As filed with the U.S. Securities and Exchange Commission on September 20, 2019.

Registration Statement No. 333-233020

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

Amendment No. 2 to
Form F-1
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Tiziana Life Sciences plc

(Exact name of Registrant as specified in its charter)

Not Applicable
(Translation of Registrant's name into English)

England and Wales
(Jurisdiction of incorporation or organization)
(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

England and Wales	**2836**	**Not Applicable**
(State or other Jurisdiction of Incorporation or Organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

3rd Floor,
11-12 St James's Square
London SW1Y 4LB
United Kingdom
+44 20 7495 2379
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Jeffrey Fessler, Esq. **Justin Anslow, Esq.** **Sheppard, Mullin, Richter & Hampton LLP** **30 Rockefeller Plaza** **New York, NY 10112-0015** **(212) 653-8700**	**Edward Dyson** **Cooley (UK) LLP** **Dashwood** **69 Old Broad Street** **London EC2M 1QS** **United Kingdom** **+44 20 7785 9355**	**Leslie Marlow, Esq.** **Hank Gracin, Esq.** **Patrick J. Egan, Esq.** **Gracin & Marlow, LLP** **The Chrysler Building** **405 Lexington Avenue, 26th Floor** **New York, NY 10174** **(212) 907-6457**

Approximate date of commencement of proposed sale to the public: As soon as practicable after this Registration Statement becomes effective.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended, check the following box. S

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. £

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. £

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. £

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act:

Emerging growth company S

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, 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 7(a)(2)(B) of the Securities Act. £

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† The term "new or revised financial accounting standard" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012.

CALCULATION OF REGISTRATION FEE

TITLE OF EACH CLASS OF SECURITIES TO BE REGISTERED	PROPOSED MAXIMUM AGGREGATE OFFERING PRICE[1][2]	AMOUNT OF REGISTRATION FEE[3]
Ordinary shares, nominal value £0.03 per share[4]	$ 3,450,000	$ 418
Representative's Warrants[5]	—	—
Ordinary shares, nominal value £0.03 per share, underlying Representative's Warrants[4][6]	$ 75,000	$ 9
Total	$ 3,525,000	$ 427[7]

(1) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(o) of the Securities Act of 1933, as amended (the "Securities Act").

(2) Includes ordinary shares represented by American Depositary Shares, or ADSs, that are issuable upon exercise of the underwriters' over-allotment option to purchase additional shares.

(3) Calculated pursuant to Rule 457(o) based on an estimate of the proposed maximum aggregate offering price.

(4) These ordinary shares are represented by ADSs, each of which represents ordinary shares of the registrant. ADSs issuable on deposit of the ordinary shares registered hereby are being registered pursuant to a separate registration statement on Form F-6 (File No. 333-227509).

(5) No fee pursuant to Rule 457(g) under the Securities Act.

(6) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(g) under the Securities Act. The Representative's Warrants are exercisable at a per share exercise price equal to 125% of the public offering price per ADS. As estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(g) under the Securities, the proposed maximum aggregate offering price of the Representative's Warrants is $75,000, which is equal to 125% of $60,000 (2% of $3,000,000).

(7) Previously Paid.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to such Section 8(a), may determine.

PRELIMINARY PROSPECTUS SUBJECT TO COMPLETION DATED SEPTEMBER 20, 2019

474,683 American Depositary Shares
Representing 4,746,830 Ordinary Shares

Tiziana Life Sciences PLC

We are offering 474,683 American Depositary Shares, or ADSs. Each ADS represents 10 ordinary shares. The ADSs may be evidenced by American Depositary Receipts, or ADRs.

The assumed public offering price is $6.32 per ADS, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019. Our ADSs are listed on the Nasdaq Global Market under the symbol "TLSA." Our Ordinary Shares are listed on AIM, a market of London Stock Exchange plc under the symbol "TLS."

Investing in our ADSs involves a high degree of risk. Before buying any ADSs, you should carefully read the discussion of material risks of investing in our ADSs in "Risk factors" beginning on page 11 of this prospectus.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and a "foreign private issuer" under applicable U.S. federal securities laws. As such, we have elected to comply with certain reduced public company reporting requirements. See "Prospectus summary — implications of being an emerging growth company and a foreign private issuer" for additional information.

Neither the U.S. Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

	Per ADS	Total
Public offering price	$	$
Underwriting discounts and commissions[(1)]	$	$
Proceeds, before expenses, to us	$	$

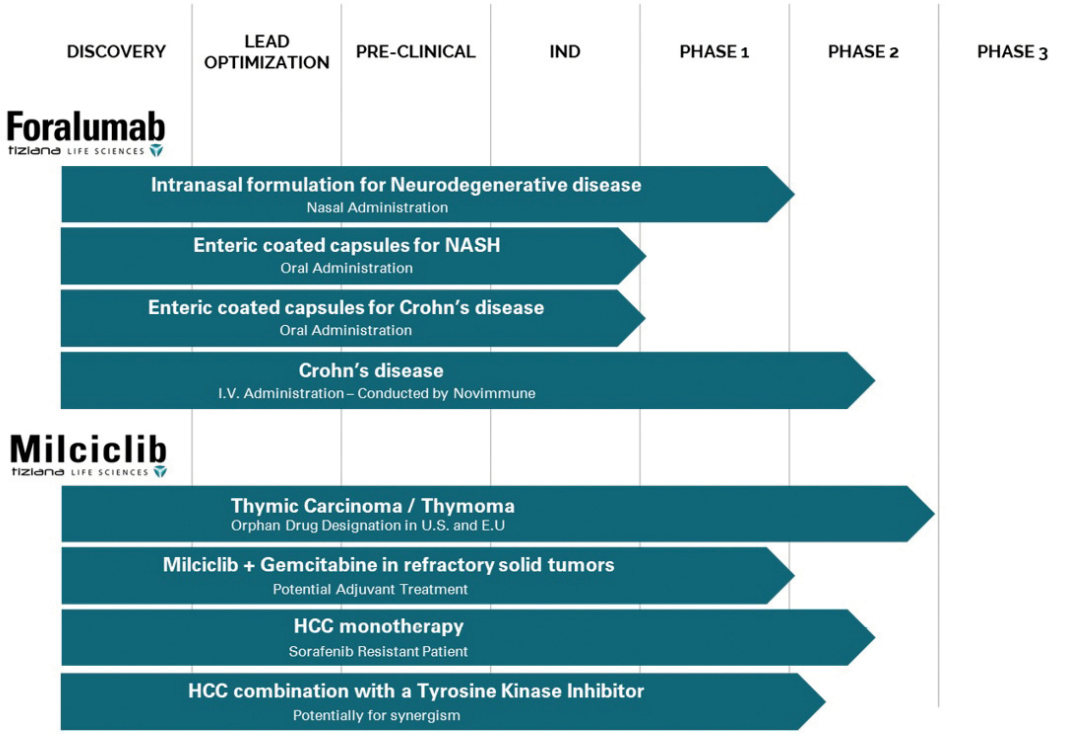
(1) The underwriters will receive compensation in addition to the discounts and commissions. See "Underwriting" for a description of compensation payable to the underwriters.

We have granted the representative of the underwriters an over-allotment option to purchase up to an additional 71,202 ADSs from us at the public offering price, less the underwriting discounts and commissions, within 45 days from the date of this prospectus to cover over-allotments, if any. If the representative of the underwriters exercises their over-allotment option in full, the total underwriting discounts and commissions payable will be $, and the total proceeds to us, before expenses, will be $.

The underwriters expect to deliver our ADSs to purchasers in this offering on or about , 2019.

ThinkEquity
a division of Fordham Financial Management, Inc.

The date of this prospectus is September , 2019


DISCOVERY
LEAD OPTIMIZATION
PRE-CLINICAL
IND
PHASE 1
PHASE 2
PHASE 3
Foralumab
tiziana LIFE SCIENCES
Intranasal formulation for Neurodegenerative disease
Nasal Administration
Enteric coated capsules for NASH
Oral Administration
Enteric coated capsules for Crohn's disease
Oral Administration
Crohn's disease
I.V. Administration – Conducted by Novimmune
Milciclib
tiziana LIFE SCIENCES
Thymic Carcinoma / Thymoma
Orphan Drug Designation in U.S. and E.U
Milciclib + Gemcitabine in refractory solid tumors
Potential Adjuvant Treatment
HCC monotherapy
Sorafenib Resistant Patient
HCC combination with a Tyrosine Kinase Inhibitor
Potentially for synergism

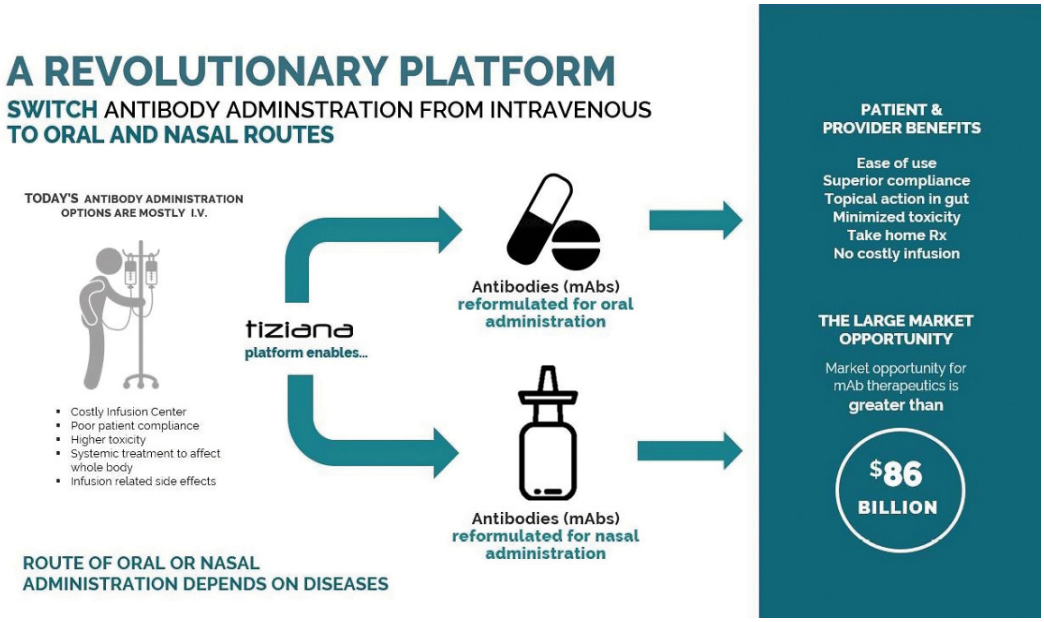

A REVOLUTIONARY PLATFORM
SWITCH ANTIBODY ADMINSTRATION FROM INTRAVENOUS TO ORAL AND NASAL ROUTES
TODAY'S ANTIBODY ADMINISTRATION OPTIONS ARE MOSTLY I.V.
Costly Infusion Center
Poor patient compliance
Higher toxicity
Systemic treatment to affect whole body
Infusion related side effects
tiziana
platform enables...
Antibodies (mAbs) reformulated for oral administration
Antibodies (mAbs) reformulated for nasal administration
ROUTE OF ORAL OR NASAL ADMINISTRATION DEPENDS ON DISEASES
PATIENT & PROVIDER BENEFITS
Ease of use
Superior compliance
Topical action in gut
Minimized toxicity
Take home Rx
No costly infusion
THE LARGE MARKET OPPORTUNITY
Market opportunity for mAb therapeutics is greater than
$86 BILLION

TABLE OF CONTENTS

We are responsible for the information contained in this prospectus and any free-writing prospectus we prepare or authorize. We have not, and the underwriters have not, authorized anyone to provide you with different information, and we and the underwriters take no responsibility for any other information others may give you. We are not, and the underwriters are not, making an offer to sell our ADSs in any jurisdiction where the offer or sale is not permitted. For the avoidance of doubt, we are not, and the underwriters are not, making an offer to sell our ordinary shares in any jurisdiction. You should not assume that the information contained in this prospectus is accurate as of any date other than the date on the front cover of this prospectus, regardless of the time of delivery of this prospectus or the sale of any ADSs.

For investors outside the United States, neither we nor the underwriters have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction, other than the United States, where action for that purpose is required. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, this offering and the distribution of this prospectus outside the United States.

We are a public limited company incorporated under the laws of England and Wales and a majority of our outstanding securities are owned by non-U.S. residents. Under the rules of the SEC, we are currently eligible for treatment as a "foreign private issuer," or FPI. As an FPI, we will not be required to file periodic reports and financial statements with the SEC as frequently or as promptly as domestic registrants whose securities are registered under the Securities Exchange Act of 1934, or Exchange Act.

ABOUT THIS PROSPECTUS

Unless otherwise indicated or the context otherwise requires, all references in this registration statement to the terms "Tiziana," "Tiziana Life Sciences plc," "the company," "we," "us" and "our" refer to Tiziana Life Sciences plc and its wholly owned subsidiaries, Tiziana Therapeutics, Inc., Tiziana Pharma Limited and Longevia Genomics S.r.l.

Solely for convenience, the trademarks, service marks and trade names in this registration statement may be referred to without the ® and ™ 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. This registration statement contains additional trademarks, service marks and trade names of others, which are the property of their respective owners. We do not intend to use or display other companies' trademarks, service marks and trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

In this registration statement, unless otherwise stated, all references to "U.S. dollars" or "US$" or "$" or "cents" are to the currency of the United States of America, and all references to "Pounds Sterling" or "Sterling" or "£" or "pence" are to the currency of the United Kingdom.

In this registration statement, any reference to any provision of any legislation shall include any amendment, modification, re-enactment or extension thereof. Words importing the singular shall include the plural and vice versa, and words importing the masculine gender shall include the feminine or neutral gender.

PRESENTATION OF FINANCIAL INFORMATION

This prospectus includes our audited consolidated financial statements as of and for the years ended December 31, 2018 and 2017, which are prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB. None of our financial statements were prepared in accordance with generally accepted accounting principles in the United States.

Our financial information is presented in U.S. dollars. Solely for the convenience of the reader, in this prospectus, unless otherwise indicated, translations from Pounds Sterling into U.S. dollars were made at the rate of £1.00 to $1.2387, which was the noon buying rate of the Federal Reserve Bank of New York on July 26, 2019. Such U.S. dollar amounts are not necessarily indicative of the amounts of U.S. dollars that could actually have been purchased upon exchange of Pounds Sterling at the dates indicated.

We have made rounding adjustments to some of the figures included in this prospectus. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them.

PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our ADSs or ordinary shares, you should carefully read this entire prospectus, including our consolidated financial statements and the related notes and the information set forth under the sections titled "Risk Factors," "Special Note Regarding Forward-Looking Statements," and "Management's Discussion and Analysis of Financial Condition and Results of Operations," in each case included elsewhere in this prospectus. Unless the context otherwise requires, we use the terms "Tiziana," "company," "our," "us," and "we" in this prospectus to refer to Tiziana Life Sciences plc and, where appropriate, our consolidated subsidiaries.

Overview

We are a biotechnology company that is focused on the discovery and development of novel molecules and related diagnostics to treat high unmet medical needs in oncology and immunology. Our mission is to design and deliver next generation therapeutics and diagnostics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. We employ a lean and virtual research and development, or R&D, model using highly experienced teams of experts for each business function to maximize value accretion by focusing resources on the drug discovery and development processes.

Our lead product candidate in immunology is Foralumab (TZLS-401), which we believe is the only fully human anti-cluster of differentiation 3, or anti-CD3, monoclonal antibody, or mAb, in clinical development. We believe that based on the concepts of mucosal tolerance, oral or intranasal administration of Foralumab has the potential to reduce inflammation while minimizing the toxicity and related side effects. We believe the switch from intravenous administration to oral and nasal administration is a 'game changer' for treatment with mAbs as it could improve patient's compliance and safety. MAbs represent a single pure antibody produced by single clones and are an important class of human therapeutics for treating cancers and autoimmune diseases. The global market opportunity for mAb therapeutics is greater than $86 billion. Generation of antibodies for use in humans developed in animals, lead to strong, immune responses limiting their effectiveness and potentially leading to severe side effects. A process known as "humanization" removes most of the animal components of the antibody thereby lowering the immune response from the human immune system. The entire omission of other animal material, as in fully human antibodies, is the optimal goal to avoid incompatibility with the human immune system.

Our lead product candidate in oncology is Milciclib (TZLS-201), which is an orally bioavailable, small molecule broad spectrum inhibitor of cyclin-dependent kinases, or CDKs, and Sarcoma, or Src, family kinases. CDKs are a highly conserved family of enzymes that phosphorylate a specific group of proteins that are involved in regulating the cell cycle. The cell cycle is a series of events that takes place in cells leading to division and duplication of its DNA to produce two daughter cells. Src family kinases are non-receptor tyrosine kinase proteins encoded by the Src gene also involved in regulating cell growth and potential transformation of normal cells to cancer cells. We have a drug discovery pipeline of small molecule new chemical entities, or NCEs, and biologics. Milciclib has Orphan Drug Designation (ODD) in the U.S. and EU for thymic cancer (thymic epithelial tumor or TET) such as thymic carcinoma dn thymoma.

We are developing Foralumab, for which we in-licensed the intellectual property from Novimmune SA, or Novimmune, in December 2014, as a potential treatment for non-alcoholic steatohepatitis, or NASH, and Crohn's disease as well as neurodegenerative diseases such as multiple sclerosis, or MS. We have developed and filed patent applications with respect to oral and nasal administration formulation of Foralumab for treatment of human diseases. These patent applications may be applicable to all mAbs for nasal and oral administration. To date, Foralumab has been studied in one Phase 1 and two Phase 2a clinical trials conducted by Novimmune in 68 patients dosed by the intravenous route of administration. In these trials, Foralumab was observed to be well-tolerated with a maximum tolerated dose (MTD) of 1 mg/dose and produced immunologic effects consistent with potential clinical benefit while demonstrating mild to moderate infusion related reactions, or IRR.

We planned to first investigate orally and nasally administered Foralumab for its safety and immunomodulatory activity in healthy volunteers in separate Phase 1 clinical trials. A Phase I single site, double-blind, placebo-controlled, dose-ranging clinical study dosed intranasally in healthy volunteers was initiated in November 2018 to evaluate safety and biomarkers of immunomodulation of clinical responses planned in healthy volunteers to dose Foralumab intranasally. in collaboration with Brigham and Women's Hospital, Harvard Medical School, Boston, MA. This clinical

trial was recently completed in July 2019 in which 18 subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated, and no drug related safety issues were reported at any of the doses. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. In addition, we submitted an IND on March 18, 2019 for the oral formulation, to the FDA. The FDA requested safety data from the phase 1 trial with nasal administration of Foralumab to justify the proposed dose-range for the phase 1 trial with oral administration of enteric-coated capsules of Foralumab in healthy volunteers. We withdrew the IND on April 17, 2019. A third IND was submitted to the FDA on July 23, 2019 for a Phase I trial in healthy volunteers using orally administered Foralumab with an intent to treat progressive multiple sclerosis, or pMS. On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. Based on successful Phase 1 data, we intend to conduct a Phase 2 study using Crohn's Disease patients starting in the second half of 2020 and file an IND for a Phase 2 trial using NASH patients.

We are developing Milciclib, for which we in-licensed the intellectual property from Nerviano Medical Sciences S.r.l., or Nerviano, in January 2015, as a potential treatment for hepatocellular carcinoma, or HCC. A novel feature of Milciclib is its ability to reduce levels of microRNAs, miR-221 and miR-222. MicroRNAs are small RNA molecules that play a significant role in the regulation of gene expression. miR-221 and miR-222 are believed to be linked to the development of blood supply (angiogenesis) in cancer tumors. Levels of these microRNAs are consistently elevated in HCC patients and may contribute towards resistance to treatment with Sorafenib, a multikinase inhibitor (a drug which may inhibit the cellular division and proliferation associated with certain cancers) often prescribed to HCC patients as the Standard of Care (SOC). To date, Milciclib has been studied in a total of eight Phase 1 and Phase 2 clinical trials in 316 patients. In these trials, Milciclib was well-tolerated with minimal adverse events. We initiated a Phase 2a trial for Milciclib as a monotherapy in patients with HCC in the third quarter of 2017. This trial is a single-arm, repeated-dose (100 mg once daily; 4 days on/3 days off every 4 weeks defining each cycle), 6-month duration study to evaluate the safety, tolerability and anti-tumor activity of Milciclib in Sorafenib-refractory or intolerant patients with unresectable or metastatic advanced HCC, the most common form of liver cancer. Enrollment of 31 patients in Italy, Greece, and Israel was completed in November 2018.

In March 2019, the Independent Monitoring Committee, or IDMC, reviewed safety data from patients as of February 26, 2019 and concluded that the administration of Milciclib to patients with advanced HCC was not associated with unexpected signs or signals of toxicity. 28 out of 31 treated patients were evaluable, 14 completed the 6-month duration study. The most frequent adverse events such as diarrhea, ascites, nausea, fatigue, asthenia, fever, ataxia, headache, and rash were manageable. No drug-related deaths were recorded.

- 9 out of 14 patients (64.2%) were approved by their respective ethical committees to continue the treatment.
- 5 of the 9 patients on compassionate use had received Milciclib for a total of 9, 9, 11, 13 and 16 months.
- As of September 1, 2019, the remaining 4 patients continuing the treatment are in their 10^{th}, 11^{th}, 11^{th} and 12^{th} months.
- Both median TTP and PFS were 5.9 months (95% Confidence Interval ("CI") 1.5-6.7 months) out of the 6-months duration of the trial.
- 17 of 28 (60.7%) evaluable patients showed 'Stable Disease' (SD; met at least once in an 8-week interval).
- One patient (3.6%) showed 'Partial Response' (PR, unconfirmed).
- 18 of 28 (64.3%) evaluable patients showed 'Clinical Benefit Rate' defined as CBR=CR+PR+SD (with CR representing Complete Remission).

Since overexpression of CDKs and dysregulation in pRB pathway (regulates transcription factors critical for cell cycle progression) are prominently associated with tumor cell resistance to certain chemotherapeutic drugs, inhibition of multiple CDKs is an appealing approach to improve clinical responses in cancer patient's refractory to existing treatment options. A Phase 1 dose-escalation study of Milciclib in combination with gemcitabine in patients with refractory solid tumors exhibited clinical activity in patients including those refractory to gemcitabine. We plan to explore a combination approach in patients with HCC.

A Phase 2b trial for Milciclib in combination with a tyrosine kinase inhibitor (TKI) such as Sorafenib (Nexavar®) or regorafenib (Stivarga®), used to treat some types of kidney, liver and thyroid cancers in patients with HCC is expected to be initiated in the second half of 2019.

In addition, we are developing a fully human mAb targeting the IL-6R (TZLS-501) for the treatment of inflammatory and autoimmune diseases. We licensed the intellectual property from Novimmune in January 2017. This fully human mAb has a novel mechanism of action, binding to both the membrane-bound and soluble forms of the IL-6R as well as depleting circulating levels of the IL-6 in the blood. Excessive production of IL-6 is regarded as a key driver of chronic inflammation, associated with autoimmune diseases such as multiple myeloma, oncology indications and rheumatoid arthritis, and we believe that TZLS-501 may have potential therapeutic value for these indications.

In preclinical studies, TZLS-501 demonstrated the potential for overcoming the limitations of other IL-6 blocking pathway drugs. Compared to tocilizumab and sarilumab, while binding to the membrane-bound IL-6R complex, TZLS-501 has been observed to have a higher affinity for the soluble IL-6 receptor from antibody binding studies conducted in cell culture. TZLS-501 also demonstrated the potential to block or reduce IL-6 signaling in mouse models of inflammation. The soluble form of IL-6 has been implicated to have a larger role in disease progression compared to the membrane- bound form (Kallen, K.J. (2002). “The role of trans-signaling via the agonistic soluble IL-6 receptor in human diseases.” Biochimica et Biophysica Acta. 1592 (3): 323–343.)

Our Competitive Strengths

Our mission is to design and deliver next generation therapeutics and diagnostics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. We believe the following strengths will allow us to continue to pursue this mission:

- ***Advanced, novel pipeline.*** We have an advanced pipeline of novel and proprietary drug candidates, including antibodies and small molecules, to address high unmet medical needs in the inflammation, autoimmune and oncology markets with significant commercial potential.
- ***Proprietary technology.*** Our proprietary technology enables the development of alternative routes of administration of antibodies, including oral delivery. We believe that oral and nasal routes of delivery will alleviate the significant time and cost burden associated with other routes of administration, including intravenous delivery.
- ***Broad and engaged network of experts.*** Our strong relationships with key opinion leaders contribute to our clinical development efforts and position us well to support our products, if approved. Dr. Napoleone Ferrara, Dr. Arun Sanyal, Dr. Kevan Herold, and Dr. Howard Weiner are among the thought leaders on our scientific advisory committee.
- ***Specialized expertise and focus on oncology and inflammation.*** Our management team, including Dr. Kunwar Shailubhai, Jules Jacob, Dr. Priya Eddy and Dr. Vaseem Palejwala, has considerable experience translating technologies from bench to market, and managing the global administration of clinical trials.
- ***Strong intellectual property and know-how.*** We believe our proprietary intellectual property portfolio, in-licensed from Nerviano and Novimmune, provides us with a substantial competitive advantage for the commercial development of small molecule NCEs, and biologics, as well as expanded possibilities for new development programs in the future. We have retained the worldwide development and commercialization rights to all of our product candidates. We have submitted additional patent applications to further strengthen our intellectual property.
- ***Lean research and development model, designed to maximize value.*** We employ a lean and virtual R&D model using highly experienced teams of experts for each business function to maximize value accretion by focusing resources on the drug discovery and development processes.

