening and optimization services contain a material right. 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 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 and external costs incurred to date as a percentage of total expected costs, which best reflects the progress towards satisfaction of the performance obligation.

For the each of the years ended December 31, 2022, 2021 and 2020, the Company recognized $0.4 million revenue. The Company recorded deferred revenue of zero and $0.4 million for the years ended December 31, 2022 and 2021, 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 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: (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 determined using the most likely amount method. The research and development funding was provided based on the costs incurred to conduct the research and development services. 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 contract term.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation. The estimated standalone selling prices for each Research License and Related Services obligation was primarily based on the nature of the services to be performed and estimates of the

associated effort and costs of the services, adjusted for a reasonable profit margin for what would be expected to be realized under similar contracts. The estimated standalone selling price for the material rights was determined based on the fees AstraZeneca would pay to exercise the license options, the estimated value of the license options 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

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. The Company recognized revenue related to amounts allocated to the Target Three Research License and Related Services as the underlying services were performed using a proportional performance model over the period of service using input-based measurements of total full-time equivalent effort incurred to date as a percentage of total full-time equivalent time expected, which best 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 October 2020, August 2021 and June 2022, AstraZeneca terminated the collaboration activities related to the third, sixth and fifth targets, respectively, and the deferred revenue related to the associated material rights was recognized. In January 2022, AstraZeneca elected to extend the Research Term for the fourth target by 12 months. As of December 31, 2022, the fourth target research program was in the AZ Research Term.

For the years ended December 31, 2022, 2021 and 2020 the Company recognized $1.2 million, $1.4 million, and $2.7 million, respectively, of revenue related to the AstraZeneca Collaboration Agreement. As of December 31, 2022 and 2021, the Company recorded $1.1 million and $2.4 million of deferred revenue, respectively, in connection with Additional Four Target Option.

Oxurion Collaboration Agreement

In August 2013, the Company entered into a Research Collaboration and License Agreement (the "Oxurion Collaboration Agreement") with Oxurion. Under the Oxurion Collaboration Agreement, the Company was responsible for identifying *Bicycle* peptides related to the collaboration target, plasma kallikrein, for use in various ophthalmic indications. Oxurion is responsible for further development and product commercialization after the defined research screening is performed by the Company. Under the Oxurion Collaboration Agreement, the Company granted certain worldwide intellectual property rights to Oxurion for the development, manufacture and commercialization of licensed compounds associated with plasma kallikrein. The Company is eligible to receive up to €8.3 million upon the achievement of specified research, development, regulatory and commercial events and research and development milestones, of which €3.8 million has been received as of December 31, 2022. 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 recognized no collaboration revenue during each of the years ended December 31, 2022 and 2021. During the year ended December 31, 2020, the Company achieved a milestone related to the initiation of a Phase II clinical trial and $2.4 million was recognized as revenue, as there are no remaining performance obligations associated with the Oxurion Collaboration Agreement. No other future development or regulatory milestones have been included in the transaction price, as none are considered probable at December 31, 2022 and 2021. As of December 31, 2022 and 2021, the Company recorded no deferred revenue related to its collaboration with Oxurion.

Summary of Contract Assets and Liabilities

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

	Beginning Balance January 1, 2022	Additions	Deductions	Impact of Exchange Rates	Ending Balance December 31, 2022
Contract liabilities:					
Deferred revenue					
Ionis collaboration deferred revenue	$ 34,115	$ 99	$ (9,347)	$ (3,378)	$ 21,489
Genentech collaboration deferred revenue	34,436	12,000	(3,565)	(3,563)	39,308
DDF collaboration deferred revenue	428	—	(386)	(42)	—
AstraZeneca collaboration deferred revenue	2,361	—	(1,165)	(120)	1,076
Total deferred revenue	$ 71,340	$ 12,099	$ (14,463)	$ (7,103)	$ 61,873

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

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

The Ionis deferred revenue balance at December 31, 2022 includes $3.4 million allocated to material rights that will commence revenue recognition when the respective option is exercised or when the option expires. The Genentech deferred revenue balance at December 31, 2022 includes $27.3 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 December 31, 2022 includes $1.1 million allocated to the Target 4 Material Right, 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 years ended December 31, 2022, 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):

	Year Ended December 31,		
	2022	2021	2020
Revenue recognized in the period from:			
Revenue recognized based on proportional performance	$ 12,358	$ 9,652	$ 6,326
Revenue recognized based on expiration of material rights	1,433	1,876	1,702
Revenue recognized based on changes in transaction price	672	169	—
Total	$ 14,463	$ 11,697	$ 8,028