Our Strategy

Our goal is to become a leading biotechnology company focused on developing and delivering therapies and related diagnostics in both oncology and immunology. The key elements of our strategy to achieve this goal are to:

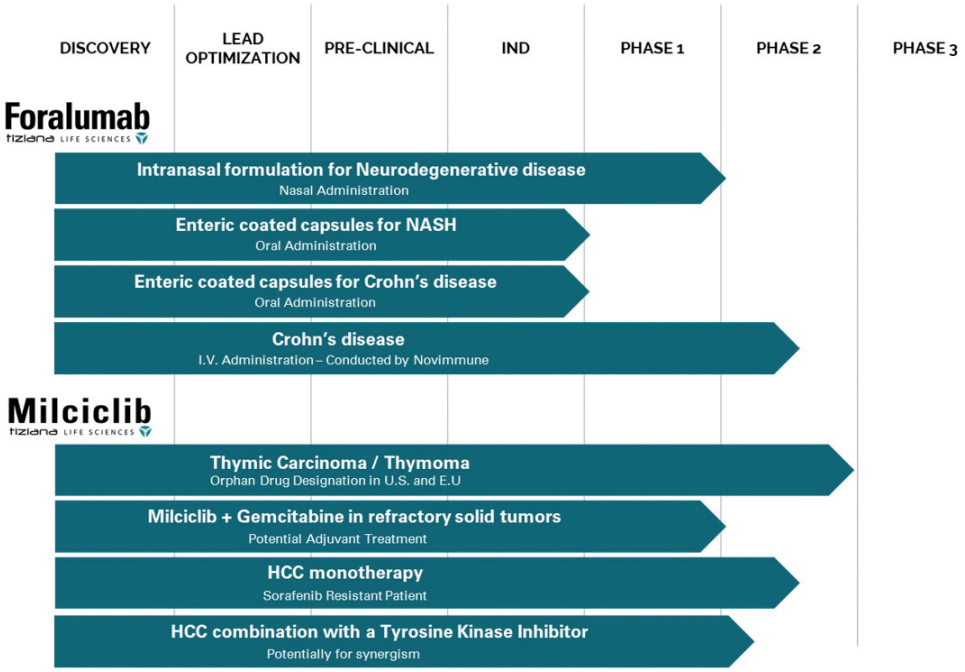
- Advance the clinical development of orally administered Foralumab for the treatment of NASH and Crohn’s disease using a novel and proprietary oral formulation by initiating a Phase 1 trial in the second half of 2019 and a Phase 2 trial in the second half of 2020. In addition, a Phase 1 trial for the first-in-human

evaluation of the nasal administration of Foralumab in healthy volunteers, for neurodegenerative disease indications such as MS, was initiated in November 2018. Topline results from this study are expected in the second half of 2019.

- Continue to advance the clinical development and obtain regulatory approval for our lead oncology product candidate, Milciclib, as a monotherapy in HCC and as a combination therapy for the treatment of refractory solid tumors (being cancers which are non-responsive or become resistant to treatment) and HCC by continuing to enroll the ongoing Phase 2a trial as a monotherapy and initiating a planned Phase 2b trial in combination with a TKI (Sorafenib or Regorafenib).
- Continue to leverage relationships with key opinion leaders to promote clinical trial success and enhance future commercialization.
- Continue preclinical studies and non-clinical development of our product candidate, TZLS-501, a fully human mAb targeting the IL-6R (a biological mAb which may control the proteins involved in cell signaling relevant to many inflammatory diseases and cancers), for treatment of inflammatory and oncology indications.
- Opportunistically identify and acquire or in-license complimentary product and technology candidates.
- Seek orphan drug, fast track or breakthrough designation for our product candidates where warranted.

Our Product Candidates

Our product candidate pipeline is set forth below:



Selected Risks Affecting Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. You should carefully consider all of the information set forth in this prospectus and, in particular, should evaluate the

specific factors set forth in the section titled “Risk Factors” before deciding whether to invest in our ADSs. These important risks include, but are not limited to, the following:

- If we encounter substantial delays in clinical trials of our product candidates, we may be unable to obtain required regulatory approvals, and therefore will be unable to commercialize our product candidates on a timely basis or at all.
- We may fail to demonstrate the safety and therapeutic utility of our product candidates to the satisfaction of applicable regulatory authorities, which would prevent or delay regulatory approval and commercialization.
- Success in preclinical studies or clinical trials may not be indicative of results in future clinical trials.
- We depend on enrollment of patients in our clinical trials for our product candidates and 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 and could materially adversely affect our R&D efforts and business, financial condition and results of operations.
- Our product candidates and the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.
- Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.
- Our independent registered public accounting firm has expressed substantial doubt about our ability to continue as a going concern, which may hinder our ability to obtain future financing.
- We need substantial additional funding to complete the development of our product candidates, which may not be available on acceptable terms, if at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development, research operations or future commercialization efforts, if any.
- Our 10% or more stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.
- Our limited operating history and no history of commercializing pharmaceutical products may make it difficult to evaluate the success of our business to date and to assess the prospects for our future viability.
- We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.
- We utilize, and expect to continue to utilize, third parties to conduct our product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily.
- We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours.
- The future commercial success of our product candidates will depend upon the degree of each product candidates’ market acceptance by physicians, patients, third-party payors and others in the medical community.
- We may not be able to protect our intellectual property rights throughout the world.
- Even if we obtain and maintain approval for our product candidates in a major pharmaceutical market such as the United States, we may never obtain approval for our product candidates in other major markets.

- Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidate that we may develop.
- We do not know whether an active, liquid and orderly trading market will develop for our ADSs or what the market price of our ADSs will be. As a result, it may be difficult for shareholders to sell their ADSs.
- We may lose our FPI status, which would then require us to comply with the Exchange Act's domestic reporting regime and cause us to incur significant legal, accounting and other expenses.
- If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. holders.

Corporate Information

We were originally incorporated under the laws of England and Wales on February 11, 1998 with the goal of leveraging the expertise of our management team as well as Dr. Napoleone Ferrara, Dr. Arun Sanyal, Dr. Howard Weiner and Dr. Kevan Herold, and to acquire and exploit certain intellectual property in biotechnology. We subsequently changed our name to Tiziana Life Sciences plc in April 2014 as a result of the acquisition of Tiziana Pharma Limited in April 2014.

Our registered office is located at 3rd Floor, 11-12 St James's Square, London SW1Y 4LB and our telephone number is +44 20 7495 2379. Our website address is www.tizianalifesciences.com. The reference to our website is an inactive textual reference only and the information contained in, or that can be accessed through, our website is not a part of this registration statement. Our agent for service of process in the United States is Tiziana Therapeutics, Inc.

"Tiziana," the Tiziana logo and other trademarks or service marks of Tiziana Life Sciences plc appearing in this prospectus are the property of Tiziana or our subsidiaries. This prospectus contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this prospectus may appear without the ® or ™ symbols.

Implications of Being an Emerging Growth Company

We are an EGC as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As such, we may take advantage of certain exemptions from various reporting requirements that are applicable to other publicly traded entities that are not EGCs. These exemptions include:

- the option to present only two years of audited financial statements and related discussion in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this prospectus;
- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley Act;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements (i.e., an auditor discussion and analysis);
- not being required to submit certain executive compensation matters to stockholder advisory votes, such as "say-on-pay," "say-on-frequency," and "say-on-golden parachutes;" and
- not being required to disclose certain executive compensation related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer's compensation to median employee compensation.

As a result, we do not know if some investors will find our ADSs or ordinary shares less attractive. The result may be a less active trading market for our ADSs and/or ordinary shares, and the price of ADSs and/or ordinary shares may become more volatile.

Section 107 of the JOBS Act also provides that an EGC can take advantage of the extended transition period provided in Section 13(a) of the Exchange Act, for complying with new or revised accounting standards. As a result,

an EGC can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We are choosing to opt out of this extended transition period and will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-EGCs. Under federal securities laws, our decision to opt out of the extended transition period is irrevocable.

We will remain an EGC until the earliest of: (1) the last day of the first fiscal year in which our annual gross revenues exceed $1.07 billion; (2) the last day of 2023; (3) the date that we become a "large accelerated filer" as defined in Rule 12b-2 under the Exchange Act, which would occur on the last day of any fiscal year that the aggregate worldwide market value of our common equity held by non-affiliates exceeds $700 million as of the last business day of our most recently completed second fiscal quarter; or (iv) the date on which we have issued more than $1.0 billion in non-convertible debt securities during any three-year period.

Implications of Being a Foreign Private Issuer

We report under the Exchange Act as a non-U.S. company with FPI status. Even after we no longer qualify as an EGC, as long as we qualify as an FPI under the Exchange Act we will be exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including:

- the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act;
- the sections of the Exchange Act requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades made in a short period of time; and
- the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specific information, and current reports on Form 8-K upon the occurrence of specified significant events.

FPIs are also exempt from certain more stringent executive compensation disclosure rules. Thus, even if we no longer qualify as an EGC, but remain an FPI, we will continue to be exempt from the more stringent compensation disclosures required of companies that are neither an EGC nor an FPI.

THE OFFERING

ADSs offered by us	474,683 ADSs.
Ordinary shares to be outstanding after this offering	141,210,643 ordinary shares, including 917,593 ordinary shares in the form of ADSs (or 141,922,663 ordinary shares if the underwriters exercise in full their over-allotment option to purchase 712,020 ordinary shares in the form of ADSs).
Over-allotment option	71,202 ADSs.
ADSs	Each ADS represents 10 ordinary shares, nominal value £0.03 per ordinary share. The depositary will hold the ordinary shares underlying your ADSs and you will have rights as provided in the deposit agreement among us, the depositary, and holders and beneficial owners of ADSs from time to time. To better understand the terms of our ADSs, see "Description of the American Depositary Shares." We also encourage you to read the deposit agreement, the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part.
Depositary	JPMorgan Chase Bank, N.A.
Use of proceeds	We estimate that the net proceeds from our sale of ADSs in this offering will be approximately $2.4 million (or approximately $2.8 million if the underwriters exercise their over-allotment option in full), assuming a public offering price of $6.32 per ADS, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds we receive from this offering to advance the clinical development of Foralumab, and our other research and development programs, working capital and other general corporate purposes. See "Use of Proceeds" for additional information.
Risk factors	See "Risk Factors" and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our ADSs.
Representative's Warrants	The registration statement of which this prospectus is a part also registers warrants to purchase 9,360 ADSs to ThinkEquity, a division of Fordham Financial Management, Inc., the representative of the underwriters, or the Representative, as a portion of the underwriting compensation payable to the underwriters in connection with this offering. The warrants, or the Representative's Warrants, will be exercisable for a four and a half-year period commencing 180 days following the effective date of the registration statement related to this offering at an exercise price equal to 125% of the public offering price of the ADSs. Please see "Underwriting — Representative's Warrants" for a description of these warrants.
Nasdaq Global Market symbol	"TLSA."

The number of shares of our ordinary shares that will be outstanding after this offering is based on 136,463,818 ordinary shares outstanding as of December 31, 2018, and excludes:

- 5,236,166 ordinary shares issuable upon the exercise of share options outstanding as of December 31, 2018 at exercise prices of between $0.19 and $2.30 per ordinary share;
- 18,617,403 ordinary shares that may be issued under our existing share option plans, as described in "Management — The Tiziana Life Sciences plc Employee Share Plan with Non-Employee Sub-Plan and US Sub-Plan," as of December 31, 2018; and

- 3,617,905 ordinary shares that may be issued upon the exercise of warrants to purchase ordinary shares outstanding as at December 31, 2018 at exercise prices of between $0.62 and $3.10 per ordinary share.

Unless otherwise indicated, this prospectus reflects and assumes the following:

- no exercise of outstanding share options after December 31, 2018;
- no exercise of the underwriters' over-allotment option; and
- no exercise of the Representative's Warrants.

SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables set forth our summary consolidated financial data for the periods indicated. We have derived the consolidated statement of comprehensive income for the years ended December 31, 2018 and 2017 and the consolidated balance sheet data as of December 31, 2018 from our audited consolidated financial statements included elsewhere in this prospectus. Our historical results are not necessarily indicative of the results that should be expected for any future period. You should read the following summary consolidated financial data together with the audited consolidated financial statements included elsewhere in this prospectus and the sections entitled "Exchange Rate Information" and "Management's Discussion and Analysis of Financial Condition and Results of Operations."

We maintain our books and records in Pounds Sterling, and we prepare our financial statements in accordance with IFRS as issued by the IASB. We report our financial results in U.S. dollars.

Consolidated Statement of Operations Data:

	Years Ended December 31,	
(in thousands, except per share data)	**2018**	**2017**
Revenue	—	—
Operating expenses:		
Research and development	$ (5,510)	$ (6,015)
General and administrative	(4,417)	(4,602)
Total operating expenses	(9,927)	(10,617)
Loss from operations	(9,927)	(10,617)
Other income (expense), net	(12)	(12)
Tax provision	1,945	1,912
Net loss attributable to ordinary shareholders	(7,994)	(8,716)
Other comprehensive loss:		
Foreign currency translation adjustment	(20)	70
Total comprehensive loss	$ (8,014)	(8,646)
Basic and diluted net loss per ordinary share	$ (0.06)	$ (0.09)

Consolidated Balance Sheet Data:

	Year ended December 31, 2018	
(in thousands)	**Actual**	**As Adjusted[(1)]**
Cash and cash equivalents	$ 5,304	$ 7,710
Working capital	$ 514	$ 2,920
Total assets	$ 6,920	$ 9,326
Total shareholders' equity (deficit)	$ 519	$ 2,925

(1) On an as adjusted basis to give effect to the sale of 474,683 ADSs in this offering at the assumed public price of $6.32 per ADS in this offering, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

RISK FACTORS

You should carefully consider the risks described below, together with all of the other information in this registration statement. The risks and uncertainties below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we believe to be immaterial may also adversely affect our business. If any of the following risks occur, our business, financial condition and results of operations could be seriously harmed and potential future investors in our ADSs could lose all or part of their investment. Further, if we fail to meet the expectations of the public market in any given period, the potential market price of our ADSs could decline. We operate in a highly competitive environment that involves significant risks and uncertainties, some of which are outside of our control. If any of these risks actually occurs, our business and financial condition could suffer and the potential market price of our ADSs could decline.

Risks Related to the Development of our Product Candidates

If we encounter substantial delays in clinical trials of our product candidates, we may be unable to obtain required regulatory approvals, and therefore will be unable to commercialize our product candidates on a timely basis or at all.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and utility of the product candidates. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all, as a failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with the U.S. Food and Drug Administration, or FDA, European Medicines Agency, or EMA, or other regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays in opening clinical trial sites or obtaining required institutional review board or independent ethics committee approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our future clinical trials;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or after an inspection of our clinical trial operations or clinical trial sites;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with good clinical practice, or GCP, or applicable regulatory guidelines in Europe and other international markets;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical trial sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- delays in having patients complete participation in a clinical trial or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a clinical trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events in clinical trials of the same class of agents conducted by other sponsors; and
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

We may fail to demonstrate the safety and therapeutic utility of our product candidates to the satisfaction of applicable regulatory authorities, which would prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Most product candidates that commence clinical trials are never approved as products. If the results of our registrational trial or future pivotal trials for our other product candidates do not demonstrate therapeutic utility of our product candidates, or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw or suspend their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications; or
- be sued or experience damage to our reputation.

Success in preclinical studies or clinical trials may not be indicative of results in future clinical trials.

Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the effectiveness and safety of our product candidate. Frequently, product candidates that have shown promising results in early clinical trials have subsequently suffered significant setbacks in later clinical trials. To date, some of our clinical trials have involved small patient populations and because of the small sample size in such trials, the interim results of these clinical trials may be subject to substantial variability and may not be indicative of either future interim results or final results. In addition, 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. In addition, there is a high failure rate for drugs and biologic products proceeding through clinical trials. In fact, many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Moreover, data obtained from preclinical and clinical activities is subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

We depend on enrollment of patients in our clinical trials for our product candidates and 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 and could materially adversely affect our R&D efforts and business, financial condition and results of operations.

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, and to see those patients through the completion of required follow-up periods. If, for any reason, patients are unwilling to enroll in our clinical trials, then the timeline for recruiting patients, conducting studies and obtaining regulatory approvals for our product candidates may be delayed. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of clinical trials altogether.

Our current product candidates are being developed to treat oncology and immune diseases of high unmet medical need. However, we may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA, EMA or other regulatory authorities. As a result, we may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner. Patient enrollment can be affected by many factors, including:

- size of the patient population and process for identifying patients;
- eligibility and exclusion criteria for our clinical trials;
- perceived risks and benefits of our product candidates;
- severity of the disease under investigation;
- proximity and availability of clinical trial sites for prospective patients;
- competition with other clinical trials for product candidates competing in the same therapeutic areas as our product candidates;
- ability to obtain and maintain patient consent;
- patient drop-outs prior to completion of clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

Our ability to successfully initiate, enroll and complete clinical trials in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with CROs and physicians;
- different standards for the conduct of clinical trials;
- absence in some countries of established groups with sufficient regulatory expertise for review of certain treatment protocols;
- 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 or finding additional clinical trial sites to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which could have an adverse effect on our business, financial condition, results of operations and prospects.

Our product candidates and the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts, to their study doctor. Often, it is not possible to determine whether the product candidate being studied caused these conditions. Regulatory authorities may draw different conclusions or require additional testing to confirm these determinations. For Milciclib, the most frequent drug-related side effects reported across studies, at all doses tested, were gastrointestinal, or GI, adverse events (nausea and diarrhea, followed by less frequent vomiting), neurological effects (mainly tremor, then ataxia, dizziness and dysgeusia), skin disorders and asthenia, fatigue, headache and anorexia. For Foralumab, the most frequent drug-related side effects reported following intravenous administration were infusion related reactions, or IRR, including fever, headaches, chills, nausea, vomiting diarrhea and hypotension considered the result of cytokine release also known as cytokine release syndrome, or CRS. Other adverse events included reactivation of Epstein-Barr virus (clinically silent); moderate lymphocytopenia, abnormalities in liver function tests. Since most of these changes are related to the infusion route of administration and dosage level, such systemic toxicities are not anticipated when administered orally or nasally due to what we assume will be minimal systemic absorption and induction of anti-inflammatory T regulatory T cells.

In addition, it is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects are only detectable after investigational products are tested in large-scale, Phase 3 clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that our product candidates cause serious or life-threatening side effects, the development of our product candidates may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, the FDA, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that any serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the clinical trial. Moreover, if we elect or are required to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidate may be harmed and our ability to generate product revenues from such product candidate may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects.

Additionally, if we or others later identify undesirable side effects caused by any of our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.

Given the nature of biologics and NCE manufacturing, there is a risk of contamination. Any contamination could adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results

of operations and cause reputational damage. In addition, some of the raw materials required in our manufacturing process are derived from biologic sources and are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Risks Related to Our Financial Position and Need For Capital

Our independent registered public accounting firm has expressed substantial doubt about our ability to continue as a going concern, which may hinder our ability to obtain future financing.

Mazars LLP, our independent registered public accounting firm for the fiscal year ended December 31, 2018, has included an explanatory paragraph in their opinion that accompanies our audited consolidated financial statements as of and for the year ended December 31, 2018, indicating that our current liquidity position raises substantial doubt about our ability to continue as a going concern. If we are unable to improve our liquidity position, we may not be able to continue as a going concern. The accompanying consolidated financial statements do not include any adjustments that might result if we are unable to continue as a going concern and, therefore, be required to realize our assets and discharge our liabilities other than in the normal course of business which could cause investors to suffer the loss of all or a substantial portion of their investment.

We have incurred net losses in every year since our inception. We anticipate that we will continue to incur losses for the foreseeable future and may never achieve or maintain profitability.

We are a clinical stage biotechnology company with a limited operating history. Since our inception in May 2013, we have incurred significant net losses. Our net losses were $8.0 million and $8.7 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated loss of $50.6 million. We have devoted substantially all of our efforts to research and development of our product candidates, including clinical development of our lead product candidates, Foralumab and Milciclib, as well as to building out our management team and infrastructure. We expect that it could be several years, if ever, before we have a commercialized product candidate. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. These net losses will adversely impact our shareholders' equity and net assets and may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if, and as, we:

- continue research and development of Foralumab, including the initiation of our orally administered Phase 1 trials in normal healthy volunteers with an intent to treat patients with NASH, Crohn's disease and MS;
- complete our Phase 2 program for Milciclib as a monotherpay in HCC patients and initiate a Phase 2b trial for Milciclib in combination with Sorafenib in HCC patients;
- initiate clinical trials and preclinical studies for any additional product candidates that we may pursue in the future;
- manufacture our product candidates in accordance with current good manufacturing practices, or cGMP, for clinical trials or potential commercial sales;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidate for which we may obtain marketing approval;
- develop, maintain, expand and protect our intellectual property portfolio;
- identify, assess, and acquire or in-license other product candidates and technologies;
- secure, maintain or obtain freedom to operate for any in-licensed technologies and products;
- address any competing technological and market developments; and
- expand our operations in the United States and Europe.

We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our R&D efforts, expand our business or continue our operations.

We need substantial additional funding to complete the development of our product candidates, which may not be available on acceptable terms, if at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development, research operations or future commercialization efforts, if any.

Our operations have consumed substantial amounts of cash since inception, and we expect our expenses to increase in connection with our ongoing activities, particularly as we continue the R&D of, initiate further clinical trials of and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for our product candidates, we expect to incur significant expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company listed on both AIM in the United Kingdom and Nasdaq in the United States. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of laboratory testing, manufacturing, preclinical and clinical development for our current and future product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the extent to which we acquire or in-license and develop other product candidates and technologies;
- our ability to establish and maintain collaborations and license agreements on favorable terms, if at all;
- the costs, timing and outcome of potential future commercialization activities, including manufacturing, marketing, sales and distribution for our product candidates for which we receive marketing approval;
- the costs of developing, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- the sales price and availability of adequate third-party coverage and reimbursement for our product candidates, if and when approved.

Developing product candidates and conducting preclinical studies 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. Our product revenues, if any, will be derived from or based on sales of product candidates that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, if at all. To the extent that additional capital is raised through the issuance of equity or equity-linked securities, the issuance of those securities could result in substantial dilution for our current shareholders and the terms of any future issuance may include liquidation or other preferences that adversely affect the rights of our current shareholders. Debt financing, if available, may involve covenants restricting our operations or our ability to incur additional debt. Any debt or additional equity financing that we raise may contain terms that are not favorable to us or our shareholders. If we raise additional funds through collaboration and licensing arrangements with third parties, it may be necessary to relinquish some rights to our technologies or our product candidates or grant licenses on terms that are not favorable to us. Furthermore, the potential issuance of additional securities in the future, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our American Depositary Shares, or ADSs, to decline and existing shareholders may not agree with our financing plans or the terms of such financings.

If we are unable to obtain adequate funding on a timely basis, we may be required to significantly curtail, delay or discontinue our R&D programs of our product candidates or any future commercialization efforts, be unable to expand our operations or be unable to otherwise capitalize on our business opportunities, as desired, which could harm our business and potentially cause us to discontinue operations.

Our limited operating history and no history of commercializing pharmaceutical products may make it difficult to evaluate the success of our business to date and to assess the prospects for our future viability.

Since our inception, we have devoted substantially all of our resources to developing Foralumab and Milciclib, and our other product candidates, building our intellectual property portfolio and providing general and administrative support for these operations. Although our R&D efforts to date have resulted in a pipeline of product candidates, we have not yet demonstrated our ability to successfully complete Phase 3 or other pivotal clinical trials, obtain regulatory approvals, or commercialize any of our product candidates. In addition, given our limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors in achieving our business objectives.

Additionally, we are not profitable and have incurred losses in each year since our inception, and we expect that our financial condition and operating results may 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. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Risks Related to Our Reliance on Third Parties

We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials and to monitor and manage data for our ongoing preclinical and clinical programs. In engaging these third parties, we typically have to, and expect to have to, negotiate budgets and contracts, which may result in delays to our development timelines and increases costs. Additionally, there is a limited number of qualified third-party service providers that specialize or have the expertise required to achieve our business objectives, and so it may be challenging to find alternative investigators or CROs, or do so on commercially reasonable terms. We rely on these parties for execution of our preclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we fail to exercise adequate oversight over any of our CROs or if we or any of our CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other 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 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.

Further, these investigators and CROs are not our employees and we will not be able to control, other than by contract, the amount of resources, including time, which they devote to our product candidates and clinical trials. If independent investigators or CROs fail to devote sufficient resources to the development of our product candidates, or if their performance is substandard, it may delay or compromise the prospects for approval and commercialization of our product candidates. These investigators and CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical studies or other drug development activities, which could affect their performance on our behalf. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which increases the risk that a competitor will discover them or that this information will be misappropriated or disclosed.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. If CROs do not successfully carry out their

contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our results of operations and commercial prospects would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Repeating clinical trials or switching or engaging additional CROs involves additional cost and requires our management's time and focus. In addition, there is a natural transition period when a clinical trial has to be repeated or when a new CRO commences work. As a result, delays could occur, which could materially impact our ability to meet our desired clinical development timelines.

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.