Cancer Research UK

BT1718

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

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

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

The Cancer Research UK Agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party). Cancer Research UK may also terminate the arrangement for safety reasons or if it determines that the objectives of the clinical trial will not be met. The Company was obligated to reimburse Cancer Research UK for certain costs if the Cancer Research UK agreement was terminated by Cancer Research UK prior to the completion of the dose escalation (Phase I) part of the clinical trial for an insolvency event of, or material breach by, the Company or upon termination for safety reasons or if Cancer Research UK determined that the objectives of the clinical trial would not be

met, however, these reimbursement obligations expired unexercised upon the completion of the Phase I portion of the clinical trial in 2020. If the Company is subject to a change in control and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party prior to the last cycle of treatment under the Phase IIa clinical trial, the Company will reimburse Cancer Research UK in full for all costs paid or committed in connection with the clinical trial and no further license payments, where applicable, shall be due. In such case, Cancer Research UK will not be obliged to grant a license to the Company in respect of the results of the clinical trial and the Company will assign or grant to CRTL an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company.

The Company concluded that the costs incurred by Cancer Research UK is a liability in accordance with ASC 730, *Research and Developmen*t, as certain payments are not based solely on the results of the research and development having future economic benefit. As such, as of December 31, 2022 and 2021, the Company recorded a liability of $3.6 million and $3.3 million, respectively, which is recorded in other long-term liabilities in the consolidated balance sheets. The liability is recorded as incremental research and development expense in the consolidated statements of operations and comprehensive loss.

BT7401

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

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

The BT7401 Cancer Research UK agreement can be terminated by either party upon an insolvency event, material breach of the terms of the contract, or upon a change in control (and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party), or upon written notice by Cancer Research UK prior to the last cycle of treatment has been completed under the clinical trial. If the trial is terminated by the Company prior to the filing of a clinical trial authorization, or by Cancer Research UK for an insolvency event or a material breach by the Company prior to the start of a clinical trial, the Company will reimburse Cancer Research UK for certain costs paid or committed prior to the start of the clinical trial. In such case where the Company is subject to a change of control and the new controlling entity develops, sells or manufactures tobacco products or generates the majority of its profits from tobacco products or is an affiliate of such party, Cancer Research UK will not be obliged to grant a license to the Company in respect of the results of the clinical trial and CRTL may elect to receive an exclusive license to develop and commercialize the product without CRTL being required to make any payment to the Company. The Company concluded that the BT7401 Cancer Research UK arrangement does not represent a liability in accordance with ASC 730, *Research and Development*, as the payments are based solely on the results of the research and development having future economic benefit and risk of repayment is substantive and genuine, and as such there was no accounting impact as of and for the year ended December 31, 2022.

10. Income taxes

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

	Year Ended December 31,		
	2022	2021	2020
United Kingdom	$ (116,275)	$ (69,546)	$ (52,521)
United States	2,034	1,064	787
Total	$ (114,241)	$ (68,482)	$ (51,734)

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

	Year Ended December 31,		
	2022	2021	2020
Current income tax provision (benefit)			
Federal	$ 2,048	$ (2)	$ (24)
State	1,404	7	(27)
Total current income tax provision (benefit)	3,452	5	(51)
Deferred income tax (benefit) provision			
Federal	(4,111)	(1,236)	(435)
State	(865)	(432)	(238)
Total deferred income tax (benefit)	(4,976)	(1,668)	(673)
Total benefit from income taxes	$ (1,524)	$ (1,663)	$ (724)

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

	Year Ended December 31,		
	2022	2021	2020
Benefit for income taxes at statutory rate	19 %	19 %	19 %
(Decreases) increases resulting from:			
Federal tax credits	0.3 %	0.6 %	0.9 %
Change in valuation allowance	(16.8)%	(27.0)%	(15.4)%
Net losses surrendered for research credit	(6.5)%	(5.9)%	(6.2)%
Impact of statutory rate change	11.3 %	12.1 %	1.8 %
Impact of foreign exchange rates	(9.9)%	— %	1.3 %
Other	3.9 %	3.6 %	— %
Effective income tax rate	1.3 %	2.4 %	1.4 %

Significant components of the Company's current and deferred tax assets are as follows (in thousands):