We have engaged contract manufacturing organizations, or CMOs, to manufacture Foralumab and Milciclib and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our platforms, we must, at times, share our proprietary technology and confidential information, including 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. 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 proprietary technology and confidential information or other unauthorized use or disclosure of such technology or information would impair our competitive position and may have an adverse effect on our business, financial condition, results of operations and prospects.

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 by third parties. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

We utilize, and expect to continue to utilize, third parties to conduct our product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily.

We currently rely on CMOs for the manufacturing of clinical batches and intend to continue to rely on third parties to manufacture our preclinical study and clinical trial product supplies. If our current CMOs, or any future third-party manufacturers, do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, or if there are disagreements between us and our CMOs or any future third-party manufacturers, we will not be able to complete, or may be delayed in completing, the preclinical studies required to support future investigational new drug, or IND, submissions and the clinical trials required for approval of our product candidates.

In addition to our current CMOs, we may rely on additional third parties to manufacture ingredients of our product candidates in the future and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval or impact our ability to successfully commercialize any of our product candidates. Some of these events could be the basis for FDA, EMA or other regulatory authority action, including injunction, recall, seizure or total or partial suspension of product manufacture.

To the extent we rely on a third-party manufacturing facility for commercial supply, that third party will be subject to significant regulatory oversight with respect to manufacturing our product candidates.

The preparation of therapeutics for clinical trials or commercial sale is subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP requirements. These regulations govern manufacturing processes and procedures, including record keeping, and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of outside agents or other contaminants, or to inadvertent changes in the properties or stability of a product candidate that may not be detectable in final product testing. To the extent that we utilize third-party facilities for commercial supply, the third party's facilities and quality systems must pass an inspection for compliance with the applicable regulations as a condition of regulatory approval. In addition, the regulatory authorities may, at any time, audit or inspect the third-party manufacturing facility or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If, for example, these facilities do not pass a plant inspection, the FDA will not approve the applicable NDA or biologics license application, or BLA.

We do not directly control the manufacturing of, and are completely dependent on, our CMOs for compliance with cGMP requirements. If our CMOs cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, EMA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our CMOs are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our CMOs to regulatory risks for the production of such materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may generally affect the regulatory clearance of our CMOs' facilities. Our failure, or the failure of third parties, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products and product candidates.

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

Risks Related to Commercialization of Our Product Candidates

We currently have no marketing and sales force. If we are unable to establish effective sales, marketing and distribution capabilities or enter into agreements with third parties to market, sell and distribute our product candidates that may be approved, we may not be successful in commercializing our product candidates if and when approved, and we may be unable to generate any product revenue.

We currently do not have a marketing or sales team for the marketing, sales and distribution of any of our product candidates. In order to commercialize any of our product candidates that may be approved, we intend to build, on a territory-by-territory basis, marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. These efforts will require significant capital expenditures, management resources and time, and we face competition in search for qualified personnel or third parties to assist with marketing, sales and distribution of any of our product candidates. We may not be successful in building these capabilities.

There are risks involved with both establishing our own sales, marketing and distribution capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate

for which we recruit a sales force and establish marketing and/or distribution 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.

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

- our 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.

We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours.

The biotechnology and pharmaceutical industries are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

New developments, including the development of other pharmaceutical technologies and methods of treating disease, occur in the pharmaceutical and life sciences industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. We anticipate that we will face intense and increasing competition as new treatments enter the market and advanced technologies become available.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger R&D, clinical, sales and marketing and manufacturing organizations. These third parties also 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, the development of our products. In addition, mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidate that we may develop. Competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly or earlier 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. Additionally, technologies developed by our competitors may render our product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any product candidate that we may develop and commercialize.

The market opportunities for our product candidates may be smaller than we anticipate.

We focus our R&D efforts on treatments for cancer and autoimmune disease. 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, is based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients 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 product candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive our potential products, if and when approved, less than the potentially addressable market. These include, for example, the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets.

The future commercial success of our product candidates will depend upon the degree of each product candidates' market acceptance by physicians, patients, third-party payors and others in the medical community.

Our product candidates are at varying stages of development, and we may never have a product that is commercially successful. To date, we have no product authorized for marketing. Due to the inherent risk in the development of pharmaceutical products, we may never successfully complete development and commercialization of any of our product candidates. Even with the requisite approvals from the FDA, EMA and other regulatory authorities internationally, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and third-party payors of our product candidates as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. Even if some product candidates achieve market acceptance, the market may not prove to be large enough to allow us to generate significant revenues. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on several factors, including:

- the effectiveness and safety of our product candidates as demonstrated in clinical trials;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the availability and cost of treatment relative to alternative treatments;
- changes in the SOC for the targeted indications for any product candidate;
- the willingness of physicians to prescribe, and the target patient population to try, new therapies;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA, EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- the timing of market introduction of competitive products;
- sales, distribution and marketing support;
- publicity concerning our product candidates or competing products and treatments;
- potential product liability claims;
- any restrictions on the use of our products together with other medications; and
- favorable third-party payor coverage and adequate reimbursement.

Even if a potential product displays favorable clinical properties and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched.

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

We expect that coverage and adequate reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, 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 health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor's determination that use of a product is:

- a covered benefit under our health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment.

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products. In the United States, third-party payors, including government payors such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payors develop their coverage and reimbursement policies. However, no uniform policy of coverage and reimbursement exists among third-party payors. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. One payor's determination to provide coverage for a product does not assure that other payors will also provide coverage, and adequate reimbursement. It is difficult to predict what the Centers for Medicare and Medicaid Services, or CMS will decide with respect to coverage and reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these types of products. Moreover, reimbursement agencies in the European Union may be more conservative than the CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European Union, or EU, member states, or Member States. It is difficult to predict what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Also, the containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures, and foreign governments have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, in the United States, the Patient Protection and Affordable Care Act of 2010 (as amended by the Health Care and Education Reconciliation Act of 2010), or the PPACA, contains provisions that may reduce the profitability of products, including, for example, increased rebates for products sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several recent congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to product pricing, contain the cost of drugs, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products.

Outside the United States, international operations generally are subject to extensive government price controls and other market regulations and increasing emphasis on cost-containment initiatives in the European Union, Canada and other countries may put pricing pressure on us. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our product candidates may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues.

In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various Member States and parallel distribution, or arbitrage between low-priced and high-priced Member States, can further reduce prices. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. 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.

Moreover, increasing efforts by government and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates.

Payors increasingly are considering new metrics as the basis for reimbursement rates, such as average sales price, average manufacturer price and actual acquisition cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. Therefore, it may be difficult to project the impact of these evolving reimbursement metrics on the willingness of payors to cover product candidates that we or our partners are able to commercialize. 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 surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours.

Risks Related to Our Intellectual Property

Our rights to develop and commercialize our product candidates are subject to the terms and conditions of licenses granted to us by others. If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to the business.

We do not currently own any patents; however, we are heavily reliant upon licenses and sublicenses from Nerviano and Novimmune to certain patent rights and proprietary technology that are important or necessary to the development of our technology and product candidates, including the patents and know-how relating to manufacture. These and other licenses may not provide exclusive rights to use such intellectual property and technology or may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and product candidates in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products, including in territories covered by our licenses.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. If our licensors fail to maintain such patents or patent applications, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our product candidates that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future.

Licenses to additional third-party technology and materials that may be required for our development programs, including additional technology and materials owned by any of our current licensors, may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have an adverse effect on our business and financial condition.

If we are unable to obtain and maintain patent protection for our current product candidates, any future product candidates we may develop and our technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours.

Our success depends, in large part, on our ability to seek, obtain and maintain patent protection in the United States and other countries with respect to our product candidates and to future innovation related to our manufacturing technology. Our licensors have sought, and we intend to seek to protect our proprietary position by filing patent applications in the United States, the United Kingdom and elsewhere, related to certain technologies and our product candidates that are important to our business. Our current patent portfolio contains a limited number of patent applications, all of which are in-licensed from third parties and relate to either composition of matter, formulation, method of use or process of manufacturing Foralumab, Milciclib and a fully human anti-interleukin-6 receptor, or IL-6r, mAb. However, the risks associated with patent rights generally apply to patent rights that we in-license now or in the future, as well as patent rights that we may own in the future. Moreover, the risks apply with respect to patent rights and other intellectual property applicable to our product candidates, as well as to any intellectual property rights that we may acquire in the future related to future product candidates, if any. We have filed a new patent application covering the composition of matter of Foralumab. However, this application is pending and there is no guarantee that the U.S. Patent and Trademark Office, or USPTO, will grant this application.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner.

In some cases, the work of certain academic researchers in the oncology and immunology fields has entered the public domain, which we believe precludes our ability to obtain patent protection for certain inventions relating to such work.

Consequently, we will not be able to assert any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our R&D output before it is too late to obtain patent protection.

Our existing license agreements impose, and we expect that future license agreements will impose, various due diligence, development and commercialization timelines, insurance, milestone payments, royalties and other obligations on us. See the description in the section titled “Business-Collaboration and License Agreements” herein. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, or, in some cases, under other circumstances, the licensor may have the right to terminate the license, in which event we would not be able to market product candidates covered by the license. In addition, certain of these license agreements are not assignable by us without the consent of the respective licensor, which may have an adverse effect on our ability to engage in certain transactions.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of any patent rights are highly uncertain. Our licensed patent applications may not result in patents being issued which protect our technology or product candidates, effectively prevent others from commercializing competitive technologies and product candidates or otherwise provide any competitive advantage. In fact, patent applications may not issue as patents at all. Even assuming patents issue from patent applications in which we have rights, changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Other parties have developed technologies that may be related or competitive to our own and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents. We may not be aware of all third-party intellectual property rights potentially relating to our current and future product candidates.

Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and in other jurisdictions are typically not published until 18 months after filing, or, in some cases, not at all. Therefore, we cannot know with certainty whether the inventors of our licensed patents and applications were the first to make the inventions claimed in those patents or pending patent applications, or that they were the first to file for patent protection of such inventions. Similarly, should we own any patents or patent applications in the future, we may not be certain that we were the first to file for patent protection for the inventions claimed in such patents or patent applications. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty.

The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our licensed patents have, or that any of our pending licensed patent applications that mature into issued patents will include, claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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 licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates, including "highly similar," or biosimilar, versions of such products. In addition, the intellectual property portfolio licensed to us by Nerviano and Novimmune may be used by them or licensed to third parties, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against our licensors or another licensee or in administrative proceedings brought by or against our licensors or another licensee in response to such litigation or for other reasons.

Even if we acquire patent protection that we expect should enable us to maintain some competitive advantage, third parties, including competitors, may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability and our licensed patents may be challenged in courts or patent offices in the United States and abroad. For example, we may be subject to a third-party submission of prior art to the USPTO challenging the validity of one or more claims of our licensed patents. Such submissions may also be made prior to a patent's issuance, precluding the granting of a patent based on one of our pending licensed patent applications. We may become involved in opposition, derivation, re-examination, inter partes review, post-grant review or interference proceedings challenging the patent rights of others from whom we have obtained licenses to such rights. Competitors may claim that they invented the inventions claimed in our licensed issued patents or patent applications prior to the inventors of such patents or applications. A competitor who can establish an earlier filing or invention date may also claim that we are infringing their patents and that we therefore cannot practice our technology as claimed under our licensed patents, if issued. Competitors may also contest our licensed patents, if issued, by showing that the invention was not patent-eligible, was not novel, was obvious or that the patent claims failed any other requirement for patentability.

An adverse determination by former employees or consultants asserting ownership rights to our patents may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar technology and therapeutics, without payment to us, or could limit the duration of the patent protection covering our technology and product candidates. Such challenges may also result in our inability to manufacture or commercialize our product candidates without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if they are unchallenged, our licensed patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our licensed patents by developing similar or alternative technologies or therapeutics in a non-infringing manner.

For example, a third party may develop a competitive therapeutic that provides benefits similar to one or more of our product candidates but that uses a different antibody or molecular active ingredient 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, which would harm our business.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

We currently depend, and will continue to depend, on our license agreements whereby we obtain rights in certain patents and patent applications owned by them. Further development and commercialization of our current product candidates may, and development of any future product candidates will, require us to enter into additional license or collaboration agreements. The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have an adverse effect on our business, financial condition, results of operations and prospects.

If any of our licenses or material relationships or any in-licenses upon which our licenses are based are terminated or breached, we may:

- lose our rights to develop and market our product candidates;
- lose patent protection for our product candidates;
- experience significant delays in the development or commercialization of our product candidates;
- not be able to obtain any other licenses on acceptable terms, if at all; or
- incur liability for damages.

In addition, a third party may in the future bring claims that our performance under our license agreements, including our sponsoring of clinical trials, interferes with such third party's rights under its agreement with one of our licensors. If any such claim were successful, it may adversely affect our rights and ability to advance our product candidates as clinical candidates or subject us to liability for monetary damages, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

These risks apply to any agreements that we may enter into in the future for our current or any future product candidates. If we experience any of the foregoing, it could have a negative impact on our business, financial condition, results or operations and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We have entered into license agreements with third parties and may need to obtain additional licenses from one or more of these same third parties or from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize our product candidates, which would harm our business. We cannot provide any assurances that third-party patents or other intellectual property rights do not exist which might be enforced against our current product candidates or future product candidates, resulting in either an injunction prohibiting our manufacture or sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In each of our existing license agreements, and we expect in our future agreements, patent prosecution of our licensed technology is controlled solely by the licensor, and we may be required to reimburse the licensor for their costs of patent prosecution. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property, or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. Our license agreements with Nerviano and Novimmune also require us to meet development thresholds to maintain each license, including establishing a set timeline for developing and commercializing product candidates. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights pursuant to our collaborative development relationships;
- our diligence obligations under the license agreements and what activities satisfy those diligence obligations;
- the inventorship or ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize our product candidates.

We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have certain rights to the intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of additional proprietary rights held by these or other third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We may collaborate with non-profit and academic institutions to accelerate our preclinical R&D under written agreements with these institutions. These institutions may provide us with an option to negotiate a license to any of the institution’s rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property or maintain the existing intellectual property rights we have, we may have to abandon development of our product candidates and our business, financial condition, results of operations and prospects could suffer. Moreover, to the extent that we seek to develop other product candidates in the future, we will likely require acquisition or in-license of additional proprietary rights held by third parties.

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

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our licensed patents and/or applications and any patent rights we may own in the future. We rely on our outside counsel or our licensing partners to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, 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. In such an event, potential competitors might be able to enter the market and this circumstance could have an adverse effect on our business.

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

Filing, prosecuting and defending patents on 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. In some cases, we may not be able to obtain patent protection for certain licensed technology outside the United States. 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, even in jurisdictions where we do pursue patent protection. 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 do 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 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 products, which could make it difficult for us to stop the infringement of our patents, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. Moreover, many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. Many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business and results of operations may be adversely affected.

In addition, proceedings to enforce our patent rights 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. 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 or license.

We may not be able to protect our trade secrets in court.

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. However, we may not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements, despite the existence generally of confidentiality agreements and other contractual restrictions.

Monitoring unauthorized uses and disclosures is difficult and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees and consultants who are parties to these agreements breach or violate the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. As a result, we could lose our trade secrets.

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 and security measures, they may still 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 could purchase our product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe 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, we would have no right to prevent them, or those to whom they communicate such trade secrets, from using that technology or information to compete with us. If our trade secrets are not adequately protected so as to protect our market against competitors' therapeutics, our competitive position could be adversely affected, as could our business.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights.

Our commercial success depends upon our ability and the ability of our future collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference proceedings, post grant review and inter partes review before the USPTO. Our competitors or other third parties may assert infringement claims against us, alleging that our therapeutics, manufacturing methods, formulations or administration methods are covered by their patents. Given the vast number of patents in our field of technology, we cannot be certain or guarantee that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional R&D programs expected in the future. Furthermore, because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of our product candidates and we may or may not be aware of such patents. If a patent holder believes the manufacture, use, sale or importation of one of our product candidates infringes its patent, the patent holder may sue us even if we have licensed other patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our licensed patent portfolio may therefore have no deterrent effect.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States may remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or

may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our product candidates or the use of our product candidates.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent or other intellectual property rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize our product candidates. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. Similarly, there is no assurance that a court of competent jurisdiction would find that product candidates or our technology did not infringe a third-party patent.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. If we are found or believe there is a risk that we may be found, to infringe a third party's valid and enforceable intellectual property rights, we could be required or may choose to obtain a license from such third party to continue developing, manufacturing and marketing our product candidates and technology. 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 and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidate. 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 or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some or all 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, financial condition, results of operations and prospects.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, are unpredictable and generally expensive and time-consuming. Competitors may infringe our patents or the patents of our licensing partners, should such patents issue, or we may be required to defend against claims of infringement. To counter infringement or unauthorized use claims or to defend against claims of infringement can be expensive and time consuming. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. Furthermore, 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. 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 us. 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 adequately conduct such litigation or proceedings. 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.

Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a negative impact on our ability to compete in the marketplace.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Certain of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors, as well as our academic partners. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. An inability to incorporate such technologies or features would harm our business and may prevent us from successfully obtaining necessary regulatory approvals and commercializing our product candidates. In addition, we may lose personnel as a result of such claims, and any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent contractors. A loss of key personnel or their work product could hamper or prevent our ability to obtain necessary regulatory approvals and commercialize our product candidates, which would have an adverse effect on our business, results of operations and financial condition. 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 it is our policy to require our employees and contractors who may be involved in the conception or 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, conceives or develops intellectual property that we regard as our own. Moreover, even when we obtain agreements assigning intellectual property to us, the assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Furthermore, individuals executing agreements with us may have pre-existing or competing obligations to a third party, such as an academic institution, and thus an agreement with us may be ineffective in perfecting ownership of inventions developed by that individual. Disputes about the ownership of intellectual property that we may own may have an adverse effect on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Recent patent reform legislation 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. The Leahy-Smith Act includes several significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent through various post-grant proceedings administered by the USPTO. 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 to govern 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.

Accordingly, it is not clear 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 negative impact effect on our business, financial condition, results of operations and prospects.

Additionally, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, the combination of new federal legislation, federal court decisions, and guidance from the USPTO has created uncertainty with respect to the

value of patents, once obtained. Depending on the decisions by the U.S. Congress, federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or enforce our existing patents and patents we might obtain in the future.

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

We do not currently have any registered trademarks and we have not filed any trademark applications to date. Any trademark applications in the United States, Europe and in other foreign jurisdictions where we may file may not be allowed or may subsequently be opposed. Once filed and registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive and time-consuming, particularly for a company of our size. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources.

Intellectual property rights and regulatory exclusivity rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to our product candidates but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our license partners or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or may own in the future;
- we, or our license partners or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- others may circumvent our regulatory exclusivities, such as by pursuing approval of a competitive product candidate via the traditional approval pathway based on their own clinical data, rather than relying on the abbreviated pathway provided for biosimilar applicants;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to now or in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- others may have access to the same intellectual property rights licensed to us on a non-exclusive basis;
- our competitors might conduct R&D activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;

- the patents or other intellectual property rights of others may have an adverse effect on our business; or
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

Risks Related to Government Regulation

Even if we complete the necessary clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize our product candidates and the approval may be for a narrower indication than we seek.

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. The FDA must review and approve any new pharmaceutical product before it can be marketed and sold in the United States. The FDA regulatory review and approval process, which includes evaluation of preclinical studies and clinical trials of a product candidate and proposed labeling, as well as the evaluation of the manufacturing process and manufacturers' facilities, all of which is lengthy, expensive and uncertain. To obtain approval, we must, among other things, demonstrate with substantial evidence from well-controlled clinical trials that the product candidate is both safe and effective for each indication where approval is sought. Even if our product candidates meet the FDA's safety and effectiveness endpoints in clinical trials, the FDA may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. The FDA has substantial discretion in the review and approval process and may refuse to file our application for substantive review or may determine after review of our data that our application is insufficient to allow approval of our product candidates. The FDA may require that we conduct additional preclinical studies, clinical trials or manufacturing validation studies and submit that data before it will reconsider our application. 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 authority policy during the period of product development, clinical trials and the review process.

The FDA, EMA or other regulatory authorities also may approve a product candidate for more limited indications than requested or may impose significant limitations in the form of narrow indications, warnings or a REMS. These regulatory authorities may require precautions or contraindications with respect to conditions of use or may grant approval subject to the performance of costly post-marketing clinical trials. In addition, the FDA, EMA or other regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could harm the commercial prospects for our product candidates and negatively impact our business, financial condition, results of operations and prospects.

Delays in obtaining regulatory approval of our manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our product development and commercialization efforts.

We do not currently operate manufacturing facilities for clinical or commercial production of our product candidates. Before we can begin to commercially manufacture our product candidates, whether in a third-party facility or in our own facility, if and when established, we must obtain regulatory approval from the FDA for our manufacturing process and facility. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities and from other foreign regulatory authorities, as applicable. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers are found to be non-compliant with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to expend time, money and effort in production, record keeping and quality assurance to confirm that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any product candidate that we may develop.

If we or our third-party manufacturers fail to comply with applicable cGMP regulations, the FDA, EMA and other regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be harmed.

Additionally, if the supply of our products from our third-party manufacturers to us is interrupted for any reason, including due to regulatory requirements or actions (including recalls), adverse financial developments at or affecting the supplier, failure by the supplier to comply with cGMPs, contamination, business interruptions or labor shortages or disputes, there could be a significant disruption in commercial supply of our products. We do not currently have a backup manufacturer of our product candidate supply for clinical trials or commercial sale. An alternative manufacturer would need to be qualified through a supplement to its regulatory filing, which could result in further delays. The regulatory authorities also may require additional clinical trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines.

If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by applicable regulatory authorities for a significant period of time. In addition, even if we obtain orphan drug exclusivity for any of our products, such exclusivity may not protect us from competition.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate products for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In the European Union, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, orphan drug designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product. In Europe, orphan drug designation entitles a party to a number of incentives, such as protocol assistance and scientific advice specifically for designated orphan medicines, and potential fee reductions depending on the status of the sponsor.

The designation as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition

if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

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

Even if we obtain regulatory approval for a product candidate, our product candidates will remain subject to regulatory oversight.

Even if we obtain regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and clinical effectiveness of the product.

Some of our product candidates are classified as biologics in the United States, and therefore, can only be sold if we obtain a BLA from the FDA. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. In addition, the holder of a BLA must comply with the FDA's advertising and promotion requirements, such as those related to the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"). Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or if a regulatory authority disagrees with the promotion, marketing or labeling of that product (in addition to our being obligated as holder of a BLA to monitor and report adverse events and any failure of a product to meet the BLA specifications), a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidates, a regulatory or enforcement authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of the product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of the EMA and other regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. 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, which would negatively impact our business, financial condition, results of operations and prospects.

Even if we obtain and maintain approval for our product candidates in a major pharmaceutical market such as the United States, we may never obtain approval for our product candidates in other major markets.

In order to market any products in a country or territory, we must establish and comply with numerous and varying regulatory requirements of such countries or territories regarding safety and effectiveness. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking regulatory approvals in all major markets could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials, which would be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our product candidates in those countries. For example, in many jurisdictions outside of 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 would also be subject to approval. Satisfying these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. In addition, our failure to obtain regulatory approval in any country may delay or have negative effects on the process for regulatory approval in other countries. We currently do not have any product candidates approved for sale in any jurisdiction, whether in the United States, Europe or any other international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be compromised.

We may seek a conditional marketing authorization in Europe for some or all of our current product candidates, but we may not be able to obtain or maintain such designation.

As part of its marketing authorization process, the EMA may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, when doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use, or CHMP, to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization.

This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and therapeutic utility of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;

- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

Granting a conditional marketing authorization allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product is generated, submitted, assessed and acted upon.

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 our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The MMA expanded Medicare coverage for outpatient drug purchases by adding a new Medicare Part D program and introduced a new reimbursement methodology based on average sales prices for Medicare Part B physician-administered drugs. In addition, the MMA authorized Medicare Part D prescription drug plans to limit the number of drugs that will be covered in any therapeutic class in their formularies. The MMA's cost reduction initiatives and other provisions could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors. Similar regulations or reimbursement policies may be enacted in international markets, which could similarly impact our business.

More recently, in March 2010, the PPACA (as amended by the Health Care and Education Reconciliation Act of 2010) was passed, which substantially changes the way healthcare is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The PPACA, among other things: (i) addresses 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; (ii) increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations; (iii) establishes annual fees and taxes on manufacturers of certain branded prescription drugs; (iv) expands the availability of lower pricing under the 340B drug pricing program by adding new entities to the program; and (v) establishes a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% 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. Additionally, in the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biologic products that are demonstrated to be biosimilar or "interchangeable" with an FDA-approved biologic product. This new pathway could allow competitors to reference data from biologic products already approved after 12 years from the time of approval. This could expose us to potential competition by lower-cost biosimilars even if we commercialize a product candidate faster than our competitors. Moreover, the creation of this abbreviated approval pathway does not preclude or delay a third party from pursuing approval of a competitive product candidate via the traditional approval pathway based on their own clinical trial data.

Additional changes that may affect our business include those governing enrollments in federal healthcare programs, reimbursement changes, rules regarding prescription drug benefits under the health insurance exchanges and fraud and abuse and enforcement. Continued implementation of the PPACA and the passage of additional laws and

regulations may result in the expansion of new programs such as Medicare payment for performance initiatives, and may impact existing government healthcare programs, such as by improving the physician quality reporting system and feedback program.