	December 31,	
	2022	2021
Deferred tax assets:		
Operating loss carryforwards	$ 45,452	$ 30,536
Research credit carryforwards	—	1,862
Operating lease liability	3,566	3,626
Share-based compensation	9,842	4,406
Capitalized research and development expenses	5,168	—
Accrued expenses and other	2,318	1,496
Total deferred tax assets	66,346	41,926
Deferred tax liabilities:		
Operating lease right-of-use asset	(3,474)	(3,665)
Depreciation & amortization	(933)	(439)
Total deferred tax liabilities	(4,407)	(4,104)
Valuation allowance	(53,743)	(34,601)
Net deferred tax assets	$ 8,196	$ 3,221

During the years ended December 31, 2022, 2021 and 2020, the Company recorded an income tax benefit of $1.5 million, $1.7 million, and $0.7 million, respectively. The Company is subject to U.K. corporate taxation. Due to the nature of its business, the Company has generated losses since inception and therefore not paid U.K. corporation tax. The Company's income tax benefit is mainly the result of deferred tax assets benefited in the United States that do not have a valuation allowance against them because of profits that will be generated by an intercompany service agreement.

Starting in 2022, amendments to Section 174 of the Internal Revenue Code of 1986, as amended ("IRC"), will no longer permit an immediate deduction for research and development expenditures in the tax year that such costs are incurred. Instead, these IRC Section 174 development costs must now be capitalized and amortized over either a five- or 15-year period, depending on the location of the activities performed. The new amortization period begins with the midpoint of any taxable year that IRC Section 174 costs are first incurred, regardless of whether the expenditures were made prior to or after July 1, and runs until the midpoint of year five for activities conducted in the United States or year 15 in the case of development conducted on foreign soil.

The Company regularly assesses its ability to realize its deferred tax assets. Assessing the realization of deferred tax assets requires significant judgment. In determining whether its deferred tax assets are more likely than not realizable, the Company evaluated all available positive and negative evidence, and weighed the evidence based on its objectivity. After consideration of the evidence, including the Company's history of cumulative net losses in the U.K., 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 U.K. The Company has considered its history of cumulative net profits in the United States and estimated future taxable income and has 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 valuation allowance increased in the year ended December 31, 2022 by $19.1 million due to the corresponding increase in U.K. deferred tax assets, primarily due to operating loss carryforwards generated during the year that were not surrendered for research credit utilization.

The Company recorded a valuation allowance against all of its U.K. deferred tax assets as of December 31, 2022 and 2021.

The Company intends to continue to maintain a full valuation allowance on its U.K. deferred tax assets until there is sufficient evidence to support the reversal of all or some portion of these allowances. The release of the valuation allowance would result in the recognition of certain deferred tax assets and an increase to the benefit for income taxes

for the period the release is recorded. However, the exact timing and amount of the valuation allowance release are subject to change on the basis of the level of profitability that the Company is able to actually achieve.

The benefit for income taxes shown on the consolidated statements of operations differs from amounts that would result from applying the statutory tax rates to income before taxes primarily because of certain permanent expenses that were not deductible and U.K., U.S. federal and state research and development credits, as well as the application of valuation allowances against the U.K. deferred tax assets.

As of December 31, 2022, the Company had $181.8 million of U.K. operating loss carryforwards that have an indefinite life.

The Company recognizes, in its consolidated financial statements, the effect of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. The Company had no uncertain tax positions during the years ended of December 31, 2022 and 2021. There are no amounts of interest or penalties recognized in the consolidated statement of operations or accrued on the consolidated balance sheet for any period presented. The Company does not expect any material changes in these uncertain tax benefits within the next 12 months.

The Company files income tax returns in the United Kingdom, and in the United States for federal income taxes and in 11 jurisdictions for state income taxes. In the normal course of business, the Company is subject to examination by tax authorities in these jurisdictions. The 2021 and 2020 tax years remains open to examination the by HM Revenue & Customs. The statute of limitations for assessment with the Internal Revenue Service is generally three years from filing the tax return. As such, all years since 2019 in the U.S. remain open to examination. The Company is currently not under examination by jurisdictions for any tax years.

11. Commitments and contingencies

Leases

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

In October 2017, the Company entered into a lease agreement for office and laboratory space in Building 900, Babraham Research Campus, Cambridge, U.K. In March 2021, prior to the expiration of the lease, the Company concluded that it was reasonably certain that it would exercise its additional five-year lease renewal option, which was not included in the original lease term, and accounted for the change in lease term as a modification of the existing lease. The Company remeasured the ROU asset and lease liability by calculating the present value of expected lease payments, discounted at 7.70%, the Company's estimated incremental borrowing rate at the date of the modification of the lease, over the remaining lease term. In December 2021, the lease was renewed. The annual rent for the new lease is approximately $0.6 million. Service charges are also payable based on floor area and are estimated to be approximately $0.2 million per year.