For each state that does not choose to expand its Medicaid program, there likely will be fewer insured patients overall, which could impact the sales, business and financial condition of manufacturers of branded prescription drugs. Where patients receive insurance coverage under any of the new options made available through the PPACA, manufacturers may be required to pay Medicaid rebates on that resulting drug utilization. The U.S. federal government also has announced delays in the implementation of key provisions of the PPACA. The implications of these delays for our and our potential partners' business and financial condition, if any, are not yet clear.

In addition, there have been judicial and congressional challenges to certain aspects of the PPACA, and we expect the current administration and Congress will likely continue to seek legislative and regulatory changes, including repeal and replacement of certain provisions of the PPACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the U.S. House of Representatives passed legislation known as the American Health Care Act of 2017, and Senate Republicans have released a draft bill known as the Better Care Reconciliation Act of 2017, each of which would repeal certain aspects of the PPACA if ultimately enacted. The prospects for enactment of these legislative initiatives remain uncertain. Further, Congress also could consider other legislation to replace elements of the PPACA. We cannot know how efforts to repeal and replace the PPACA or any future healthcare reform legislation will impact our business.

We expect that the PPACA, as well as 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 product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. 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.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

We are subject to governmental regulation and other legal obligations related to privacy, data protection and data security. Our actual or perceived failure to comply with such obligations could harm our business.

We are subject to diverse laws and regulations relating to data privacy and security in the EU, and shortly in the European Economic Area, including the GDPR. New global privacy rules are being enacted and existing ones are being updated and strengthened. We are likely to be required to expend capital and other resources to ensure ongoing compliance with these laws and regulations.

The GDPR applies extraterritorially and implements stringent operational requirements for controllers and processors of personal data. For example, the GDPR: (i) requires detailed disclosures to data subjects; (ii) requires disclosure of the legal basis on which personal data is processed; (iii) makes it harder to obtain valid consent for processing; (iv) requires the appointment of a data protection officers where sensitive personal data (i.e. health data) is processed on a large scale; (v) provides more robust rights for data subjects; (vi) introduces mandatory data breach notification through the EU; (vii) imposes additional obligations when contracting with service providers; and (viii) requires an appropriate privacy governance framework to be implemented including policies, procedures, training and data audit. The GDPR permits Member State derogations for certain issues and, accordingly, we are also subject to EU national laws relating to the processing of certain data such as genetic data, biometric data and data concerning health. Complying with these numerous, complex and often changing regulations is expensive and difficult. Failure by us, or our partners or service providers, to comply with the GDPR could result in regulatory investigations, enforcement notices and/ or fines of up to the higher of 20,000,000 Euros or up to 4% of our total worldwide annual turnover. In addition to

the foregoing, any breach of privacy laws or data security laws, particularly those resulting in any security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and financial condition.

As a data controller, we are accountable for any third party data service providers we engage to process personal data on our behalf. We attempt to address the associated risks by performing security assessments, detailed due diligence and regularly performing privacy and security reviews of its vendors and requiring all such third-party providers with data access to sign agreements, including business associate agreements, and where required under EU law, obligating them to only process data according to our instructions and to take sufficient security measures to protect such data. There is no assurance that these contractual measures and our own privacy and security-related safeguards will protect us from the risks associated with the third-party processing, storage and transmission of such information. Any violation of data or security laws by our third party processors could have a material adverse effect on our business and result in the fines and penalties outlined above. We are also subject to evolving European privacy laws on electronic marketing and cookies. The EU is in the process of replacing the e-Privacy Directive (2002/58/EC) with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each Member State. The draft e-Privacy Regulation imposes strict opt-in marketing rules with limited exceptions for business-to-business communications, alters rules on third-party cookies, web beacons and similar technology and significantly increases fining powers to the same levels as GDPR (i.e. the greater of 20,000,000 Euros or 4% of total global annual revenue). While the e-Privacy Regulation was originally intended to be adopted on May 25, 2018 (alongside the GDPR), it is still going through the European legislative process and commentators now expect it to be adopted during the second half of 2020 or during 2021 following a transition period.

We are subject to the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act 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 U.K. Bribery Act 2010, or the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, or the FCPA, the U.S. domestic bribery statute contained in 18 §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The U.K. Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the U.K. 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 U.K. 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 U.K. 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 U.K. Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the U.K. 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 U.K. Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our relationships with customers, physicians and third-party payors will 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 healthcare laws and regulations. If we are found in violation of these laws and regulations, we may be required to pay a penalty or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operations.

If we obtain FDA approval for our product candidates and begin commercializing them in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal laws and Physician Payments Sunshine Act of 2010 and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the U.S. 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 federal 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, in return for either the referral of an individual, or the purchase, leasing, furnishing or arranging for the purchase, lease or order of a good, facility, item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amended the intent requirement of the federal Anti-Kickback Statute, such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;

- federal civil and criminal false claims laws and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent. The PPACA provides, and recent government cases against pharmaceutical and medical device manufacturers support the view that federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, may implicate the False Claims Act of 1863;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit, among other things, a person from knowingly and willfully executing a scheme or from making false or fraudulent statements to defraud any healthcare benefit program, regardless of the payor (e.g., public or private);

- HIPAA (as amended by the Health Information Technology for Economic and Clinical Health Act of 2009), and their implementing regulations, which impose certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses and health care providers, and their respective business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf;

- federal transparency laws, including the federal Physician Payment Sunshine Act, that require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the CMS information related to: (i) payments or other "transfers of value" made to physicians and teaching hospitals and (ii) ownership and investment interests held by physicians and their immediate family members;

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

- state and foreign law equivalents of each of the above federal laws, state and local laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment, and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and we may be required to curtail or restructure our operations, any of which could adversely affect our ability to operate our business and our results of operations.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain robust and expandable systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the possibility that a healthcare company may run afoul of one or more of the requirements.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur substantial costs.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. We contract with third parties that conduct operations on our behalf that involve the use of hazardous and flammable materials, including chemicals and biologic materials. Our contractors also produce and dispose of hazardous waste products. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our contractors' use of hazardous materials, we could be held liable for any resulting damages and any liability could exceed our resources, and our clinical trials or regulatory approvals could be suspended. We also could incur significant costs associated with civil or criminal fines and penalties. Our third-party contractors may not carry specific biological or hazardous waste insurance coverage, and their property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination.

Although we maintain workers' compensation insurance for certain 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. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. 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 adversely affect our business, financial condition, results of operations and prospects.

Risks Related to our Business Operations

We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.

The success of our business depends upon our ability to identify, develop and commercialize product candidates. Research programs to identify new product candidates require substantial technical, financial and human resources. Although a substantial amount of our efforts will focus on the continued preclinical and clinical testing and potential

approval of our product candidates, a key element of our long-term growth strategy is to develop and market additional products and product candidates. However, we may fail to identify other potential product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our spending on current and future R&D programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

Our long-term growth strategy to develop and market additional products and product candidates is heavily dependent on precise, accurate and reliable scientific data to identify, select and develop promising pharmaceutical product candidates and products. Our business decisions may therefore be adversely influenced by improper or fraudulent scientific data sourced from third parties. Any irregularities in the scientific data used by us to determine our focus in R&D of product candidates and products could have a material adverse effect on our business, prospects, financial condition and results of operations.

If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a negative impact on our business, financial condition, results of operations and prospects.

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

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We currently do not have “key person” insurance on any of our 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.

Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, also will be critical to our success. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. In addition, failure to succeed in preclinical studies or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of certain executives, key employees, consultants or advisors, may impede the progress of our research, development and commercialization objectives and have an adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

At December 31, 2018, we had 5 full-time employees who were engaged in R&D activities. If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our R&D activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management and, to a potentially significant extent, divert our management and business development resources away from their current uses. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and any future product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas, to attract and retain sufficient numbers of talented employees and to expand the group of contractors we use.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading, which could have a material adverse impact on our business.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to: comply with FDA or EMA regulations or the regulations applicable in other jurisdictions, provide accurate information to the FDA, EMA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. 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 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. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA, EMA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. Additionally, we are subject to the risk that a person could allege fraud or other misconduct, even in none occurred. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent these activities may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws 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, financial condition, results of operations and prospects, including the imposition of significant criminal, civil and administrative sanctions, such as monetary penalties, damages, fines, disgorgement, individual imprisonment, and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and we may be required to curtail or restructure our operations. We are also subject to the data privacy regime in the EU, which imposes obligations and restrictions on the collection and use of personal data relating to individuals located in the EU and includes the General Data Protection Regulation, or the GDPR, and any national laws implementing or supplementing the GDPR. If we do not comply with our obligations under the EU privacy regime, we could be exposed to significant fines and we may be the subject of litigation and/or adverse publicity, which could have a material adverse effect on our reputation and business.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidate that we may develop.

We face an inherent risk of product liability exposure related to the testing of our current and future product candidates in clinical trials and may face an even greater risk if we commercialize any product candidate that we may develop. For example, we may be sued if our current or future product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal of clinical trial participants;

- the inability to commercialize any product candidates that we may develop; or
- injury to our reputation and significant negative media attention.

Although we maintain product liability insurance coverage, such insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

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

On June 23, 2016, the U.K. held a referendum in which a majority of the eligible members of the electorate voted for the U.K. to leave the EU. The U.K's withdrawal from the EU is commonly referred to as Brexit. Pursuant to Article 50 of the Treaty on European Union, the U.K. will cease to be an EU Member State either on the effective date of a withdrawal agreement (entry into such a withdrawal agreement will require U.K. parliamentary approval) or, failing that, two years following the U.K.'s notification of its intention to leave the EU (the "Brexit Date"), unless the European Council (together with the U.K.) unanimously decides to extend the two year period. On March 29, 2017, the U.K. formally notified the European Council of its intention to leave the EU. It is unclear how long it will take to negotiate a withdrawal agreement, but it appears likely that Brexit will continue to involve a process of lengthy negotiations between the U.K. and EU Member States to determine the future terms of the U.K's relationship with the EU. For example, in March 2018, the U.K. reached a provisional agreement (the "Withdrawal Agreement") with the EU on transitional arrangements following the U.K's exit (which are intended to enable the U.K. to remain within the EU single market and customs union for a transitional period through 2020), but this Withdrawal Agreement needs to be formally agreed as part of the withdrawal arrangements currently under negotiation. The U.K. and the European Council had agreed an extension of the Brexit Date until May 22, 2019, which was conditional upon endorsement of the Withdrawal Agreement by the U.K. House of Commons by March 29, 2019. The Withdrawal Agreement was not so endorsed, therefore the Brexit Date is unconditionally extended until October 31, 2019 instead.

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

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

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

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

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

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of the U.K's withdrawal from the EU, the U.K. could lose the benefits of global trade agreements negotiated by the EU on behalf of its members, which may result in increased trade barriers that could make our doing business in the EU and the EEA more difficult. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the U.K., or what, if any, role the EMA may have in the approval process. Even prior to any change to the U.K's relationship with the EU, the announcement of Brexit has created economic uncertainty surrounding the terms of Brexit and its consequences could adversely impact customer confidence resulting in customers reducing their spending budgets on our solutions, which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our ADSs and our ordinary shares.

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 Pounds Sterling and the U.S. dollar, may adversely affect us. Although we are based in the United Kingdom, we may source R&D, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the potential value of our ADSs may be affected by fluctuations in foreign exchange rates not only between the Pounds 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.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed, and the further development and commercialization of our product candidates could be delayed.

Risks Related to the Ownership of Our Securities

If you purchase ADSs in this offering, you will suffer immediate dilution of your investment.

The public offering price of our ADSs is substantially higher than the pro forma as adjusted net tangible book value per ADS. Therefore, if you purchase ADSs in this offering, you will pay a price per ADS that substantially exceeds our pro forma as adjusted net tangible book value per ADS after this offering. Based on an assumed public offering price of $6.32 per ADS in this offering, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, you will experience immediate dilution of $0.61 per ordinary share (equal to $6.11 per ADS), representing the difference between our as adjusted net tangible book value per ADS after this offering and the public offering price per ADS. After this offering, we may have outstanding options to purchase ordinary shares with exercise prices lower than the public offering price. To the extent these outstanding options are exercised, there will be further dilution to investors in this offering. For further information regarding the dilution resulting from this offering, see the section titled "Dilution" in this prospectus.

The prices of the ADSs and our ordinary shares may be volatile and fluctuate substantially, which could result in substantial losses for holders of the ADSs and our ordinary shares.

The market prices of the ADSs on the Nasdaq Global Market and of our ordinary shares on AIM may be volatile and fluctuate substantially. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, holders of the ADSs and our ordinary shares may not be able to sell their ADSs or ordinary shares at or above the price at which they were purchased. The market price for the ADSs and ordinary shares may be influenced by many factors, including:

- the success of competitive products or technologies;
- results of clinical trials of Miciclib and Foralumab and any other future product candidate that we develop;
- results of clinical trials of product candidates of our competitors;
- changes or developments in laws or regulations applicable to Miciclib and Foralumab and any other future product candidates that we develop;
- our entry into, and the success of, any collaboration agreements with third parties;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates, products or technologies;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- market conditions in the biotechnology and pharmaceutical sectors;
- general economic, industry and market conditions;
- the trading volume of ADSs on the Nasdaq Global Market and of our ordinary shares on AIM; and
- the other factors described in this “Risk Factors” section.

The dual listing of our ordinary shares and the ADSs may adversely affect the liquidity and value of the ADSs.

The ADSs are traded on the Nasdaq Global Market, and our ordinary shares are listed on AIM. The dual listing of our ordinary shares and the ADSs may dilute the liquidity of these securities in one or both markets and may adversely affect the maintenance of an active trading market for the ADSs in the United States. The price of the ADSs could also be adversely affected by trading in our ordinary shares on AIM. Although our ordinary shares are currently listed on AIM, we may decide at some point in the future to delist our ordinary shares from AIM, and our ordinary shareholders may approve such delisting.

In this circumstance, shareholders on the AIM market, either because they are not permitted to hold such securities or for other reasons, may seek to convert their shares into ADSs and sell them on NASDAQ as the date for de-listing from the AIM market draws near, which could cause the trading price of our ADSs on NASDAQ to decline. We are also contemplating eliminating our ADS facility, with the intent of having common shares traded on NASDAQ, which would then be our only publicly-traded security. Terminating the facility may obligate us to pay fees to our Depositary. There can be no assurance that the liquidity of the our shares or ADS would not be impaired.

Securities traded on AIM may carry a higher risk than shares traded on other exchanges that may impact the value of your investment.

Our ordinary shares are currently traded on AIM. Investment in equities traded on AIM is perceived by some to carry a higher risk than an investment in equities quoted on exchanges with more stringent listing requirements, such as the London Stock Exchange, New York Stock Exchange or the Nasdaq Stock Market. This is because AIM imposes less stringent corporate governance and ongoing reporting requirements than those other exchanges. In addition, AIM requires only semi-annual, rather than quarterly, financial reporting. You should be aware that the value of our ordinary shares may be influenced by many factors, some of which may be specific to us and some of which may affect AIM-listed companies generally, including the depth and liquidity of the market, our performance, a large or small volume of trading in our ordinary shares, legislative changes and general economic, political or regulatory conditions, and that the prices may be volatile and subject to extensive fluctuations. Therefore, the market price of our ordinary shares underlying the ADSs may not reflect the underlying value of our company.

Holders of our ADSs have fewer rights than our shareholders and must act through the depositary to exercise their rights.

Holders of our ADSs do not have the same rights as our shareholders and may only exercise their voting rights with respect to the underlying ordinary shares in accordance with the provisions of the deposit agreement. Holders of the ADSs will appoint the depositary or its nominee as their representative to exercise the voting rights attaching to the ordinary shares represented by the ADSs. When a general meeting is convened, if you hold ADSs, you may not receive sufficient notice of a shareholders' meeting to permit you to withdraw the ordinary shares underlying your ADSs to allow you to vote with respect to any specific matter. We will make all commercially reasonable efforts to cause the depositary to extend voting rights to you in a timely manner, but we cannot assure you that you will receive voting materials in time to instruct the depositary to vote, and it is possible that you, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, you may not be able to exercise your right to vote and you may lack recourse if your ADSs are not voted as you request. In addition, in your capacity as an ADS holder, you will not be able to call a shareholders' meeting.

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 any potential future 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, or Articles. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. See "Description of Share Capital and Articles of Association-Differences in Corporate Law" in this report for a description of the principal differences between the provisions of the Companies Act applicable to us and, for example, the Delaware General Corporation Law relating to stockholders' rights and protections.

We may re-incorporate in another jurisdiction, and the laws of such jurisdiction will likely govern all of our material agreements and we may not be able to enforce our legal rights.

We may relocate the home jurisdiction of our business from the United Kingdom to another jurisdiction. If we determine to do this, the laws of such jurisdiction would likely govern all of our material agreements. In this circumstance, the rights of shareholders could be substantially different under the corporate law of the jurisdiction to which we might migrate than they are under English law. Moreover, the system of laws and the enforcement of existing laws in such jurisdiction may not be as certain in implementation and interpretation as in the United States or the United Kingdom. The inability to enforce or obtain a remedy under any of our future agreements could result in a significant loss of business, business opportunities or capital.

If we engage in future acquisitions or strategic partnerships, this may increase our capital requirements, dilute our AIM shareholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We intend to continue to evaluate various acquisitions and strategic partnerships, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing drug programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or drug candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or drugs sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

As an FPI, we are exempt from a number of rules under the U.S. securities laws and are permitted to file less information with the SEC than U.S. public companies.

We are an FPI, as defined in the SEC rules and regulations and, consequently, we are not subject to all of the disclosure requirements applicable to companies organized within the United States. For example, we are exempt from certain rules under the Exchange Act, that regulate disclosure obligations and procedural requirements related to the solicitation of proxies, consents or authorizations applicable to a security registered under the Exchange Act. In addition, our officers and directors are exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchases and sales of our securities. Moreover, we are not required to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. public companies. Accordingly, there may be less publicly available information concerning our company than there is for U.S. public companies.

As an FPI, we will file an annual report on Form 20-F within four months of the close of each fiscal year ended December 31 and reports on Form 6-K relating to certain material events promptly after we publicly announce these events. However, because of the above exemptions for FPIs, our ADS holders will not be afforded the same protections or information generally available to investors holding shares in public companies organized in the United States.

While we are an FPI, we are not subject to certain Nasdaq corporate governance rules applicable to U.S. listed companies.

We are entitled to rely on a provision in Nasdaq's corporate governance rules that allows us to follow English corporate law and the Companies Act with regard to certain aspects of corporate governance. This allows us to follow certain corporate governance practices that differ in significant respects from the corporate governance requirements applicable to U.S. companies listed on Nasdaq.

For example, we are exempt from Nasdaq regulations that require a listed U.S. company to (i) have a majority of the board of directors consist of independent directors, (ii) require non-management directors to meet on a regular basis without management present and (iii) promptly disclose any waivers of the code for directors or executive officers that should address certain specified items.

In accordance with our Nasdaq listing, our audit committee is required to comply with the provisions of Section 301 of the Sarbanes-Oxley Act and Rule 10A-3 of the Exchange Act, both of which are also applicable to Nasdaq-listed U.S. companies. Because we are an FPI, however, our audit committee is not subject to additional

Nasdaq requirements applicable to listed U.S. companies, including an affirmative determination that all members of the audit committee are "independent," using more stringent criteria than those applicable to us as an FPI. Furthermore, Nasdaq's corporate governance rules require listed U.S. companies to, among other things, seek shareholder approval for the implementation of certain equity compensation plans and issuances of ordinary shares, which we are not required to follow as an FPI.

We may lose our FPI status, which would then require us to comply with the Exchange Act's domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

As an FPI, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. We may no longer be an FPI as early as June 30, 2019 (the end of our second fiscal quarter in the fiscal year following this Nasdaq listing), which would require us to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers as of January 1, 2019. In order to maintain our current status as an FPI, either (a) a majority of our ADSs must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors cannot be U.S. citizens or residents, (ii) more than 50% of our assets must be located outside the United States and (iii) our business must be administered principally outside the United States. If we lose our status as an FPI, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for FPIs. We may also be required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as an FPI. As a result, we expect that a loss of FPI status would increase our legal and financial compliance costs and is likely to make some activities highly time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

We are an emerging growth company within the meaning of the Securities Act of 1933 and will take advantage of certain reduced reporting requirements.

We are an EGC, as defined in the JOBS Act. For as long as we continue to be an EGC, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not EGCs, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. As an EGC, we are required to report only two years of financial results and selected financial data compared to three and five years, respectively, for comparable data reported by other public companies. We may take advantage of these exemptions until we are no longer an EGC. We could be an EGC for up to five years, although circumstances could cause us to lose that status earlier, including if the aggregate market value of our ADSs held by non-affiliates exceeds $700 million as of any June 30 (the end of our second fiscal quarter) before that time, in which case we would no longer be an EGC as of the following December 31 (our fiscal year-end). We cannot predict if investors will find our ADSs less attractive because we may rely on these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and the price of our ADSs may be more volatile in the event that we decide to make an offering of our ADSs following our Nasdaq listing.

If we fail to establish and maintain proper internal controls, our ability to produce accurate financial statements or comply with applicable regulations could be impaired.

Section 404(a) of the Sarbanes-Oxley Act, or Section 404(a), requires that beginning with our second annual report following our initial public offering, management assess and report annually on the effectiveness of our internal control over financial reporting and identify any material weaknesses in our internal control over financial reporting. Although Section 404(b) of the Sarbanes-Oxley Act, or Section 404(b), requires our independent registered public accounting firm to issue an annual report that addresses the effectiveness of our internal control over financial reporting, we have opted to rely on the exemptions provided in the JOBS Act, and consequently will not be required to comply with SEC rules that implement Section 404(b) until such time as we are no longer an EGC.

We expect our first Section 404(a) assessment will take place for our annual report for the fiscal year ending December 31, 2019. The presence of material weaknesses could result in financial statement errors which, in turn, could lead to errors in our financial reports, delays in our financial reporting, which could require us to restate our operating results or our auditors may be required to issue a qualified audit report. We might not identify one or more material weaknesses in our internal controls in connection with evaluating our compliance with Section 404 (a). In order to maintain and improve the effectiveness of our disclosure controls and procedures and internal control over financial reporting, we will need to expend significant resources and provide significant management oversight.

Implementing any appropriate changes to our internal control may require specific compliance training of our directors and employees, entail substantial costs in order to modify our existing accounting systems, take a significant period of time to complete and divert management's attention from other business concerns. These changes may not, however, be effective in maintaining the adequacy of our internal control.

If either we are unable to conclude that we have effective internal control over financial reporting or, at the appropriate time, our independent auditors are unwilling or unable to provide us with an unqualified report on the effectiveness of our internal control over financial reporting as required by Section 404(b), then in the event we have decided to make an offering of our ADSs following our Nasdaq listing, investors may lose confidence in our operating results, the price of our ADSs could decline and we may be subject to litigation or regulatory enforcement actions. In addition, if we are unable to meet the requirements of Section 404, we may not be able to remain listed on Nasdaq.

Pursuant to Section 404, we will be required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To prepare for eventual compliance with Section 404, once we no longer qualify as an EGC, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Our 10% or more stockholders and management own a significant percentage of our stock and are able to exercise significant influence over matters subject to stockholder approval.

As of the date of this prospectus, our executive officers, directors and 10% or more stockholders, together with their respective affiliates, owned approximately 49% of our outstanding securities. Accordingly, this group of security holders will be able to exert a significant degree of influence over our management and affairs and over matters requiring security holder approval, including the election of our Board of Directors, future issuances of our securities, declaration of dividends and approval of other significant corporate transactions. As a result, if these shareholders were to choose to act together, they would be able to exert significant influence over matters submitted to our shareholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would exercise sufficient voting power to influence the election of directors and approve any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other shareholders may desire.

Panetta Partners Limited, Planwise Group Limited and Gabriele Cerrone, together the Cerrone Concert Party, are considered to be a "concert party" for the purposes of the Takeover Code. Following this offering, the Cerrone Concert Party holds shares carrying voting rights equal to approximately 42.6%. Accordingly, the Cerrone Concert Party will not, save in limited circumstances, be able to acquire further interests in shares carrying voting rights

without being obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights.

ADS holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could augur less favorable results to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that holders and beneficial owners of ADSs irrevocably waive the right to a trial by jury in any legal proceeding arising out of or relating to the deposit agreement or the ADSs, including claims under federal securities laws, against us or the depositary to the fullest extent permitted by applicable law. If this jury trial waiver provision is prohibited by applicable law, an action could nevertheless proceed under the terms of the deposit agreement with a jury trial. To our knowledge, the enforceability of a jury trial waiver under the federal securities laws has not been finally adjudicated by a federal court. However, we believe that a jury trial waiver provision is generally enforceable under the laws of the State of New York, which govern the deposit agreement, by a court of the State of New York or a federal court, which have non-exclusive jurisdiction over matters arising under the deposit agreement, applying such law. In determining whether to enforce a jury trial waiver provision, New York courts and federal courts will consider whether the visibility of the jury trial waiver provision within the agreement is sufficiently prominent such that a party has knowingly waived any right to trial by jury. We believe that this is the case with respect to the deposit agreement and the ADSs. In addition, New York courts will not enforce a jury trial waiver provision in order to bar a viable setoff or counterclaim sounding in fraud or one which is based upon a creditor's negligence in failing to liquidate collateral upon a guarantor's demand, or in the case of an intentional tort claim (as opposed to a contract dispute), none of which we believe are applicable in the case of the deposit agreement or the ADSs. No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any provision of the federal securities laws. If you or any other holder or beneficial owner of ADSs brings a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and / or the depositary. If a lawsuit is brought against us and / or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may augur different results than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

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. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

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

Under the Internal Revenue Code of 1986, or the Internal Revenue Code, we will be a PFIC for any taxable year in which either (1) 75% or more of our gross income consists of "passive income" or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income generally 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 if it held its proportionate share of the assets and received directly its proportionate share of the income of such other corporation. If we are a PFIC for any taxable year during which a U.S. Holder (as defined below under "Material Tax Considerations-Material U.S. Federal Income Tax Considerations for U.S. Holders") holds our shares, the U.S. Holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements.

We believe that we were a PFIC for our taxable year ended December 31, 2018 but cannot provide any assurances regarding our PFIC status for any past, current or future taxable years. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies which in some circumstances are unclear and subject to varying interpretation. In particular, the characterization of our assets as active or passive may depend in part on our current and intended future business plans, which are subject to change. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how, and how quickly, we spend the cash we raise in any offering.

In certain circumstances, a U.S. Holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making a qualified electing fund, or QEF, election to include in income its pro rata share of the corporation's income on a current basis. However, a U.S. Holder may make a QEF election with respect to our ordinary shares or ADSs only if we agree to furnish such U.S. Holder annually with a PFIC annual information statement as specified in the applicable U.S. Treasury Regulations. We currently do not intend to prepare or provide the information that would enable U.S. Holders to make a QEF election if we are treated as a PFIC for any taxable year, and prospective investors should assume that a QEF election will not be available.

For further discussion of the PFIC rules and the adverse U.S. federal income tax consequences in the event we are classified as a PFIC, see the section of this report entitled "Material Tax Considerations-Material U.S. Federal Income Tax Considerations for U.S. Holders."

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 a U.K. resident trading entity, we are subject to U.K. corporate taxation. Due to the nature of our business, we have generated losses since inception. As of December 31, 2018, we had cumulative carryforward tax losses of $19.6 million. Subject to any relevant restrictions, we expect these to be available to carry forward and offset against future operating profits. As a company that carries out extensive research and development activities, we benefit from the U.K. research and development tax credit regime for small and medium-sized companies, whereby we are able to surrender the trading losses that arise from our qualifying research and development activities for a payable tax credit of up to 33.35% of eligible research and development expenditures. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects. Certain subcontracted qualifying research expenditures are eligible for a cash rebate of up to 21.67%. The majority of our pipeline research, clinical trials management and manufacturing development

activities are eligible for inclusion within these tax credit cash rebate claims. Our ability to continue to claim payable research and development tax credits in the future may be limited because we may no longer qualify as a small or medium-sized company.

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

Changes and uncertainties in the tax system in the countries in which we have operations could materially adversely affect our financial condition and results of operations, and reduce net returns to our shareholders.

Our tax position could be adversely impacted by changes in tax rates, tax laws, tax practice, tax treaties or tax regulations or changes in the interpretation thereof by the tax authorities in the United Kingdom, the United States and other jurisdictions as well as being affected by certain changes currently proposed by the Organization for Economic Co-operation and Development and their action plan on Base Erosion and Profit Shifting. Such changes may become more likely as a result of recent economic trends in the jurisdictions in which we operate, particularly if such trends continue.

Our actual effective tax rate may vary from our expectation and that variance may be material. A number of factors may increase our future effective tax rates, including: (1) the jurisdictions in which profits are determined to be earned and taxed; (2) the resolution of issues arising from any future tax audits with various tax authorities; (3) changes in the valuation of our deferred tax assets and liabilities; (4) increases in expenses not deductible for tax purposes, including transaction costs and impairments of goodwill in connection with acquisitions; (5) changes in the taxation of share-based compensation; (6) changes in tax laws or the interpretation of such tax laws, and changes in generally accepted accounting principles; and (7) challenges to the transfer pricing policies related to our structure.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, Her Majesty's Revenue & Customs, or HMRC, the U.S. Internal Revenue Service, or IRS, 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 methodologies for valuing developed technology and 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, for example where there has been a technical violation of contradictory laws and regulations that are relatively new and have not been subject to extensive review or interpretation, in which case we expect that we might contest such assessment. High-profile companies can be particularly vulnerable to aggressive application of unclear requirements. Many companies must negotiate their tax bills with tax inspectors who may demand higher taxes than applicable law appears to provide. 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.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains statements that constitute forward-looking statements. Many of the forward-looking statements contained in this prospectus can be identified by the use of forward-looking words such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “plan,” “potential” and “should,” among others.

Forward-looking statements appear in a number of places in this prospectus and include, but are not limited to, statements regarding our intent, belief, or current expectations. Forward-looking statements are based on our management’s beliefs and assumptions and on information currently available to our management. Such statements are subject to substantial risks and uncertainties, and actual results may differ materially from those expressed or implied in the forward-looking statements due to various important factors, including, but not limited to, those identified under “Risk Factors.” In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a guarantee by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

Forward-looking statements include, but are not limited to, statements about:

- the development of Milciclib, Foralumab and any of our other product candidates, including statements regarding the timing of initiation, completion and the outcome of clinical studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- our ability to obtain and maintain regulatory approval of our product candidates, including Milciclib and Foralumab, in the indications for which we plan to develop them, and any related restrictions, limitations or warnings in the label of an approved drug or therapy;
- our plans to research, develop, manufacture and commercialize our product candidates;
- the timing of our regulatory filings for our product candidates;
- the size and growth potential of the markets for our product candidates;
- our ability to raise additional capital;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our expectations regarding our ability to obtain and maintain intellectual property protection;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third party suppliers and manufacturers and their ability to perform adequately;
- our estimates regarding future revenue, expenses and needs for additional financing; and
- regulatory developments in the United States, European Union and other jurisdictions.

Forward-looking statements speak only as of the date they are made, and we do not undertake any obligation to update them in light of new information or future developments or to release publicly any revisions to these statements in order to reflect later events or circumstances or to reflect the occurrence of unanticipated events.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

MARKET AND INDUSTRY DATA

Certain industry data and market data included in this prospectus were obtained from independent third-party surveys, market research, publicly available information, reports of governmental agencies, and industry publications and surveys. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. We believe that the information from these industry publications and surveys included in this prospectus is reliable. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of factors, including those described in "Risk Factors." These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

TRADEMARKS, SERVICE MARKS AND TRADENAMES

Solely for convenience, the trademarks, service marks, logos and trade names referred to in this prospectus are without the ® and ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensors to these trademarks, service marks, and trade names. For the avoidance of doubt, "Tiziana," the Tiziana logo and other trademarks or service marks of Tiziana Life Sciences plc appearing in this prospectus are the property of Tiziana or our subsidiaries. This prospectus contains additional trademarks, service marks, and trade names of others, which are the property of their respective owners. All trademarks, service marks, and trade names appearing in this prospectus are, to our knowledge, the property of their respective owners. We do not intend our use or display of other companies' trademarks, service marks, copyrights, or trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately $2.4 million, or approximately $2.8 million if the underwriters exercise their over-allotment option in full, assuming a public offering price of $6.32 per ADS, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

Each $1.00 increase (decrease) in the public offering price per ADS would increase (decrease) our net proceeds, after deducting estimated underwriting discounts and commissions and offering expenses, by approximately $0.4 million (assuming no exercise of the over-allotment option by the underwriters).

We intend to use the net proceeds from the offering to fund our planned clinical trials, manufacturing and process development, analytical testing, regulatory expenses and for general corporate purposes, including working capital, as follows:

- approximately $2.0 million to advance the clinical development of Foralumab, which we expect will be sufficient to complete a Phase 1 trial evaluating oral administration of Foralumab in healthy subjects ($1.0 million) and to commence a Phase 2 trial for nasal administration of Foralumab for treatment of progressive MS patients ($1.0 million)
- and the remainder ($0.4 million) to fund our other research and development programs, working capital and other general corporate purposes.

The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. We may also use a portion of the net proceeds to in-license, acquire, or invest in additional products or assets, businesses, or technologies, although currently we have no specific agreements, commitments, or understandings in this regard. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the closing of this offering or the amounts that we will actually spend on the uses set forth above. Predicting the costs necessary to develop product candidates can be difficult. The amounts and timing of our actual expenditures and the extent of clinical development may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from ongoing clinical trials or clinical trials we may commence in the future, as well as any collaborations that we may enter into with third parties and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

We anticipate that our existing cash resources, together with the net proceeds from the offering, will enable us to fully fund our operating expenses for the planned trials outlined above and our planned capital expenditure requirements for at least the 12 months following the date of this prospectus. We have based this estimate on assumptions that may prove to be incorrect, and we could use our available capital resources sooner than we currently expect.

Pending their use, we plan to invest the net proceeds from the offering in short- and intermediate-term interest-bearing obligations and certificates of deposit. The goal with respect to the investment of these net proceeds is capital preservation and liquidity so that such funds are readily available to fund our operations.

DIVIDEND POLICY

We have never paid or declared any cash dividends on our ordinary shares, and we do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Under English law, among other things, we may only pay dividends if we have sufficient distributable reserves (on a non-consolidated basis), which are our accumulated realized profits that have not been previously distributed or capitalized less our accumulated realized losses, so far as such losses have not been previously written off in a reduction or reorganization of capital.

CAPITALIZATION

You should read the information in this "Capitalization" section together with "Selected Consolidated Financial Data," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and the related notes appearing elsewhere in this prospectus.

The table below sets forth our cash and short-term deposits and short-term investments and capitalization as of December 31, 2018 derived from our audited consolidated financial statements included elsewhere in this prospectus:

- on an actual basis;
- on an as adjusted basis to give effect to the sale of 474,683 ADS in this offering at the assumed public price of $6.32 per ADS in this offering, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

	As of December 31, 2018	
(in thousands)	**Actual**	**As Adjusted[1]**
Cash and short-term deposits and short-term investments	$ 5,304	$ 7,710
Equity:		
Issued capital	8,592	8,782
Share premium	40,862	43,078
Other reserves	1,695	1,695
Accumulated loss	(50,630)	(50,630)
Total equity (deficit)	519	2,925
Total capitalization	$ 519	$ 2,925

(1) Each $1.00 increase or decrease in the assumed public offering price of $6.32 per ADS in this offering, would increase or decrease the as adjusted total equity and total capitalization by approximately $0.4 million after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The table above excludes:

- 5,236,166 ordinary shares issuable upon the exercise of share options outstanding as of December 31, 2018 at exercise prices of between $0.19 and $2.30 per ordinary share;
- 18,617,403 ordinary shares that may be issued under our existing share option plans, as described in "Management — The Tiziana Life Sciences plc Employee Share Plan with Non-Employee Sub-Plan and US Sub-Plan," as of December 31, 2018; and
- 3,617,905 ordinary shares that may be issued upon the exercise of warrants to purchase ordinary shares outstanding as at December 31, 2018 at exercise prices of between $0.62 and $3.10 per ordinary share.

DILUTION

If you invest in our ADSs in this offering, your interest will be diluted to the extent of the difference between the public offering price per ADS paid by purchasers in this offering and our pro forma as adjusted net tangible book value per ADS after completion of this offering.

At December 31, 2018, we had a historical net tangible book value of $0.004 per ordinary share (equal to $0.04 per ADS). Net tangible book value per ordinary share represents the amount of our total assets less our total liabilities, excluding goodwill and other intangible assets, divided by the total number of our ordinary shares outstanding as of December 31, 2018.

After giving effect to the sale by us of 474,683 ADS in this offering at the assumed public price of $6.32 per ADS in this offering, which was the last reported sale price of our ADSs on the Nasdaq Global Market on September 19, 2019, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value per ordinary share as of December 31, 2018 would have been $0.021 (equal to $0.02 per ADS). This represents an immediate increase in net tangible book value of $0.02 per ordinary share (equal to $0.17 per ADS) to existing shareholders and an immediate dilution of $0.61 per ordinary share (equal to $6.11 per ADS) to new investors purchasing ADSs in this offering. Dilution per ADS or ordinary share to new investors is determined by subtracting the as adjusted net tangible book value per ADS or ordinary share after this offering from the assumed public offering price per ADS paid by new investors.

The following table illustrates this dilution to new investors purchasing ADSs in this offering.

Assumed public offering price per ADS			$	6.32
Net tangible book value per ADS	$	0.04		
Increase in net tangible book value per ADS attributable to this offering	$	0.17		
As adjusted net tangible book value per ADS after this offering				0.21
Dilution per ADS to new investors in this offering			$	6.11

If the underwriters exercise in full their over-allotment option to purchase an additional 71,202 ADSs, our as adjusted net tangible book value after this offering would be $0.02 per ordinary share (equal to $0.24 per ADS), representing an immediate increase in as adjusted net tangible book value of $0.02 per ordinary share (equal to $0.20 per ADS) to existing shareholders and immediate dilution of $0.61 per ordinary share (equal to $6.08 per ADS).

Each $1.00 increase (decrease) in the assumed public offering price of $6.32 per ADS in this offering, would increase (decrease) the as adjusted net tangible book value after this offering by $0.03 per ADS and the dilution to new investors in this offering by $0.97 per ADS, assuming that the number of ADSs offered by us in this offering, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The tables above are based on 136,463,818 ordinary shares outstanding as of December 31, 2018. The tables above exclude:

- 5,236,166 ordinary shares issuable upon the exercise of share options outstanding as of December 31, 2018 at exercise prices of between $0.19 and $2.30 per ordinary share;
- 18,617,403 ordinary shares that may be issued under our existing share option plans, as described in “Management — The Tiziana Life Sciences plc Employee Share Plan with Non-Employee Sub-Plan and US Sub-Plan,” as of December 31, 2018; and
- 3,617,905 ordinary shares that may be issued upon the exercise of warrants to purchase ordinary shares outstanding as at December 31, 2018 at exercise prices of between $0.62 and $3.10 per ordinary share.

To the extent that share options or warrants are exercised, or we issue additional ADSs or ordinary shares in the future, there will be further dilution to investors participating in this offering. In addition, we may choose to raise additional capital because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our shareholders.

SELECTED CONSOLIDATED FINANCIAL DATA

The following tables set forth our selected consolidated financial data for the periods indicated.

We maintain our books and records in Pounds Sterling, and we prepare our financial statements in accordance with IFRS as issued by the IASB. We report our financial results in U.S. dollars.

Consolidated Statement of Operations and Comprehensive Loss Data:

	Years Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands except share and per share data)				
Operating expenses:					
Research and development	$ (5,510)	$ (6,015)	$ (4,007)	$ (9,609)	$ (1,309)
General and administrative	(4,417)	(4,602)	(5,872)	(3,557)	(4,189)
Total operating expenses	(9,927)	(10,617)	(9,879)	(13,166)	(5,497)
Loss from operations	(9,927)	(10,617)	(9,879)	(13,166)	(5,497)
Other income (expense), net	(12)	(12)	(12)	(28)	(86)
Tax provision	1,945	1,912	121	—	99
Net loss attributable to ordinary shareholders	(7,994)	(8,716)	(9,770)	(13,193)	(5,484)
Other comprehensive loss:					
Foreign currency translation adjustment	(20)	70	650	3,063	(942)
Total comprehensive loss	(8,014)	(8,646)	(9,120)	(10,130)	(6,426)
Basic and diluted net loss per ordinary share	(0.06)	(0.09)	(0.11)	(0.15)	(0.24)

Consolidated Balance Sheet Data:

	As of December 31,				
	2018	2017	2016	2015	2014
	(in thousands except share and per share data)				
Cash and cash equivalents	$ 5,304	$ 64	$ 5,802	$ 13,128	$ 3,530
Working capital	514	(2,302)	4,054	12,540	2,768
Total assets	6,920	2,471	6,231	13,640	3,832
Total shareholders’ equity/(deficit)	519	(2,278)	4,088	12,540	2,768

You should read the following discussion and analysis of our financial condition and results of operations together with "Selected Consolidated Financial Data" and our consolidated financial statements and the related notes thereto appearing in this prospectus. We present our consolidated financial statements in U.S. dollars and in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB.

Some information included in this discussion and analysis, including statements regarding industry outlook, our expectations regarding our future performance, liquidity and capital resources and other statements regarding our plans and strategy for our business and related financing, are forward-looking statements. These forward-looking statements are subject to numerous risks and uncertainties. You should read the "Risk Factors" section of this prospectus for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

We maintain our books and records in Pounds Sterling, and we prepare our financial statements in accordance with IFRS as issued by the IASB. We report our financial results in U.S. dollars.

Overview

Introduction to Tiziana

We are a biotechnology company that is focused on the discovery and development of novel molecules and related diagnostics to treat high unmet medical needs in oncology and immunology. Our mission is to design and deliver next generation therapeutics and diagnostics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. We employ a lean and virtual research and development, or R&D, model using highly experienced teams of experts for each business function to maximize value accretion by focusing resources on the drug discovery and development processes.

Our lead product candidate in immunology is Foralumab (TZLS-401), which we believe is the only fully human anti-CD3 mAb in clinical development. We believe that based on the concepts of mucosal tolerance, oral or nasal administration of Foralumab has the potential to reduce inflammation while minimizing the toxicity and related side effects. We believe the switch from intravenous inflammation to oral and nasal administration is a 'game changer" for treatment with mAbs as it could improve patient's compliance and safety. MAbs represent a single pure antibody produced by single clones and are an important class of human therapeutics for treating cancers and autoimmune diseases. The global market opportunity for mAb therapeutics is greater than $86 billion. Generation of antibodies for use in humans developed in animals, lead to strong, immune responses limiting their effectiveness and potentially leading to severe side effects. A process known as "humanization" removes most of the animal components of the antibody thereby lowering the immune response from the human immune system. The entire omission of other animal material, as in fully human antibodies, is the optimal goal to avoid incompatibility with the human immune system.

Our lead product candidate in oncology is Milciclib (TZLS-201), which is an orally bioavailable, small molecule broad spectrum inhibitor of cyclin-dependent kinases, or CDKs, and Src family kinases. CDKs are a highly conserved family of enzymes that phosphorylate a specific group of proteins that are involved in regulating the cell cycle. The cell cycle is a series of events that takes place in cells leading to division and duplication of its DNA to produce two daughter cells. Src family kinases are non-receptor tyrosine kinase proteins encoded by the Src gene also involved in regulating cell growth and potential transformation of normal cells to cancer cells. We also have a drug discovery pipeline of small molecule NCEs, and biologics. Milciclib has Orphan Drug Designation (ODD) in the U.S. and EU for thymic cancer (thymic epithelial tumor or TET) such as thymic carcinoma and thymoma.

We are developing Foralumab, for which we in-licensed the intellectual property from Novimmune, in December 2014, as a potential treatment for NASH, and Crohn's disease as well as neurodegenerative diseases such as MS. To date, Foralumab has been studied in one Phase 1 and two Phase 2a clinical trials conducted by Novimmune in 68 patients dosed by the intravenous route of administration. In the Novimmune intravenous trails, Foralumab was observed to be well-tolerated and immunologic findings are ongoing. In the Novimmune intravenous trials Foralumab was well tolerated and produced immunologic effects consistent with clinical benefits while demonstrating mild to moderate IRRs.

We planned to first investigate orally and nasally administered Foralumab for its safety and immunomodulatory activity in healthy volunteers in separate Phase 1 clinical trials. A Phase I single site, double-blind, placebo-controlled, dose-ranging clinical study dosed intranasally in healthy volunteers was initiated in November 2018 to evaluate safety and biomarkers of immunomodulation of clinical responses planned in healthy volunteers to dose Foralumab intranasally. in collaboration with Brigham and Women's Hospital, Harvard Medical School, Boston, MA. This clinical trial was recently completed in July 2019 in which 18 subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated, and no drug related safety issues were reported at any of the doses. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. In addition, we submitted an IND on March 18, 2019 for the oral formulation, to the FDA. The FDA requested safety data from the phase 1 trial with nasal administration of Foralumab to justify the proposed dose-range for the phase 1 trial with oral administration of enteric-coated capsules of Foralumab in healthy volunteers. We withdrew the IND on April 17, 2019. A third IND was submitted to the FDA on July 23, 2019 for a Phase I trial in healthy volunteers using orally administered Foralumab with an intent to treat pMS. On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. Based on successful Phase 1 data, we intend to conduct a Phase 2 study using Crohn's Disease patients starting in the second half of 2020 and file an IND for a Phase 2 trial using NASH patients.

We are developing Milciclib, for which we in-licensed the intellectual property from Nerviano, in January 2015, as a potential treatment for HCC. A novel feature of Milciclib is its ability to reduce levels of microRNAs, miR-221 and miR-222. MicroRNAs are small RNA molecules that play a significant role in the regulation of gene expression. miR-221 and miR-222 are believed to be linked to the development of blood supply in cancer tumors. Levels of these microRNAs are consistently elevated in HCC patients and may contribute towards resistance to treatment with Sorafenib, a multikinase inhibitor (a drug which may inhibit the cellular division and proliferation associated with certain cancers) often prescribed to HCC patients as the SOC. To date, Milciclib has been studied in a total of eight Phase 1 and Phase 2 clinical trials in a total of 316 patients conducted by Nerviano. In these trials, Milciclib was well-tolerated with minimal adverse events. We initiated a Phase 2a trial for Milciclib as a monotherapy in patients with HCC in the third quarter of 2017. This trial is a single-arm, repeated-dose (100 mg once daily; 4 days on/3 days off every 4 weeks defining each cycle), 6-month duration study to evaluate the safety, tolerability and anti-tumor activity of Milciclib in Sorafenib-refractory or intolerant patients with unresectable or metastatic advanced HCC, the most common form of liver cancer. Enrollment of 31 patients in Italy, Greece, and Israel was completed in November 2018.

In March 2019, the IDMC reviewed safety data from patients as of February 26, 2019 and concluded that the administration of Milciclib to patients with advanced HCC was not associated with unexpected signs or signals of toxicity. 28 out of 31 treated patients were evaluable, 14 completed the 6-month duration study. The most frequent adverse events such as diarrhea, ascites, nausea, fatigue, asthenia, fever, ataxia, headache, and rash were manageable. No drug-related deaths were recorded.

Cumulative Patient Exposure in Milciclib Clinical Studies:

Clinical Study	Drug	Indication	Number of Patients Treated
CDKO-125a-001 Phase 1	Milciclib	Solid tumors	37
CDKO-125a-002 Phase 1 / Phase 2	Milciclib	Malignant glioma (Phase 1) Glioblastoma (Phase 2)	62
CDKO-125a-003 Phase 1	Milciclib	Solid tumors	30
CDKO-125a-004 Phase 1	Milciclib + gemcitabine	Solid tumors	16
CDKO-125a-005/-006/-007 Phase 2	Milciclib	Malignant Pleural Mesothelioma (-005) Thymic carcinoma and malignant thymoma (-006 and -007)	140
CDKO-125a-010 Phase 2	Milciclib	HCC monotherapy	31
		Total Patients Exposed	**316**

Source: Development Safety Update Report No. 8, February 28, 2019, Tiziana Life Sciences plc; Investigator Brochure, Version 14, 2019.

Since our inception in March 2014, we have devoted substantially all our resources to conducting preclinical studies and clinical trials, organizing and staffing our company, business planning, raising capital and establishing our intellectual property portfolio. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations to date primarily with proceeds from the sale of ordinary shares. Through December 31, 2018, we had received net cash proceeds of $39.7 million from sales of our ordinary shares, issuance of convertible loans, short term loans and warrants.

Since our inception, we have incurred operating losses. Our net loss after taxation was $8.0 million for the year ended December 31, 2018, $8.7m for the year ended December 31, 2017 and $9.8m for the year ended December 31, 2016 respectively. As of December 31, 2018, we had cash and cash equivalents of $5.3 million.

We expect to continue to incur significant expenses for the foreseeable future as we advance our product candidates through preclinical and clinical development and seek regulatory approval and pursue commercialization of any approved product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution.

Trend information

Recent developments

In March 2019, we announced the submission of an IND to the FDA (Liver Division) to initiate a Phase 1 clinical trial of enteric-coated capsules of Foralumab in healthy volunteers. This single-site clinical study is expected to enroll 36 subjects and it will be conducted at the BWH, Harvard Medical School. The primary objective of this study is to evaluate safety, tolerability and immunomodulatory effects of orally administered Foralumab in healthy volunteers with a dose-escalating regimen comprising of placebo, 1.25, 2.50 and 5.0 mg/day for 5 consecutive days. The trial will also investigate the established biomarkers with anti-inflammatory effects and stimulation of T regulatory cells. The FDA requested safety data from the phase 1 trial with nasal administration of Foralumab to justify the proposed dose-range for the phase 1 trial with oral administration of enteric-coated capsules of Foralumab in healthy volunteers. We withdrew the current IND on April 17, 2019. A Type B pre-IND meeting was held with the FDA (GI division, Crohn’s Disease) on July 24, 2019. The FDA provided clear guidance on design of the clinical trials in healthy subjects. A revised IND will be submitted following FDA review of safety data from the nasal trial. The FDA (Neurology Division) approved initiation of a Phase I trial of orally administered enteric-coated capsule formulation of Foralumab in healthy subjects in the second half of 2019 following submission of an IND on July 23, 2019 with an intent to treat pMS patients. We expect to initiate a Phase 1 trial of the oral, enteric capsule formulation of Foralumab in healthy subjects in the second half of 2019. Based on successful Phase 1 data, we intend to conduct a Phase 2 study using Crohn’s Disease patients starting in the second half of 2020 and file an IND for a Phase 2 trial using NASH patients.