In September 2017, Bicycle Therapeutics Inc. entered into a lease agreement for office and laboratory space in Lexington, Massachusetts, which commenced on January 1, 2018. In conjunction with the lease agreement, Bicycle Therapeutics Inc. paid a security deposit of $0.2 million as well as prepaid rent of $0.1 million for the first month of the

third, fourth, and fifth year of the lease. The deposit is recorded in other assets in the consolidated balance sheets. In March 2022, Bicycle Therapeutics Inc. notified the landlord of its intent to exercise its option to extend the lease, originally set to expire on December 31, 2022, for a successive period through December 31, 2027, which successive period was not included in the original lease term. The Company accounted for the change in lease term as a modification of the existing lease and remeasured the ROU asset and lease liability by calculating the present value of lease payments, discounted at 7.0%, the Company's incremental borrowing rate at the date of the modification of the lease, over the remaining lease term. In May 2022, the lease was extended. The payments for the extended lease are approximately $0.2 million remaining through December 31, 2022, $0.7 million in 2023, and increases annually pursuant to an escalation clause with the last year of the lease term having a per annum fixed rent obligation of $0.8 million.

The components of the Company's lease expense are as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Operating lease cost	$ 3,790	$ 1,224	$ 896
Variable lease cost	1,643	612	662
Total lease cost	$ 5,433	$ 1,836	$ 1,558

The weighted average remaining operating lease term was 4.2 years and 4.8 years as of December 31, 2022 and 2021, respectively, and the weighted average discount rate was 7.0% and 7.1% as of December 31, 2022 and 2021, respectively.

The following table summarizes the maturities of the Company's operating leases as of December 31, 2022 (in thousands):

Year Ending December 31,	
2023	3,972
2024	3,994
2025	4,016
2026	3,236
2027	821
Present value adjustment	(2,029)
Total lease liabilities	14,010
Less: current lease liabilities	(3,125)
Long term lease liabilities	$ 10,885

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 as 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, the Company is 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 or its subsidiaries may become involved in various legal proceedings and claims, either asserted or unasserted, which arise in the ordinary course of business. The Company is not currently subject to any material legal proceedings.

In September 2016, the Company's subsidiary, BicycleRD, filed a complaint in the District Court of the Hague against Pepscan Systems B.V. and its affiliates ("Pepscan") to contest the right of Pepscan to terminate a non-exclusive patent license agreement entered into with Pepscan in 2009 ("PLA"). On November 20, 2020, the Company entered into a settlement and license agreement with Pepscan regarding Bicycle's use of Pepscan's CLIPS peptide technology. The companies agreed to settle all intellectual property disputes worldwide. Under the terms of the settlement, Bicycle has been granted a license to use CLIPS peptide technology in the development of its product candidates BT1718 and THR-149. Bicycle paid €3 million in November 2020, paid €1 million on the first anniversary of the date of settlement, and will make additional future milestone payments upon the achievement of development, regulatory and commercial milestones, with an aggregate total value of $92.4 million. The Company recorded $4.7 million of expense related to the settlement and license agreement with Pepscan during the year ended December 31, 2020.

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 Founder Royalty Agreement, as amended, to date.

Indemnification obligations

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

12. Net loss per share

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

	Year Ended December 31,		
	2022	2021	2020
Numerator:			
Net loss	$ (112,717)	$ (66,819)	$ (51,010)
Denominator:			
Weighted average ordinary shares outstanding, basic and diluted	29,660,659	25,061,734	19,145,938
Net loss per share, basic and diluted	$ (3.80)	$ (2.67)	$ (2.66)

The Company's potentially dilutive securities, which include options to purchase ordinary shares and restricted share units for ordinary shares, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of ordinary shares outstanding used to calculate both basic and diluted net loss per share is the same. The Company excluded the following potentially dilutive

ordinary shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect:

	December 31,		
	2022	2021	2020
Restricted ordinary shares	187,725	—	—
Options to purchase ordinary shares	5,898,888	4,603,486	3,736,663
	6,086,613	4,603,486	3,736,663

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 years ended December 31, 2022, 2021 and 2020, the Company made contributions totaling $0.5 million, $0.3 million and $0.2 million, respectively, to the 401(k) Plan.

The Company provides a pension contribution plan for its employees in the United Kingdom, pursuant to which the Company may make contributions each year ("U.K Plan"). During the years ended December 31, 2022, 2021 and 2020, the Company made contributions totaling $1.4 million, $0.7 million and $0.5 million, respectively, to the U.K. Plan.