Legal proceedings

From time to time, we may be a party to litigation or subject to claims incident to the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we currently believe that the final outcome of these ordinary course matters will not have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. We are not currently a party to any material legal proceedings.

Foreign currency translations

Items included in the financial statements are measured using the currency of the primary economic environment in which the entity operates (the functional currency). The consolidated financial statements are presented in U.S. dollars, which is our presentation currency.

Foreign currency transactions are translated into the functional currency using exchange rates prevailing at the dates of the transactions. Foreign exchange gains and losses resulting from the settlement of foreign currency transactions and from the translation at year-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recognized in the income statement.

The financial statements of overseas subsidiary undertakings are translated into U.S. dollars on the following basis:

- Assets and liabilities at the rate of exchange ruling at the year-end date.
- Profit and loss account items at the average rate of exchange for the year.

Exchange differences arising from the translation of the net investment in foreign entities, borrowings and other currency instruments designated as hedges of such investments, are taken to equity (and recognized in the statement of comprehensive income) on consolidation.

Components of Our Results of Operations

Revenues

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the near future. If our development efforts for our product candidates are successful and result in regulatory approval, we may generate revenue in the future from product sales.

Operating Expenses

Research and Development Expenses

R&D expenses consist primarily of costs incurred in connection with the R&D of our product candidates and are expensed as incurred. These expenses consist of:

- expenses incurred under agreements with CROs, CMOs, as well as investigative sites and consultants that conduct our clinical trials, preclinical studies and other scientific development services;
- manufacturing scale-up expenses and the cost of acquiring and manufacturing materials for preclinical studies and clinical trial materials;
- employee-related expenses, including salaries, related benefits, travel and share-based compensation expense for employees engaged in R&D functions;
- costs related to compliance with regulatory requirements;
- facilities costs, depreciation and other expenses, which include rent and utilities; and
- fees for maintaining our third-party licensing agreements.

We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers.

Our direct R&D expenses are tracked on a program-by-program basis for our product candidates and consist primarily of external costs, such as fees paid to outside consultants, CROs and CMOs in connection with our preclinical development, manufacturing and clinical development activities. Our direct R&D expenses by program also include fees incurred under our license agreements. We do not allocate employee costs or facility expenses,

including depreciation or other indirect costs, to specific programs because these costs are deployed across multiple programs and, as such, are not separately classified. We use internal resources primarily to oversee the R&D as well as for managing our preclinical development, process development, manufacturing and clinical development activities. These employees work across multiple programs and, therefore, we do not track their costs by program.

The table below summarizes our R&D expenses incurred by program:

	Year ended December 31,	
	2018	2017
	(in thousands)	
Direct research and development expense by program:		
Foralumab	$ 2,261	$ 1,202
Milciclib	2,581	2,625
BCL-3	—	347
TZLS-0501	—	—
StemPrintER	166	1,201
Total direct research and development expense	$ 5,008	$ 5,375
Indirect research and development expense	502	640
Total research and development expense	$ 5,510	$ 6,015

R&D 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 and related product manufacturing expenses. As a result, we expect that our R&D expenses will increase substantially over the next several years as we increase personnel costs and prepare for regulatory filings related to our product candidates. We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

The successful development and commercialization of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our product candidates or when, if ever, material net cash inflows may commence from any of our product candidates. This uncertainty is due to the numerous risks and uncertainties associated with development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our preclinical development activities, clinical trials and other R&D activities;
- establishing an appropriate safety profile with IND- and CTA-enabling studies;
- successful patient enrollment in, and the initiation and completion of, clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials and for commercial launch;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others; and
- maintaining a continued acceptable safety profile of the product candidates following approval.

We may never succeed in achieving regulatory approval for any of our product candidates. We may obtain unexpected results from our clinical trials. We may elect to discontinue, delay or modify clinical trials.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, related benefits, travel and share-based compensation expense for personnel in executive, finance and administrative functions. General and administrative expenses also include professional fees for legal, consulting, accounting and audit services.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance, director and officer insurance costs, as well as investor and public relations expenses associated with being a public company.

Other Income (Expense)

Other expense consists of interest on a convertible loan note.

Taxation

The tax expense for a period represents the total of current taxation and deferred taxation. The charges in respect of current taxation are based on the estimated taxable profit for the relevant year. Taxable profit for the year is based on the profit as shown in the income statement, as adjusted for items of income or expenditure which are not deductible or chargeable for tax purposes. The current tax liability for the year is calculated using tax rates which have either been enacted or substantively enacted at the relevant balance sheet date.

Under UK tax legislation, small and medium entity R&D relief allows us to claim back up to 14.5% of our surrenderable losses as a tax cash credit.

Results of Operations

The results of operations that follow reflect the historic periods under review and should not be taken as indicative of future performance.

Comparison of Years Ended December 31, 2018 and 2017

The following tables summarizes our results of operations for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		
	2018	2017	Change
	(in thousands)		
Operating Expenses:			
Research and development	$ (5,510)	$ (6,015)	$ 505
General and administrative	$ (4,417)	$ (4,601)	$ 184
Total Operating Expenses	$ (9,927)	$ (10,616)	$ 689
Other Income/ (Expense)	(12)	(12)	—
Income tax provision	1,945	1,912	33
Loss for the year	$ (7,994)	$ (8,716)	$ 722
Other comprehensive loss:			
Currency translation	(20)	70	(90)
Comprehensive (Loss)	$ (8,014)	$ (8,646)	$ 632

Research and Development Expenses

Research and development activities were $5.5 million for the year ended December 31, 2018 compared to $6 million for the year ended December 30, 2017. In the year ended December 31, 2018 the research and development activities were focused on the Milciclib and Foralumab projects. The slowdown in activities for StemPrinER enabled an extra $1 million to be used for the continuation of Phase 2 clinical trials in Foralumab.

General and Administrative Expenses

General and administrative expenses were $4.4 million and $4.6 million for the years ended December 30, 2018 and 2017, respectively. Within general and administrative expenses, there were decreases in consultancy fees of $0.2 million.

Income Tax Credit

Income tax credits of $1.9 million and $1.9 million are recognized for the years ended December 31, 2018 and 2017, respectively. The credits are obtained at a rate of 14.5% of 230% of our qualifying research and development expenditure, and the increase in the credit amount was primarily attributable to a true up on the amount claimed for the years ended December 31, 2017, 2016, and 2015.

Liquidity and Capital Resources

Since our inception, we have not generated any revenue and have incurred operating losses and negative cash flows from our operations. We have funded our operations to date primarily with proceeds from the sale of ordinary shares, American Depository Shares, or ADSs, and convertible loan notes.

As of December 31, 2018, we had cash and cash equivalents of $5.3 million.

Through December 31, 2018, we had received net cash proceeds of $39.7 million from sales of our ordinary shares, issuance of convertible loan notes, conversion of warrants and long term loan agreements In November 2018, in our initial public offering in the United States, we received net proceeds of $2.8 million from the issuance and sale of 442,910 American Depositary Shares which represent 4,429,100 ordinary shares.

Cash Flows

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

	Year ended December 31,	
	2018	**2017**
Net cash used in operating activities	$ (4,551)	$ (7,533)
Net cash used in investing activities	—	(1)
Net cash provided by financing activities	10,041	1,542
Effect of exchange rate changes on cash and cash equivalents	(249)	254
Net decrease in cash and cash equivalents	$ 5,241	$ (5,738)

Net Cash Used in Operating Activities

Our use of cash in each of the years ended December 31, 2018 and 2017, resulted primarily from our net losses, adjusted for non-cash charges and changes in components of working capital. Net cash used in operating activities of $4.6 million during the year ended December 31, 2018 decreased by $3.0 million compared to the year ended December 31, 2017. The decrease in net cash used in operating activities was primarily due to the cash inflow from the R&D taxation credit.

Net Cash Used in Investing Activities

During the year ended December 31, 2017, we used $0.1 million of cash in investing activities for the purchases of property and equipment and the acquisition of SharDNA Srl.

Net Cash Provided by Financing Activities

During the years ended December 31, 2018 and 2017, net cash provided by financing activities was $10 million and $1.5 million, respectively, consisting of net cash proceeds from our sale and issuance of ordinary shares and convertible loan notes.

Funding Requirements

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

- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure in anticipation of commercializing any product candidates for which we may obtain marketing approval and intend to commercialize on our own or jointly;
- hire additional clinical, medical and development personnel;
- expand our infrastructure and facilities to accommodate our growing employee base; and
- maintain, expand and protect our intellectual property portfolio.

We believe that our existing cash along with the proceeds from this offering, will enable us to fund our operating expenses and capital expenditure requirements for at least the 12 months following the date of this prospectus. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. If we receive regulatory approval for our other product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical product candidates, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements will depend on and could increase significantly as a result of many factors, including:

- the scope, progress, outcome and costs of our preclinical development activities, clinical trials and other research and development activities;
- the costs, timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- the costs of future activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sale of our products, should any of our product candidates receive marketing approval;
- the costs and timing of hiring new employees to support our continued growth;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- the extent to which we acquire technologies.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through equity offerings. To the extent that we raise additional capital through the sale of equity, your ownership interest will be diluted. If we raise additional funds through other third-party funding, collaboration agreements, strategic alliances, licensing arrangements 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. If we are unable to raise additional funds through equity financings 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 products or product candidates that we would otherwise prefer to develop and market ourselves.

Borrowings

On May 15 2018, we entered into a fixed term unsecured loan agreement with an existing shareholder for $127,369 at an interest rate of 8% per annum to be repaid no later than 24 months after the date of the agreement.

On June 22, 2018, we entered into a fixed term unsecured loan agreement with an existing shareholder for $382,107 at an interest rate of 20% per annum to be repaid no later than 24 months after the date of the agreement.

The May 2018 and June 2018 loans were converted into ordinary shares in November 2018.

On August 16, 2017, we completed a conversion of all of our outstanding convertible loan notes through the issuance of 28,455,214 ordinary shares.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements.

Tabular Disclosure of Contractual Obligations

The following table summarizes our contractual commitments and obligations as of December 31, 2018.

As at December 31, 2018

	Payments Due by Period		
(in thousands)	**Total**	**Less than 1 Year**	**Between 1 and 5 Years**
Borrowings	—	—	—
Operating lease obligations	$ 1,114	$ 423	$ 691
Total	$ 1,114	$ 423	$ 691

Overview

We are a biotechnology company that is focused on the discovery and development of novel molecules and related diagnostics to treat high unmet medical needs in oncology and immunology. Our mission is to design and deliver next generation therapeutics and diagnostics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. We employ a lean and virtual research and development, or R&D, model using highly experienced teams of experts for each business function to maximize value accretion by focusing resources on the drug discovery and development processes.

Our lead product candidate in immunology is Foralumab (TZLS-401), which we believe is the only fully human anti-CD3 monoclonal antibody, or mAb, in clinical development. We believe that based on the concepts of mucosal tolerance, oral or intranasal administration of Foralumab has the potential to reduce inflammation while minimizing the toxicity and related side effects. We believe the switch from intravenous administration to oral and nasal administration is a "game changer" for treatment with mAbs as it could improve patient's compliance and safety. MAbs represent a single pure antibody produced by single clones and are an important class of human therapeutics for treating cancers and autoimmune diseases. The global market opportunity for mAb therapeutics is greater than $86 billion. Generation of antibodies for use in humans developed in animals, leads to strong, immune responses limiting their effectiveness and potentially leading to severe side effects. A process known as "humanization" removes most of the animal components of the antibody thereby lowering the immune response from the human immune system. The entire omission of other animal material, as in fully human antibodies, is the optimal goal to avoid incompatibility with the human immune system.

Our lead product candidate in oncology is Milciclib (TZLS-201), which is an orally bioavailable, small molecule broad spectrum inhibitor of cyclin-dependent kinases, or CDKs, and Src family kinases. CDKs are a highly conserved family of enzymes that phosphorylate a specific group of proteins that are involved in regulating the cell cycle. The cell cycle is a series of events that takes place in cells leading to division and duplication of its DNA to produce two daughter cells. Src family kinases are non-receptor tyrosine kinase proteins encoded by the Src gene also involved in regulating cell growth and potential transformation of normal cells to cancer cells. We have a drug discovery pipeline of small molecule new chemical entities, or NCEs, and biologics. Milciclib has Orphan Drug Designation (ODD) in the U.S. and EU for thymic cancer (thymic epithelial tumor or TET) such as thymic carcinoma and thymoma.

We are developing Foralumab, for which we in-licensed the intellectual property from Novimmune SA, or Novimmune, in December 2014, as a potential treatment for non-alcoholic steatohepatitis, or NASH, and Crohn's disease as well as neurodegenerative diseases such as MS. To date, Foralumab has been studied in one Phase 1 and two Phase 2a clinical trials conducted by Novimmune in 68 patients dosed by the intravenous route of administration. In these trials, Foralumab had a favorable safety profile and was well-tolerated with an MTD of 1 mg/dose and produced immunologic effects consistent with potential clinical benefit while demonstrating mild to moderate infusion related reactions, or IRR.

We planned to first investigate orally and nasally administered Foralumab for its safety and immunomodulatory activity in healthy volunteers in separate Phase 1 clinical trials. A Phase I single site, double-blind, placebo-controlled, dose-ranging clinical study dosed intranasally in healthy volunteers was initiated in November 2018 to evaluate safety and biomarkers of immunomodulation of clinical responses planned in healthy volunteers to dose Foralumab intranasally. in collaboration with Brigham and Women's Hospital, Harvard Medical School, Boston, MA. This clinical trial was recently completed in July 2019 in which 18 subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated, and no drug related safety issues were reported at any of the doses. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. In addition, we submitted an IND on March 18, 2019 for the oral formulation, to the FDA. The FDA requested safety data from the phase 1 trial with nasal administration of Foralumab to justify the proposed dose-range for the phase 1 trial with oral administration of enteric-coated capsules of Foralumab in healthy volunteers. We withdrew the IND on April 17, 2019. A third IND was submitted to the FDA on July 23, 2019 for a Phase I trial in healthy volunteers using orally administered Foralumab with an intent to treat pMS. On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. Based on successful Phase 1 data, we intend to conduct a Phase 2 study using Crohn's Disease patients starting in the second half of 2020 and file an IND for a Phase 2 trial using NASH patients.

We are developing Milciclib, for which we in-licensed the intellectual property from Nerviano Medical Sciences S.r.l., or Nerviano, in January 2015, as a potential treatment for hepatocellular carcinoma, or HCC. A novel feature of Milciclib is its ability to reduce levels of microRNAs, miR-221 and miR-222. MicroRNAs are small RNA molecules that play a significant role in the regulation of gene expression. miR-221 and miR-222 are believed to be linked to the development of blood supply (angiogenesis) in cancer tumors. Levels of these microRNAs are consistently elevated in HCC patients and may contribute towards resistance to treatment with Sorafenib, a multikinase inhibitor (a drug which may inhibit the cellular division and proliferation associated with certain cancers) often prescribed to HCC patients as the SOC. To date, Milciclib has been studied in a total of eight Phase 1 and Phase 2 clinical trials in 316 patients. In these trials, Milciclib was well-tolerated with minimal adverse events. We initiated a Phase 2a trial for Milciclib as a monotherapy in patients with HCC in the third quarter of 2017. This trial is a single-arm, repeated-dose (100 mg once daily; 4 days on/3 days off every 4 weeks defining each cycle), 6-month duration study to evaluate the safety, tolerability and anti-tumor activity of Milciclib in Sorafenib-refractory or intolerant patients with unresectable or metastatic advanced HCC, the most common form of liver cancer. Enrollment of 31 patients in Italy, Greece, and Israel was completed in November 2018.

In March 2019, the IDMC reviewed safety data from patients as of February 26, 2019 and concluded that the administration of Milciclib to patients with advanced HCC was not associated with unexpected signs or signals of toxicity. 28 out of 31 treated patients were evaluable, 14 completed the 6-month duration study. The most frequent adverse events such as diarrhea, ascites, nausea, fatigue, asthenia, fever, ataxia, headache, and rash were manageable. No drug-related deaths were recorded.

As per the study protocol, data collection was limited to 6-months. Thus, clinical data were not collected from patients under compassionate use treatment. The clinical activity assessment in evaluable patients was based on the investigators' review using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

- 9 out of 14 patients (64.2%) were approved by their respective ethical committees to continue the treatment.
- 5 of the 9 patients on compassionate use had received Milciclib for a total of 9, 9, 11, 13 and 16 months.
- As of 1 September 2019, the remaining 4 patients continuing the treatment are in their 10^{th}, 11^{th}, 11^{th} and 12^{th} months.
- Both median TTP and PFS were 5.9 months (95% Confidence Interval ("CI") 1.5-6.7 months) out of the 6-months duration of the trial.
- 17 of 28 (60.7%) evaluable patients showed 'Stable Disease' (SD; met at least once in an 8-week interval).
- One patient (3.6%) showed 'Partial Response' (PR, unconfirmed).
- 18 of 28 (64.3%) evaluable patients showed 'Clinical Benefit Rate' defined as CBR=CR+PR+SD (with CR representing Complete Remission).

Since overexpression of CDKs and dysregulation in pRB pathway (regulates transcription factors critical for cell cycle progression) are prominently associated with tumor cell resistance to certain chemotherapeutic drugs, inhibition of multiple CDKs is an appealing approach to improve clinical responses in cancer patient's refractory to existing treatment options. A Phase 1 dose-escalation study of Milciclib in combination with gemcitabine in patients with refractory solid tumors exhibited clinical activity in patients including those refractory to gemcitabine. We plan to explore combination approach in patients with HCC.

A Phase 2b trial for Milciclib in combination with a tyrosine kinase inhibitor (TKI) such as Sorafenib (Nexavar®) or regorafenib (Stivarga®), used to treat some types of kidney, liver and thyroid cancers) in patients with HCC is expected to be initiated in the second half of 2019.

In addition, we are developing a fully human mAb targeting the IL-6R (TZLS-501) for the treatment of inflammatory and autoimmune diseases. We licensed the intellectual property from Novimmune in January 2017. This fully human mAb has a novel mechanism of action, binding to both the membrane-bound and soluble forms of the IL-6R as well as depleting circulating levels of the IL-6 in the blood. Excessive production of IL-6 is regarded as a key driver of chronic inflammation, associated with autoimmune diseases such as multiple myeloma, oncology indications and rheumatoid arthritis, and we believe that TZLS-501 may have potential therapeutic value for these indications.

In preclinical studies, TZLS-501 demonstrated the potential for overcoming the limitations of other IL-6 blocking pathway drugs. Compared to tocilizumab and sarilumab, while binding to the membrane-bound IL-6R complex, TZLS-501 has been observed to have a higher affinity for the soluble IL-6 receptor from antibody binding studies conducted in cell culture. TZLS-501 also demonstrated the potential to block or reduce IL-6 signaling in mouse models of inflammation. The soluble form of IL-6 has been implicated to have a larger role in disease progression compared to the membrane- bound form (Kallen, K.J. (2002). "The role of trans-signaling via the agonistic soluble IL-6 receptor in human diseases." Biochimica et Biophysica Acta. 1592 (3): 323–343).

Our Competitive Strengths

Our mission is to design and deliver next generation therapeutics and diagnostics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. We believe the following strengths will allow us to continue to pursue this mission:

- ***Advanced, novel pipeline***. We have an advanced pipeline of novel and proprietary drug candidates, including antibodies and small molecules, to address high unmet medical needs in the inflammation, autoimmune and oncology markets with significant commercial potential.

- ***Proprietary technology***. Our proprietary technology enables the development of alternative routes of administration of antibodies, including oral delivery. We believe that oral and nasal routes of delivery will alleviate the significant time and cost burden associated with other routes of administration, including intravenous delivery.

- ***Broad and engaged network of experts.*** Our strong relationships with key opinion leaders contribute to our clinical development efforts and position us well to support our products, if approved. Dr. Napoleone Ferrara, Dr. Arun Sanyal, Dr. Kevan Herold, and Dr. Howard Weiner are among the thought leaders on our scientific advisory committee.

- ***Specialized expertise and focus on oncology and inflammation***. Our management team, including Dr. Kunwar Shailubhai, Jules Jacob, Dr. Priya Eddy and Dr. Vaseem Palejwala, has considerable experience translating technologies from bench to market, and managing the global administration of clinical trials.

- ***Strong intellectual property and know-how***. We believe our proprietary intellectual property portfolio, in-licensed from Nerviano and Novimmune, provides us with a substantial competitive advantage for the commercial development of small molecule NCEs, and biologics, as well as expanded possibilities for new development programs in the future. We have retained the worldwide development and commercialization rights to all of our product candidates. We have submitted additional patent applications to further strengthen our intellectual property.

- ***Lean research and development model, designed to maximize value***. We employ a lean and virtual R&D model using highly experienced teams of experts for each business function to maximize value accretion by focusing resources on the drug discovery and development processes.

Our Strategy

Our goal is to become a leading biotechnology company focused on developing and delivering therapies and related diagnostics in both oncology and immunology. The key elements of our strategy to achieve this goal are to:

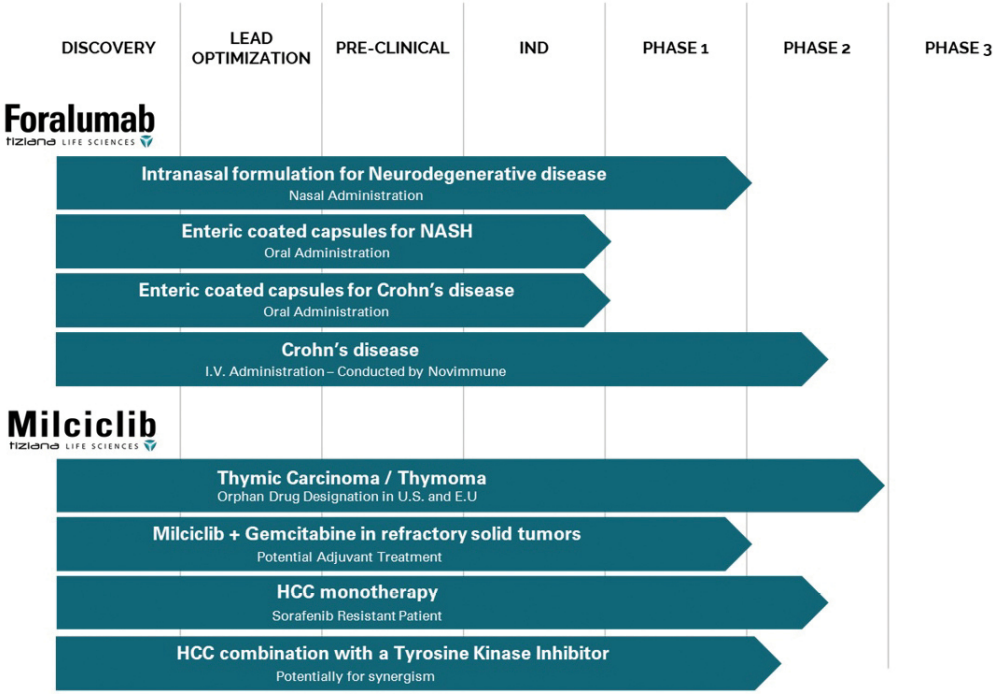
- Advance the clinical development of orally administered Foralumab for the treatment of NASH and Crohn's disease using a novel and proprietary oral formulation by initiating a Phase 1 trial in the second half of 2019 and a Phase 2 trial in the second half of 2020. In addition, a Phase 1 trial for the first-in-human evaluation of the intranasal administration of Foralumab in healthy volunteers, for neurodegenerative disease indications such as MS, was initiated in November 2018. Topline results from this study are expected in the second half of 2019.

- Continue to advance the clinical development and obtain regulatory approval for our lead oncology product candidate, Milciclib, as a monotherapy in HCC and as a combination therapy for the treatment of refractory solid tumors (being cancers which are non-responsive or become resistant to treatment) and HCC by completing the ongoing Phase 2a trial as a monotherapy and initiating a planned Phase 2b trial in combination with a TKI (Sorafenib or Regorafenib).

- Continue to leverage relationships with key opinion leaders to promote clinical trial success and enhance future commercialization.
- Continue preclinical studies and non-clinical development of our product candidate, TZLS-501, a fully human mAb targeting the IL-6R (a biological mAb which may control the proteins involved in cell signaling relevant to many inflammatory diseases and cancers), for treatment of inflammatory and oncology indications.
- Opportunistically identify and acquire or in-license complimentary product and technology candidates.
- Seek orphan drug, fast track or breakthrough designation for our product candidates where warranted.

Our Product Candidates

Our product candidate pipeline is set forth below:



Foralumab (TZLS-401 formerly known as NI-0401)

We believe Foralumab is the only fully human anti-CD3 mAb in clinical development, in contrast to the previous non-human or humanized anti-CD3 mAbs. Foralumab targets the CD3 epsilon (CD3ε) receptor, which is a recognized approach for modulating T-Cell response and achieving immunosuppression. We believe Foralumab could have broad application to autoimmune and inflammatory diseases, such as NASH, Crohn's disease, MS, type-1 diabetes, or T1D, inflammatory bowel disease, psoriasis and rheumatoid arthritis, where modulation of a T-cell response is desirable. In July 2017, we announced publication of a research article in, Clinical Immunology, entitled: "Oral treatment with Foralumab, a fully human anti-CD3 mAb, prevents skin xenograft rejection in humanized mice." We believe this is the first-ever published report demonstrating the potential of oral therapy with Foralumab for inflammatory diseases and is based on the landmark discovery by Prof. Howard Weiner of Harvard University, one of our Scientific Advisory Committee members. We planned to first investigate orally and nasally administered Foralumab for its safety and immunomodulatory activity in healthy volunteers in separate Phase 1 clinical trials. A Phase I single site, double-blind, placebo-controlled, dose-ranging clinical study dosed intranasally in healthy volunteers was initiated in November 2018 to evaluate safety and biomarkers of immunomodulation of clinical responses planned in healthy volunteers to dose Foralumab intranasally. in collaboration with Brigham and Women's Hospital, Harvard Medical School, Boston,

MA. This clinical trial was recently completed in July 2019 in which 18 subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated, and no drug related safety issues were reported at any of the doses. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. In addition, we submitted an IND on March 18, 2019 for the oral formulation, to the FDA. The FDA requested safety data from the phase 1 trial with nasal administration of Foralumab to justify the proposed dose-range for the phase 1 trial with oral administration of enteric-coated capsules of Foralumab in healthy volunteers. We withdrew the IND on April 17, 2019. A third IND was submitted to the FDA on July 23, 2019 for a Phase I trial in healthy volunteers using orally administered Foralumab with an intent to treat pMS. On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. Based on successful Phase 1 data, we intend to conduct a Phase 2 study using Crohn's Disease patients starting in the second half of 2020 and file an IND for a Phase 2 trial using NASH patients.

Non-alcoholic steatohepatitis

Non-alcoholic fatty liver disease, or NAFLD, comprises a spectrum of progressive liver diseases, which currently affects approximately one-third of the western world. It is associated with liver-related morbidity and mortality and with increased risk of cardiovascular disease, type 2 diabetes mellitus, or T2DM, hyperlipidemia (acquired or genetic disorders resulting in elevated levels of lipids circulating in the blood) and abdominal obesity. NASH, one of the manifestations of NAFLD, leads to inflammation and fat and fibrous tissue buildup in the liver, and elevated liver enzymes levels, and can lead to liver cirrhosis, end-stage liver disease and primary liver cancer, or HCC (as shown in the graphic on page 82 under "— Milciclib — Hepatocellular Cancer." NASH is predicted to become the leading cause of liver transplantation in the U.S. by 2020. Drug companies and liver organizations have signaled that NASH medicines represent a $35 billion market. Both genetic predisposition and environmental factors have been implicated in its onset, and inflammation and associated fibrogenesis contribute to its perpetuation.

Chronic inflammatory processes involve an imbalance in pro-versus anti-inflammatory cytokines (small proteins which are secreted by certain cells of the immune system and have an effect on other cells), altered insulin responses due to inflammation and fat and fibrous tissue buildup. Therapeutic avenues must provide for multifactorial effects, with focus on reduced insulin resistance and inflammatory processes. Mild inflammation imparts a hepatoprotective effect (preventing damage to the liver), while excessive inflammation triggers hepatocyte damage (damage to cell membranes and tissue death) and irreversible liver damage, fibrosis and carcinogenesis. Such detrimental effects are associated with overexpression of inflammatory genes and increased activity of Kupffer cells, natural killer T-cells, hepatic stellate cells, sinusoidal endothelial cells, dendritic cells, monocytes and lymphocytes, which secrete a range of proinflammatory factors, including cytokines, chemokines, lipid messengers and reactive oxygen species.

While several drugs, such as pioglitazone (Actos®), have proven effective in improving NASH-related features, side effects, including weight gain, adipose tissue insulin resistance, increased risk of bone fracture in women, congestive heart failure, heightened risk of bladder cancer, increased mortality, risk of hemorrhage stroke, prostate cancer in men over 50 years of age, pruritus and increased low-density lipoprotein cholesterol have been measured following their chronic use.

Crohn's Disease

Crohn's disease is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect all parts of the intestinal tract as well as extra-intestinal organs. Crohn's disease affects between 400,000 and 600,000 people in North America. Prevalence estimates for Northern Europe have ranged from 27–48 per 100,000. Although the incidence and prevalence of Crohn's disease are beginning to stabilize in high-incidence areas such as northern Europe and North America, they continue to rise in low-incidence areas such as southern Europe, Asia, and much of the developing world. Differences in incidence across age, time, and geographic region suggest that environmental factors significantly modify the expression of Crohn's disease. The strongest environmental factors identified are cigarette smoking and appendectomy. The disease affects slightly more females than males and is most commonly diagnosed in young adults, e.g. late adolescence to the third decade of life (Kim, S.C. and G.D. Ferry. Gastroenterology (June 2004) 126 (6): 1550-1560). It is expected that the Crohn's disease treatment market will exceed $10 billion by 2025. Although the exact etiology remains unknown, the occurrence of Crohn's disease is strongly associated with mutations of a receptor for microbial pathogens, or NOD2, that lead to increased activation of antigen presenting cells

and a defect in the release of antimicrobial defensins. It is now widely accepted that as a result of this altered balance of immune homeostasis, exposure to commensal bacterial antigens causes increased stimulation and proliferation of mucosal T-lymphocytes, leading to immune inflammation. Additional pathogenic mechanisms may include a defect in T-cell programmed death, or apoptosis, and possibly a defect in regulatory T-cell function.

Crohn's disease usually presents as acute or chronic bowel inflammation then the inflammatory process evolves toward one of two patterns of the disease: a fibrostenotic-obstructing pattern or a penetrating-fistulous pattern, each with different treatments and prognoses. The site of disease influences the clinical manifestations and can include diarrhea, abdominal pain, fever, clinical signs of bowel obstruction, as well as passage of blood or mucus or both.

Up to 25% of patients with Crohn's disease will develop extraintestinal disease manifestations which usually respond to treatment of the underlying disease (e.g. arthritis, uveitis, primary sclerosing cholangitis) (Harrison's Principles of Internal Medicine 2008).

Crohn's disease is histologically characterized by a discontinuous transmural granulomatous inflammation of the intestinal wall, but typical granulomas are found on mucosal biopsies in a minority of subjects. Surgical resection reveals granulomas in about half of cases (Harrison's 17th edition).

The pharmacological management of Crohn's disease is based on the control of the inflammatory process. Current treatment regimens include:

- anti-inflammatory drugs (e.g. corticosteroids, aminosalicylates), which are the first-line treatment to induce remission in acute active disease;
- immunosuppressants such as azathioprine, 6-mercaptopurine and methotrexate (Feagan, 2000) which are used to maintain remission or treating chronic active disease; biologic immunotherapies (e.g. anti-TNF mAbs including infliximab and adalimumab) which are used to induce and maintain remission.

All of these treatments have limited long-term efficacy and potential for serious adverse effects (Targan, 1997; Present, 1999).

Previously reported studies using anti-cluster definition 4, or anti-CD4, and tumor necrosis factor, or TNF, binding mAbs provide a strong rationale for targeting T-cells in Crohn's disease (van Deventer et. al. Intl. J. Clin. Pharm. (1997) 19(2): 55-9). It is now known that TNF targeting mAbs in Crohn's disease and IBD are effective because of the bringing about of programmed cell death (apoptosis) of activated T-lymphocytes rather than neutralization of soluble TNF (Chowers et.al., Current Drug Targets (2010) 11: 138-142; Atreya et. al. Gastroenterology (2011) 141 (6): 2026-2038.

In addition, there are few published clinical data on the use of anti-CD3 mAbs in subjects with Crohn's disease. One product in development, visilizumab (Nuvion®, PDL Biopharma) is a humanized IgG2 anti-CD3 monoclonal antibody has been tested in the clinical setting. Two studies with visilizumab in patients with severe Crohn's disease have been performed: An open-label study (ClinicalTrials.gov Identifier: NCT00267709) in patients with Crohn's disease having peri-anal fistulas and an open-label study (ClinicalTrials.gov Identifier: NCT00267722) in patients with moderate-to-severe inflammatory, non-structuring, non-penetrating Crohn's disease. Eighteen patients were expected to be enrolled in each study. Results form this study suggested that 10 µg/kg visilizumab administered by IV bolus injection appeared to have promising clinical activity as determined by a drop in the Crohn's Disease Activity Index (CDAI) scores of 100 points.

Preliminary results from the second study suggested that two 10 µg/kg doses of visilizumab administered by IV bolus injection on consecutive days appeared to have clinical activity. Ten of the 14 patients reported a clinical response by day 59, as determined by a drop in the Crohn's disease Activity Index, or CDAI score, of 100 points. Five patients achieved a complete remission, as defined by a CDAI score of <150 during the 59 days. Of note, two patients who never responded to infliximab, as well as seven patients who lost their response to infliximab, responded to visilizumab.

Multiple Sclerosis

MS is an inflammatory-mediated demyelinating disease of the human central nervous system. The disease develops in young adults with a complex predisposing genetic trait and most likely involves an environmental insult

such as a viral infection to trigger the disease. The activation of CD4+ autoreactive T cells and their differentiation are crucial initial steps in the progression of this disease. The therapeutic use of monoclonal antibodies was initially viewed with great skepticism owing to the high rates of sensitization against mouse proteins, their pharmacokinetic properties, and the difficulties in their production. However, most of these problems have been overcome, and monoclonal antibodies are now among the most promising therapies for MS.

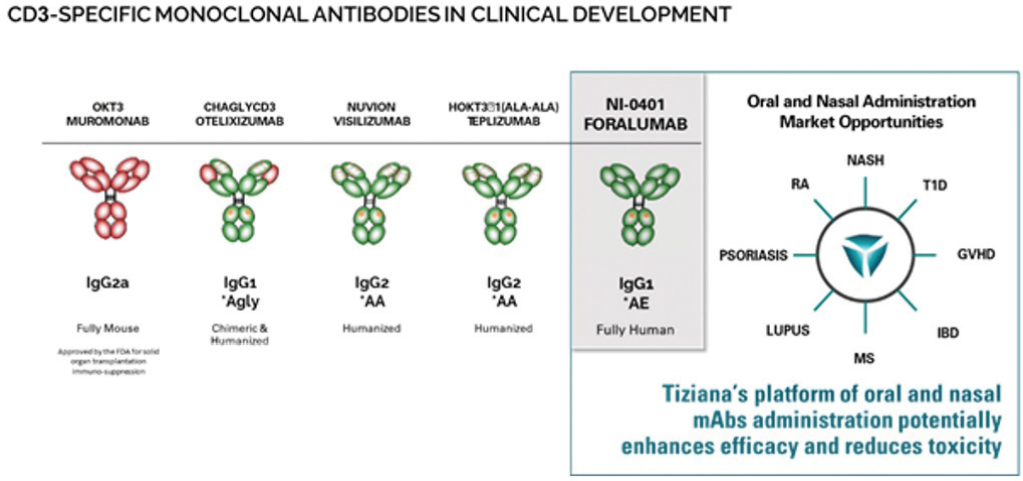
Autoimmune and Inflammatory Diseases

Autoimmune diseases are primarily due to a malfunction when the immune system attacks certain cells in the body as foreign invaders. This can result in irreparable damage to critical organs and tissues eventually resulting in autoimmune diseases.

In humans, CD3-epsilon is encoded by the CD3ε gene on Chromosome 11. The CD3ε molecule, along with four other membrane-bound polypeptides (CD3-gamma, -delta, -zeta, and -eta) form the CD3 complex, which is associated with the T-cell receptor. Upon antigen bindings, the CD3 complex sends signals through the cell membrane to the cytoplasm inside the T-cell. This leads to activation of the T-cell that rapidly divides to produce new T-cells sensitized to fight the particular antigen to which the TCR was exposed. While T-cell activation is critical for the human immune system to properly fight bacterial, viral or parasitic infections, abnormal T-cell induction can cause and worsen numerous human diseases, including T-cell lymphoma and leukemia, human malignancies, autoimmune disorders, cardiovascular disease and transplant rejection.

Our Solution

We believe Foralumab is the only fully human anti-CD3 mAb in clinical development. Since the discovery of the hybridoma technology, a method to generate large quantities of a single (monoclonal) antibody, the production and manufacture of mAbs has become widely available showing promise in several autoimmune and inflammatory disease clinical trials and therapeutic utility in animal models. The first murine anti-CD3 mAb (IgG2a) was developed and approved by the FDA in 1985 under the name of muromonab, OKT3, (Ortho Kung T3; Orthoclone®) to treat allograft rejection in kidney, liver and heart transplantation by exerting its potent immunosuppressive effects, mainly due to depletion of T-cells in tissues and thereby preventing rejection of the allografts. Subsequently, OKT3 was administered in clinical trials to patients with MS, T1D, inflammatory bowel disease, rheumatoid arthritis and NASH. Although showing promise to alleviate the disease process, the mAb being of murine origin and extremely immunogenic in humans, was associated with a wide range of side effects that included the typical Cytokine Release Syndrom (CRS) or flu-like syndrome, limiting its clinical development. The side effect profile of OKT3 is a consequence of T-cell activation resulting in the release of numerous cytokines into the systemic circulation. These shortcomings of the murine OKT3 led to the development of a new generation of anti-CD3 mAbs using genetic engineering of the mAb structure, as depicted below.



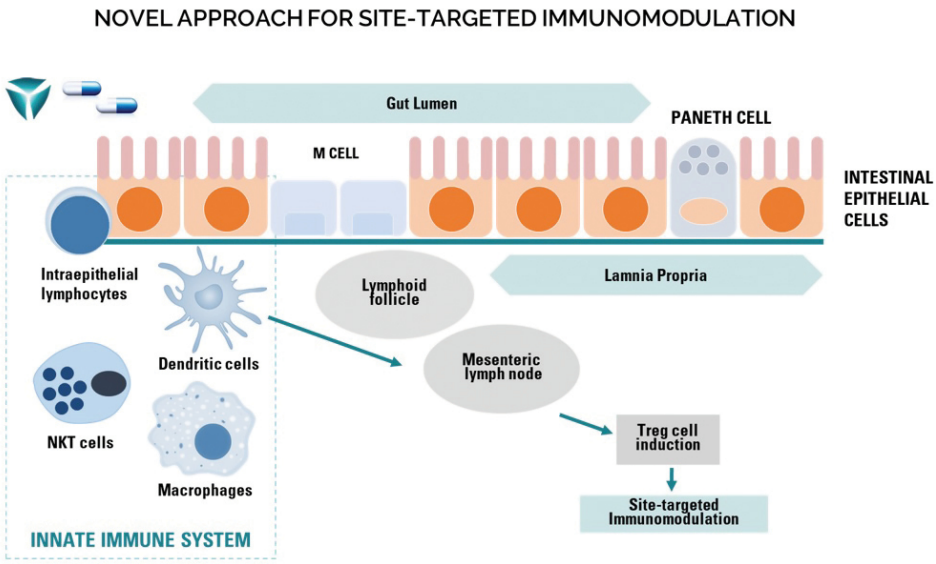
Foralumab dosed intravenously has been observed to alter T-cell function via antigenic modulation, that is, removal of the CD3/TCR complex from the T-cell surface. Modulation has two therapeutic benefits:

- It transiently renders the T-cells incapable of recognizing an antigen and thus unable to orchestrate an immune response such as an allograft rejection; and
- It has a favorable long-term effect on generation and maintenance of regulatory T-cells, or Tregs, a specialized subset of T-cells that promote immunological tolerance.

In comparison with the two other anti-CD3 mAbs evaluated in patients with T1D (otelixizumab and teplizumab), Foralumab, being fully human, was less mitogenic (capable of causing cell division), therefore allowing re-treatment, and to have a better risk/benefit profile. As such, Foralumab was previously developed by Novimmune as an intravenous formulation for the treatment of autoimmune indications: Crohn's disease and in renal allograft recipients.

Further, recent data from studies conducted in the laboratories of our Scientific Advisory Committee members, Prof. Howard Weiner of Harvard University and Prof. Kevan Herold of Yale University, suggest that oral administration of Foralumab has the potential for therapeutic utility while minimizing toxicity associated with intravenous administration, such as CRS.

The mechanism of action of orally administered enteric-coated Foralumab capsules is indicated below:



Importantly, recent clinical studies conducted by Prof. Yaron Ilan with oral administration of anti-CD3 (OKT3; murine mAb) in HCV infected patients (non-respondents) and in NASH patients suggested that the treatment was well-tolerated and produced immunologic effects consistent with potential clinical benefits.

In addition, increasing appreciation for the gut-liver cross-talk and of its role in the initiation of NASH-associated inflammation and fibrogenesis has led to the understanding that systemic inflammatory processes can be alleviated by modulating the gut immune system, without inducing generalized immunosuppression. This has been achieved in multiple approaches, including oral administration of fatty liver-derived proteins, anti-CD3 antibodies, TNF, fusion protein, anti-lipopolysaccharide antibodies, glucosylceramide, delayed-release mercaptopurine and soy-derived extracts. Several of these compounds were shown to be effective in patients with NASH.

Orally administered OKT3 was evaluated in a Phase 2 trial in 36 patients with NASH and type 2 diabetes and was found to be well tolerated by all patients in all groups with no systemic drug-related adverse events. Increases in regulatory T-cell markers consistent with induction of regulatory T-cells was observed as well as increases in

other anti-inflammatory markers. Although not powered sufficiently to evaluate efficacy endpoints, positive trends were observed including lowering of liver enzymes and lowering of glucose levels (Lalazar et.al, J. Clin. Immunol. (2015) 34 (4):399-407).

More recent animal studies conducted separately by Prof. Howard Weiner and Prof. Kevan Herold demonstrated therapeutic utility of orally administered Foralumab for immune-inflammatory diseases. Our strategy is to build on these findings to develop orally administered Foralumab for the treatment of NASH, Crohn's disease and other autoimmune diseases. We believe Foralumab may also be combined with our other product candidate, TZLS-501, a fully human anti-IL-6R mAb, for the treatment of rheumatoid arthritis and other diseases.

Importantly, a recent study conducted by Boden et al., 2019 (Crohn's and Colitis 360) reported that oral treatment with the murine anti-human anti-CD3 monoclonal antibody OKT3 in moderate-to-severe ulcerative colitis patiets was well tolerated and no evidence of CRS or development of human anti-mouse antibodies at 1 mg/dose for 30 days and 3/6 patients showed clinical response and amelioration of gut inflammation and one patient showed clinical remission. It is likely that the OKT3 was not bioavailable and that immunomodulation occurred in the intestinal mucosa with little systemic drug exposure. These results are extremely important and provides promise for oral Foralumab human trials.

Kevan Herold et al recently published results of a Phase 2 study (New England Journal of Medicine, June 2019) in subjects at risk to develop Type 1 diabetes (T1D) that were treated with intravenous administration of the humanized anti-CD3 monoclonal antibody, teplizumab. Teplizumab slowed progression to clinical Type 1 diabetes in high risk participants in which only 43% of the subjects who received teplizumab went on to develop T1D indicating 57% of participants slowed progression to develop Type 1 diabetes compared to 72% of the subjects who received placebo. Teplizumab (humanized OKT3), administered intravenously, significantly slowed progression to clinical Type 1 diabetes, with a median delay in the diagnosis of diabetes of 2 years. 20 Grade 3 adverse events were observed, most of which (75%) consisted of lymphopenia that resolved by day 45. The study demonstrates the capacity of anti-CD3 treatment to be effective in treating autoimmune diseases such as T1D.

On April 16, 2018 we entered into an exclusive license agreement with BWH relating to intranasal administration of Foralumab in a medical device. An IND for the first-in-human evaluation of Foralumab in healthy human volunteers was filed on June 1, 2018 and accepted by the FDA on August 20, 2018. Dosing was initiated in November 2018 for the dose ranging Phase 1 trial to evaluate safety and tolerability as well as biomarkers of immunomodulation resulting in clinical responses. Three doses of Foralumab (10 µg, 50 µg and 250 µg/dose) were administered without any drug-related safety concerns so far. Topline results from this study are expected in the third quarter of 2019.

Clinical Development Plan

Proposed Phase 1 Clinical Trial for Foralumab in Healthy Volunteers

The proposed Phase 1 clinical trial for Foralumab in healthy volunteers is a single center single arm ascending study in which low doses (0.5, 1.25, 2.5 and 5.0 mg/dose) of Foralumab will be orally administered for 5 consecutive days followed by monitoring for tolerance and adverse events for 5 days. At each dose level, starting with the low dose if the resultant data indicates that the drug is well tolerated and free from significant adverse events, the next higher dose will be administered orally further for 5 consecutive days followed by 5 days of monitoring for tolerance and adverse events. If data from the Phase 1 trials indicate that the drug is well tolerated and free from adverse events, a Phase 2a trial is expected to be initiated in the second quarter of 2020 with the intent to treat patients with NASH and/or Crohn's disease. The primary endpoint of the Phase 1 study is safety and tolerability of Foralumab in humans.

Proposed Phase 2 Clinical Trial for Foralumab for the Treatment of NASH

The proposed Phase 2 clinical trial for Foralumab is a randomized, placebo-controlled, four-arm, double-blind study. Subjects (48) will be randomized (1:1:1:1) to receive either a once daily oral placebo or Foralumab dose of 1.25 mg, 2.5 mg or 5.0 mg for 30 consecutive days. Patients will record adverse events and daily administration of study medication in a subject diary. This will serve as a measure of compliance and record of adverse events and tolerability. Patients will be followed up for 30 days following completion of treatment. Study visits performed on Days 14, 30 and 60 of the study, will monitor metabolic parameters (body mass index and waist circumference), serum lipid profiles, immunological markers (C-reactive protein and an array of cytokines), hepatic enzymes and functions (^{13}C-methacetin breath test and liver steatosis/fibrosis), which will be compared to baseline levels (Day 1).

The safety and tolerability of the treatment regimen is the primary endpoint and will be determined by monitoring vital signs, laboratory values, adverse events and physical findings throughout the study. In addition, efficacy/immunomodulatory activity will be established using the following criteria: (1) reduced Day 30 serum alanine aminotransferase (ALT) levels; (2) reduced hemoglobin A1c; (3) improved homeostasis model assessment (HOMA); (4) HOMA of insulin resistance (HOMA-IR) scores; as well as (5) levels of T cells and cytokines as compared to baseline (Day 1).

Phase 1 Clinical Trials of Foralumab for the Treatment of Multiple Sclerosis

The Phase 1 clinical trial of nasally-administered Foralumab in healthy volunteers is a single center single arm ascending study in which low doses (10, 50 and 250 µg/dose) of Foralumab was nasally administered for 5 consecutive days followed by monitoring for tolerance and adverse events for 30 days. At each dose level, starting with the low dose administered nasally for 5 consecutive days followed by 30 days subjects were monitored for tolerance and adverse events and biomarkers for immunomodulation. In September 2019, we announced preliminary data from the Phase 1 trials indicating that the nasally administered drug is well tolerated and free from adverse events. Biomarker analysis showed significant immunomodulatory effects at the 50 µg dose with minimal effects at the 10 and 250 µg doses. Phase 2a trials will be initiated at a later date for the treatment of MS. The primary endpoint of the Phase 1 study was safety and tolerability of Foralumab in humans dosed intranasally using a hand-held nasal spray device. An IND was submitted to the FDA on July 23, 2019, to conduct a Phase I clinical trial in healthy volunteers using a newly developed novel enteric-coated capsule formulation of Foralumab in collaboration with the BWH, Harvard Medical School, Boston, MA with an intent to treat pMS. On September 9, 2019, the FDA granted approval to initiate Phase I clinical trials to evaluate the safety and pharmacokinetics of the oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study.

Intravenous Foralumab has been studied in a total of one Phase 1 and two Phase 2 clinical trials conducted by Novimmune. A total of 68 patients were exposed to Foralumab:

Study NI-0401-01: a Phase 1/2a randomized, double-blind, placebo-controlled and dose escalation study NI-0401-01 in subjects with moderate to severe active CD. The study was completed and 33 subjects were exposed to Foralumab. The study NI-0401-01 was designed to assess tolerability of Foralumab and was not powered to evaluate efficacy parameters included the proportion of patients achieving, clinical response and change from baseline of Crohn's Disease Endoscopy Index of Severity. A trend, although not statistically significant, was seen when analyzing the clinical response and endoscopic response. Single and repeat intravenous doses of 0.05, 0.1, 0.5, 1.0, 2.0 and 10.0 mg Foralumab were administered to subjects and serum pharmacokinetics evaluated for up to five days. Limited pharmacokinetic data was collected, however it was observed that at doses over 1.0 mg, severe infusion related reactions (IRRs) were observed that led to discontinuation of the 2 and 10 mg groups. Therefore, the 1.0 mg dose was considered the MTD in this study. CD3 modulation on CD4 positive and CD8 positive T cells was related to Foralumab dose. There was a dose response for the reduction of peripheral T-cell (CD2 positive) count. The main adverse events were infusion related reactions related to the route of administration of the drug.

Study NI-0401-02: an open-label, dose titration, multicenter Phase 1 study of Foralumab for the treatment of subjects with biopsy-proven acute cellular renal allograft rejection (BpACR). The study was completed and 11 subjects were exposed to Foralumab. Patients were dosed with 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg of Foralumab daily for five days and most were pre-treated with methylprednisolone. The data from study NI-0401-02 has confirmed the dose response in terms of CD3 modulation and reduction of peripheral T-cell count. A CD3 modulation of up to 90% was achieved at study NI-0401-02 day five with a daily dose of 2.5 mg during the 5 days of treatment period. Although there was no dose-response relationship, treatment with Foralumab seems to be globally effective to reverse protocol defined acute cellular rejection and in the mormalization of serum creatinine levels, a primary efficacy objective. The main adverse events were infusion related reactions in patients that were not premedication with prednisolone.