14. Related party transactions

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

The Chairman of the Company's board of directors is associated with Stone Sunny Isles Inc. and Stone Atlanta Estates LLC, the successor-in-interest to Stone Sunny Isles Inc., which provided consultancy services to the Company totaling $0.2 million, $0.2 million and $0.2 million during each of the years ended December 31, 2022, 2021 and 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 ROU assets, held in different geographic regions is presented in the table below (in thousands):

	December 31,	
	2022	2021
United States	$ 4,466	$ 1,095
United Kingdom	28,302	16,694
	$ 32,768	$ 17,789

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

16. Subsequent events

On January 26, 2023, the Company entered into a lease agreement for office and laboratory space in Cambridge, Massachusetts. The lease has a contractual period of approximately three years, which, subject to certain conditions, may be extended for an additional two years at the Company's option. The annual rent is approximately $2.1 million in the first year of the lease and increases annually with the last year of the lease having annual rent of approximately $2.3 million. Annual rent is payable monthly in advance following a two-month rent-free period. In connection with the lease agreement, the Company is required to deliver to the landlord a security deposit in the form of a letter of credit of approximately $0.3 million.

SIGNATURES

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

Bicycle Therapeutics plc

Dated: February 28, 2023

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

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

POWER OF ATTORNEY

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

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

Name	Title	Date
/s/ Kevin Lee Kevin Lee, Ph.D., MBA	Chief Executive Officer and Director (Principal Executive Officer)	February 28, 2023
/s/ Lee Kalowski Lee Kalowski, MBA	Chief Financial Officer and President (Principal Financial and Accounting Officer)	February 28, 2023
/s/ Pierre Legault Pierre Legault, MBA, CPA	Chairman of the Board and Director	February 28, 2023
/s/ Janice Bourque Janice Bourque, MBA	Director	February 28, 2023
/s/ Jose-Carlos Gutierrez-Ramos Jose-Carlos Gutierrez-Ramos, Ph.D	Director	February 28, 2023
/s/ Veronica Jordan Veronica Jordan, Ph.D.	Director	February 28, 2023
/s/ Richard Kender Richard Kender, MBA	Director	February 28, 2023
/s/ Sir Gregory Winter Sir Gregory Winter, FRS	Director	February 28, 2023

(This page has been left blank intentionally.)

(This page has been left blank intentionally.)

(This page has been left blank intentionally.)

EXECUTIVE TEAM

* Executive officers as defined under Rule 3b-7 under the Securities Exchange Act of 1934, as amended.

Kevin Lee, PhD, MBA

Lee Kalowski, MBA

Santiago Arroyo, MD, PhD

Nigel Crockett, PhD

Nick Keen, PhD

Alistair Milnes

Michael Skynner, PhD

BOARD OF DIRECTORS

Pierre Legault, MBA, CPA

Janice Bourque, MBA

Jose-Carlos Gutierrez-Ramos, PhD

Veronica Jordan, PhD

Richard Kender, MBA

Kevin Lee, PhD, MBA

Sir Greg Winter, FRS

INVESTOR RELATIONS

David Borah, CFA
SVP, Capital Markets & Corporate Communications

david.borah@bicycletx.com

FORM 10-K

A copy of our Form 10-K filed with the SEC will be made available to all stockholders at no charge.

The Form 10-K also can be accessed through the SEC website at www.sec.gov, or through our SEC filings website at investors.bicycletherapeutics.com/sec-filings.

To receive a copy by mail please contact Investor Relations.

SCIENTIFIC ADVISORY BOARD

Sir Keith Peters, GBE, ScD, FRCP, FRS, FMedSci

Garret Fitzgerald, MD, FRS

Jane Grogan, PhD

Caetano Reis e Sousa, DPhil, FRS, FMedSci

Geoffrey Shapiro, MD, PhD

Charles Swanton, MD, PhD, FRS, FMedSci, FRCP

Sir Greg Winter, PhD, FRS

GENERAL COUNSEL

Zafar Qadir

ANNUAL GENERAL MEETING

Our annual meeting of shareholders will be held on Tuesday, June 13, 2023 at 12:00 p.m. (midday) London time (7:00 a.m. Eastern Daylight Time), at our principal executive offices, located at Blocks A & B, Portway Building, Granta Park, Great Abington, Cambridge, CB21 6GS, United Kingdom.

STOCK INFORMATION

Nasdaq Global Select Market: BCYC

ADDRESS

Blocks A & B Portway Building, Granta Park,
Great Abington, Cambridge CB21 6GS,
England, United Kingdom.

WEBSITE

www.bicycletherapeutics.com