Study NI-0401-03: a Phase 2a study with an open label dose escalation phase followed by a double-blind phase to assess safety and efficacy of Foralumab in subjects with moderate to severe active CD. The study NI-0401-03 was completed and 24 subjects were exposed to Foralumab. 74% of patients had achieved a clinical response at week 2 and 87% of patients at week 4. At weeks 6, 8 and 12 the proportion of patients with a clinical response decreased to 75%, 70% and 67%, respectively. 30% of patients had achieved clinical remission at week 2, 42% by weeks 4, 38% by week 6, 43% at week 8 and 46% at week 12. Treatment failures were 12.5%. There was a reduction in the mean Crohn's Disease Activity Index (CDAI) scores in all treatment cohorts and an overall improvement in the Crohn's Disease

Endoscopic Index of Severity (CDEIS) scores across all treatment groups following 5 daily doses of Foralumab treatment. Pharmacokinetic evaluations were performed, and no dose-response relationship was established due to variability between patients. The observed half-life of Foralumab was approximately 180 hours. A rapid and almost complete disappearance of CD45 positive lymphocytes, CD3 positive T-cells, CD3 positive and CD4 positive helper T-cells and CD3 positive and CD8 positive cytotoxic T-cells from the circulation was observed was observed within 24 hours of infusion for all dose cohorts. The lowest unit dose in the study NI-0401-03 was equivalent to the 1 mg daily unit dose that was the maximum tolerated dose in study NI-0401-01. Pre-medication with prednisolone reduced the severity and frequency of infusion related reactions.

In two Phase 2a trials conducted by Novimmune, patients with Crohn's disease and renal allograft rejection in kidney transplants demonstrated Foralumab's immunomodulatory activity in humans. We have decided not to pursue evaluation of intravenous Foralumab in Crohn's Disease because we believe the market for this disease is saturated by other FDA approved drugs. Further, while intravenous administration of antibodies has been widely used, side effects from the intravenous administration still are prevalent as well as patient compliant issues come into play. We intend to move forward with an oral formulation of Foralumab for treatment of Crohn's disease.

Two of Novimmune's clinical trials were in patients with Crohn's disease and the third clinical trial was conducted in patients undergoing kidney transplantation and suffering with renal allograft rejection. Sixty-eight subjects with active Crohn's disease and 11 subjects with acute cellular renal allograft rejection were treated with Foralumab. The route of administration of Foralumab in these studies was via intravenous administration.

In these trials, it was observed that:

- The short-term tolerability profile of Foralumab was very similar to those reported with other anti CD3 antibodies and no new emerging concerns have been identified.
- Total daily doses of up to 1mg (~ 500 µg/m2) per patient were generally well tolerated without corticosteroid premedication. The most common adverse events following exposure to Foralumab were IRRs, which occurred in all patients treated with the compound. In the majority of cases, these symptoms were mild (66%) in intensity and were reported following the first two infusions of the 5-infusion treatment course. The number of affected patients and the severity of symptoms tended to increase with increasing dose level, or DL.
- A clear reduction of CRS and its associated IRRs were observed with steroid pre-medication. All patients who received pre-medication with steroids had mild or no IRRs, and CRS was reduced. Only one patient who did not receive steroid pre-medication had significant levels of CRS, in particularly IL-6.
- Usage of steroid pre-medication allows the administration of higher doses.
- Both the magnitude and duration of CD3 modulation increased in a dose related manner.
- No anti-drug antibodies were detected.

Prior Clinical Experience

Oral anti-CD3 antibodies, as opposed to the narrow therapeutic window of its intravenous counterpart, have been shown to impact the gut immune system and mesenteric lymph nodes, thereby promoting regulatory T-cells activity, without inducing immunosuppression. The treatment alleviated experimental autoimmune encephalitis and T1D mellitus, which was associated with regulatory T-cells induction. Orally and nasally administered anti-CD3 suppressed autoantibody production in a mouse lupus model. Oral anti-CD3 yielded reduced pancreatic hyperplasia, hepatic fat accumulation and muscle inflammation in a leptin-deficient model of NASH and diabetes.

Pharmacology Summary (In Vitro Studies)

The key conclusions arising from the non-clinical studies of Foralumab by Novimmune are:

- Foralumab is a specific anti-CD3 epsilon mAb, as it binds to human T-cells and the recombinant human CD3 epsilon chain, and can be displaced by another specific anti-CD3 epsilon mAb, muromonab CD3.

- When bound to its target, Foralumab triggers calcium flux into the cell and modulates the CD3/TCR complex causing its' transient removal from the cell surface.

- The combination of the two-point mutations introduced into the Fc portion (the constant region of the antibody that has limited structural variability and is responsible for adverse side effects) of Foralumab, resulting in the abrogation of the binding to Fc gamma receptors, and C1q, consequently eliminates T-cell proliferation and the release of numerous cytokines including TNF, and interferon gamma, or IFNγ *in vitro*.

- Foralumab does not cross react with CD3 molecules expressed by T-cells of other species including baboon, *Rhesus* monkey, *Cynomolgus* monkey, rabbit, dog, rat and mouse. As a consequence, options for the most relevant species selection for pharmacology and toxicology assessment of Foralumab are limited. Novimmune addressed this limitation by studying LCD3 transgenic mice. This transgenic mouse line expresses the human as well as the mouse CD3 epsilon chain on the surface of their T-cells.

- Using a transgenic line of mice expressing both human and mouse CD3 molecules (1:1 ratio) at the surface of T-cell (LCD3*)*, following a single intravenous injection, Foralumab dose dependently:

- Modifies human CD3 epsilon expression; that is, more than 80% of the cell surface protein was removed within 24 hours when given at a saturating dose. This modulation was transient as receptor expression levels returned to baseline values within 7 days of dosing.

- Caused a transient reduction of 70-80% in the number of circulating T-cells when given at a saturating dose. The maximal effect was observed at hour 6 post dose. Cell counts returned to baseline levels within 3.5 days.

- Demonstrated a half-life of 1.4 and 1.7 days for doses of 5 and 200 µg per mouse, respectively. This seemingly short half-life is similar to that observed in vivo for other anti-CD3 mAbs and reflects internalization of Foralumab by the human CD3 molecule on the T-cells of these transgenic mice. It was therefore expected that Foralumab will be internalized by human T-cells in patients and consequently have a half-life comparable to other therapeutic anti-CD3 mAbs.

Milciclib (TZLS-201)

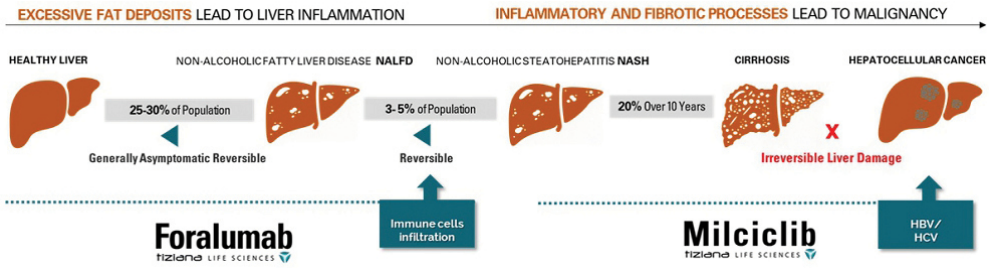
Milciclib is an orally bioavailable, small molecule broad spectrum inhibitor of CDKs (CDKs): 1, 2, 4, 5 and 7 and Src family kinases. CDKs are a family of highly conserved enzymes that are involved in regulating the cell cycle, which is a series of events that takes place in cells leading to division and duplication of its DNA to produce two daughter cells. Src family kinases regulate cell growth and potential transformation of normal cells to cancer cells. A novel feature of Milciclib is its ability to reduce microRNAs, miR-221 and miR-222, that silence gene expression. miR-221 and miR-222 promote the formation of blood vessels (angiogenesis) that are important for spread of cancer cells (metastasis). Levels of these microRNAs are consistently increased in HCC patients and may contribute towards resistance to treatment with Sorafenib. As a result, we are investigating Milciclib both as a monotherapy and plan a combination treatment with Sorafenib. To date, Milciclib has been studied in a total of eight Phase 1 and Phase 2 clinical trials in 316 patients. In these trials, Milciclib was observed to be well-tolerated and showed initial signals of anti-tumor action. We have completed a Phase 2a trial (CDKO-125a-010) for Milciclib as a single therapy in patients with HCC in June 2019 and expect to initiate a Phase 2b trial (TZLS (201)-125a-011) for Milciclib in combination with a TKI (either Sorafenib for first line treatment or Regorafenib for second line therapy, the standards of care for treatment of HCC) in patients with HCC in the second half of 2019.

Hepatocellular Cancer

We are initially developing Milciclib for the treatment of HCC. HCC, or liver cancer, is the sixth most common of all malignancies and second most common cause of cancer related deaths in the world. Liver cancer incidence and death rates are steadily rising. As of 2012, rates of new liver cancer cases went up 38% from 2003 to 2012 according to the Centers for Disease Control and Prevention. It is estimated that the liver cancer drug market will be approximately $1.5 billion by 2022.

Most HCC patients present with advanced disease and do not benefit from transplantation, surgical resection, or locoregional therapies. The SOC, Sorafenib and Lenvatinib, are approved in the United States and EU for advanced HCC patients but have a limited impact on overall survival.

The primary risk factor for HCC is hepatic cirrhosis, with an estimated 78% of HCC cases and 57% of cases of liver cirrhosis caused by chronic infection with hepatitis B virus or HCV. Recently, the combination of insulin resistance, hypertension, dyslipidemia and obesity, termed "metabolic syndrome," has also been recognized as a cause of NAFLD, which is the most common liver disease, cirrhosis and HCC. The following graphic represents the progression from a healthy liver to NAFLD, NASH and HCC.



Generally, cancer is primarily due to deficiencies in cell cycle control, eventually resulting in transformation of normal cells to rapidly growing cancer cells. Therapeutic intervention to control cell cycle has long been anticipated as effective cancer therapies. CDKs are a family of enzymes first discovered as regulators of the cell cycle. CDKs have been found to be overexpressed in a variety of human diseases with abnormal cell growth such as cancers, viral infections, neurodegenerative disorders and other proliferative diseases. We believe that modulating CDK activity with targeted therapies is an attractive strategy to reinforce cell cycle control and decrease the rate of abnormal proliferation of cancer cells. The first FDA approval in March 2015 of a CDK inhibitor for palbociclib, and more recently in 2017, ribociclib, for a type of breast cancer, has led to great interest in the development of this class of drugs as oncology therapeutics.

Our Solution

Milciclib is an oral, broad-spectrum inhibitor of CDKs, as well as several other protein kinases responsible for controlling cell growth and replication. Milciclib has an unusual kinase inhibitory profile making it active against other receptors such as, tyrosine kinase, Src family and splicing kinases, which play a role in cell growth and transformation from normal to cancerous cell types.

In tumor cells exposed to Milciclib, a block in G1 phase (first phase of the growth cycle where the cell synthesizes messenger RNA and proteins before cell division) of the cell cycle was observed, supporting the postulated mechanism of action of the compound as determined in biochemical assays. Additionally, Milciclib was able to modulate the phosphorylation of the Retinoblastoma protein, a substrate of the CDK/cyclin complex as well as to reduce phosphorylation status of proteins of the TRKa signaling pathway in cells expressing the tyrosine kinase receptor. These results supported that Milciclib was active against several families of protein kinases that actively controlled cell growth and transformation from normal to cancerous cell types. This is important because many chemotherapeutic agents are effective at only a single point in the cell cycle, allowing cells to "escape" the biochemical blockage through alternative biochemical pathways.

Significant anti-tumor activity was observed in all tested preclinical animal models with different oral treatment schedules of Milciclib. Cancerous cell types were transplanted into immunosuppressed animals and the number and volume of cancerous lesions were evaluated by magnetic resonance imaging after oral administration of Milciclib at different dose levels (DLs) and dose schedules compared to untreated, control animals. In various human xenograft and transgenic models (prostate cancer, lung adenocarcinoma and hepatocarcinoma), consistent tumor growth inhibition, up to 91%, (evaluated by measuring the number and volume of tumors for treated animals versus control animals) was observed -with repeat daily treatment at tolerated doses. Similar results were obtained in a mammary carcinoma model (stasis and partial remission in 58% and 25% of the primary tumors, respectively) with repeat daily dosing. In an

orthotopic mouse model of HCC, statistically significant reduction in tumor growth was observed following five weeks of treatment with Milciclib (-20% reduction,30mg/kg/day),sorafenib (-20% reduction, 20 mg/kg/day) vs combination of Milciclib with Sorafenib (-38% reduction) as compared to vehicle control. The treatment also reduced serum levels of human alpha-fetoprotein. Preliminary mechanistic and gene expression studies suggest that downregulation of miR-221, miR-222 by Milciclib results in upregulation of its molecular targets, cyclin dependent kinase inhibitors p27 and p57. Additionally, Milciclib treatment upregulated relative expression of tumor suppressors p21 and p53, which are important regulators of cellular proliferation. Milciclib treatment reduced expression of pAKT, c-Myc and cyclin D1, which are known to be overexpressed in HCC tumor tissues. These preclinical data demonstrating the synergistic effect of Milciclib with Sorafenib were presented at the AASLD meeting in November 2018.

Clinical Development Plan

Phase 2a Clinical Trial (CDKO-125a-010) for Milciclib as a Monotherapy for the Treatment of HCC

In July 2017, we initiated dosing in a single-arm, multicenter, Phase 2a clinical trial (CDK-125a-010) for Milciclib in adult patients with unresectable or metastatic HCC and good liver function. The trial is studying the tolerability and safety of Milciclib in these adult patients. As of 2019, we have enrolled and treated 31 patients at sites in Italy, Greece and Israel. Eligible patients are receiving Milciclib orally, 100 mg/day for four consecutive days a week (four days on followed by three days off) for a total of 12 weeks.

The primary endpoint for the study is the overall safety profile, evaluated based on laboratory findings and adverse events emerging during the trial. The occurrence of adverse events and laboratory tests will be performed weekly during treatment. All the enrolled patients who receive at least one drug administration were evaluated for safety. An interim evaluation of tolerability and adverse events was undertaken when the 10th patient had completed the first cycle of treatment. Enrollment of additional patients was allowed after a positive safety evaluation of the first 10 patients by an IDMC. On December 8, 2017 we announced the results of the first interim review by the IDMC that treatment with Milciclib was well-tolerated with no drug-related serious adverse events. The IDMC recommended continuing with the trial. The second IDMC meeting held on January 25, 2018 recommended that all patients (first cohort) who received at least one dose of Milciclib should be assessed for safety and tolerability at the end of protocol mandated follow up before enrolling the second cohort. The IDMC reconvened on its scheduled date on May 9, 2018 to evaluate the complete safety data for all 11 patients who completed the study mandated visits. The IDMC concluded that there are no major signals of safety concern that preclude continuation of enrollment of the remaining cohorts as planned. Secondary endpoints include Objective Tumor Response Rate, based on the modified Response Evaluation Criteria in Solid Tumors, or mRECIST, a set of criteria developed to assess tumor response in HCC. In this study, objective response by RECIST will also be evaluated as supportive analysis, along with several secondary parameters. The decrease in alpha-fetoprotein, or AFP, as compared to baseline in patients with high AFP at baseline will also be considered, based on reports suggesting a better outcome for patients who achieve an AFP response. As an exploratory endpoint, the expression of micro-RNAs and their possible association with Milciclib treatment will be investigated. Enrollment of 31 patients was completed in November 2018.

In March 2019, the IDMC reviewed safety data from patients as of February 26, 2019 and concluded that the administration of Milciclib to patients with advanced HCC was not associated with unexpected signs or signals of toxicity. 28 out of 31 treated patients were evaluable, 14 completed the 6-month duration study. The most frequent adverse events such as diarrhea, ascites, nausea, fatigue, asthenia, fever, ataxia, headache, and rash were manageable. No drug-related deaths were recorded.

As per the study protocol, data collection was limited to 6-months. Thus, clinical data were not collected from patients under compassionate use treatment. The clinical activity assessment in evaluable patients was based on the investigators' review using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

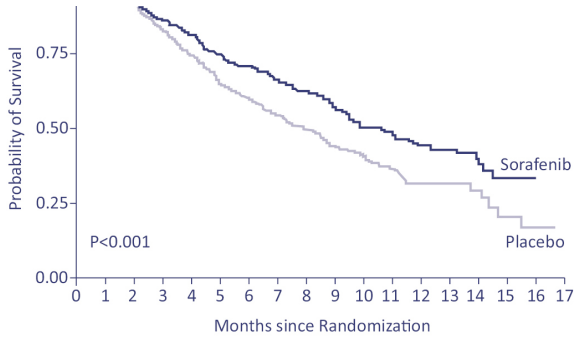
- 9 out of 14 patients (64.2%) were approved by their respective ethical committees to continue the treatment.
- 5 of the 9 patients on compassionate use had received Milciclib for a total of 9, 9, 11, 13 and 16 months.
- As of 1 September 2019, the remaining 4 patients continuing the treatment are in their 10th, 11th, 11th and 12th months.

- Both median TTP and PFS were 5.9 months (95% Confidence Interval (“CI”) 1.5-6.7 months) out of the 6-months duration of the trial.
- 17 of 28 (60.7%) evaluable patients showed ‘Stable Disease’ (SD; met at least once in an 8-week interval).
- One patient (3.6%) showed ‘Partial Response’ (PR, unconfirmed).
- 18 of 28 (64.3%) evaluable patients showed ‘Clinical Benefit Rate’ defined as CBR=CR+PR+SD (with CR representing Complete Remission).

Phase 2b Clinical Trial (TZLS (201)-125a-011) for Milciclib as a Combination Therapy with a TKI (Sorafenib or Regorafenib) for the Treatment of HCC

Since overexpression of CDKs and dysregulation in pRB pathway (regulates transcription factors critical for cell cycle progression) are prominently associated with tumor cell resistance to certain chemotherapeutic drugs, inhibition of multiple CDKs is an appealing approach to improve clinical responses in cancer patient’s refractory to existing treatment options. A Phase 1 dose-escalation study of Milciclib in combination with gemcitabine (CDK-125a-004) in patients with refractory solid tumors exhibited clinical activity in patients including those refractory to gemcitabine. Tiziana plans explore combination approach in patients with HCC. In 2019, we intend to initiate a randomized, multicenter study to explore tolerability and antitumor activity, of Milciclib in combination with a TKI (either Sorafenib or Regorafenib), administered as systemic therapy in adult patients with recurrent, unresectable or metastatic HCC and good liver function.

Sorafenib (Nexavar®) is the SOC for treatment of HCC, yet treatment extends survival probability from 7.9 months (placebo control) to 10.7 months (Llovet et al. N Engl J Med (2008) 359:378-390). There is a need for improvement which may be realized by combination of Milciclib with Sorafenib. Milciclib modulates cell cycle, DNA replication and growth factor receptor cell signaling (Albanese et.al, Mol. Cancer Therap. (2010) 9(8):2243-54). Sorafenib is a multikinase inhibitor which has demonstrated both anti-proliferative and anti-angiogenic properties in vitro and in vivo. The combination of Sorafenib with Milciclib should exert a combined anti-proliferative effect on tumor cells, involving targets different from the ones modulated by Milciclib, together with antiangiogenesis properties.



Milciclib has been studied in a total of eight Phase 1 and Phase 2 clinical trials in approximately 316 patients. Milciclib was observed to be well tolerated by patients with thymoma in Phase 1 and Phase 2 clinical trials.

Phase 1 Development

Milciclib has been investigated in each of the below, open-label, multi-center, non-randomized, dose-escalation Phase 1 clinical trials.

Trial	Patient Population	Treatment Schedule / Dosing	Key Findings
CDKO-125a-001	Advanced/metastatic solid tumors 37 patients	1st Schedule: Orally, once daily for 7 consecutive days every 14 days in a 2-week cycle at escalating doses of 50, 100, 150, 200 and 300 mg	*Pharmacokinetics:* Comparable plasma pharmacokinetic parameters between the two schedules were observed.
		2nd Schedule: Orally, once daily for 4 consecutive days a week for 3 weeks in a 4-week cycle at escalating doses of 150, 180 and 200 mg	The exposure to Milciclib increased with the dose and there was a 3-fold accumulation in the daily systemic exposure after repeated dosing, in good agreement with expectations on the basis of the half-life of the compound (24-43 h). *Clinical observations:* No objective responses were achieved on 1st schedule; Disease stabilizations, defined as cancer disease that is neither increasing nor decreasing in extent or severity, was observed in 6 of 14 evaluable patients (42.9%). A partial response, or PR, was achieved in 2 out of 14 evaluable patients (14.3%) on 2nd schedule; Disease stabilization (no change in extent or severity of disease state) was reported in 3 patients (21.4%), all treated at 180 mg/day DL, including a stabilization lasting 31 weeks in a patient with pancreatic cancer and stable disease, or SD, lasting 29 weeks in a patient with carcinoid.

Trial	Patient Population	Treatment Schedule / Dosing	Key Findings
CDKO-125a-002	Recurrent malignant glioma 28 patients (Phase 1)	Escalating oral doses of 18, 36, 54 and 72 mg/m2 once a day for 14 consecutive days followed by 7 days of rest in a 3-week cycle	*Pharmacokinetics:* Results indicated that the pharmacokinetics of Milciclib was dose-independent in the dose range 18 — 72 mg/m2.
	34 patients (Phase 2)	54 mg/m2 (RP2D)	Systemic exposure values of Milciclib maleate accumulated by a factor of 3 *Clinical observations:* Phase 1: No evidence of clinical effect was observed in all the 28 treated patients. However 5 patients seemed to have benefitted from therapy with SD observed (no change in extent or severity of cancer). Phase 2: One out of 34 patients achieved the primary endpoint. PFS at 6 months or PFS-6 rate was 2.9%. No complete response, or CR (disappearance of all signs of cancer in response to treatment) or PR (decrease in tumor size or extent of cancer in the body) were reported. 4 patients showed SD as best overall response (11.8%). Prolonged SD (≥ 6 months) was observed in one patient whose SD lasted for 24.9 months. *Safety:* 34 patients were enrolled and treated: 29 patients of non-Enzyme Inducing Anti-Epileptic Drugs, or non-EIAED, population and 5 of EIAEDs population. The primary clinical endpoint was not met. Only one patient (non-EIAEDs) achieved the study primary endpoint out of 34 treated patients. PFS-6 rate evaluated in the treated patients was 2.9% (95% CI, 0.07-15.33). No CR or PR was reported; 4 patients in the treated patients showed SD as best overall response on treatment (11.8%). Prolonged SDs (≥6 months) was observed in one patient whose SD lasted for 24.9 months. Median OS in treated patients was 7.03 months (95% CI, 5.72-10.58). The exploration of the role play by potential prognostic factors, such as Karnofsky Performance Scale (≥90 vs. <90), age (<40 vs. ≥40) and interval between initial diagnosis and current recurrence (≥52 weeks vs. <52 weeks) indicated a better survival outcome for patients whose interval between initial diagnosis and current recurrence was (≥52 weeks). Given the non-comparative nature of the study, it cannot be said whether the treatment played any role in this result. The influence of other factors cannot be excluded but was not apparent in the current sample.

Trial	Patient Population	Treatment Schedule / Dosing	Key Findings
CDKO-125a-003	Advanced/metastatic solid tumors 30 patients	1st Schedule: Orally, once daily for 21 consecutive days followed by 7 days of rest in a 4-week cycle at escalating doses of 16 and 24 mg/m2 2nd Schedule: Orally, once daily for 14 consecutive days followed by 7 days of rest in a 3-week cycle at escalating doses of 24, 48, 54 and 72 mg/m2	*Pharmacokinetics:* No differences in the pharmacokinetics were observed between the two schedules after both single and repeated dosing. The systemic exposure to Milciclib (amount of Milciclib available systemically in the patient) increased with dose in terms of both Cmax (maximum concentration of Milciclib in plasma) and daily Area Under the Plasma Drug Concentration, or AUC, vs Time Curve, a measure of drug bioavailability without deviations from dose-proportionality (plasma concentration changes in a linear relationship to amount of drug dosed). After repeated administrations, Milciclib Cmax and AUC accumulated by a factor of 2-4, independent of the dose-level. *Clinical observations:* No objective (measurable) responses were achieved. SDs were reported in 5 out of 16 evaluable patients (31.3%), starting from the dose of 48 mg/m2/day. One disease stabilization maintained for 12 cycles (10.5 months) at 48 mg/m2/day, was achieved in a parotid gland patient.
CDKO-125a-004	Advanced/metastatic solid tumors 16 patients	Orally administered at 45, 60 and 80 mg/m2 once daily for 7 days on / 7 days off (Days 1 to 7 and 15 to 21) in a 4-week cycle in combination with fixed dose of IV gemcitabine (1000 mg/m2/day) on Days 1, 8, 15 over 30 minutes every 4 weeks	*Pharmacokinetics:* Pharmacokinetic parameters (Cmax, AUC) of Milciclib after Milciclib maleate/ gemcitabine combination were consistent with those previously observed after Milciclib maleate administration as single agent, suggesting no influence of gemcitabine on the pharmacokinetics of the compound. *Clinical observations:* One PR in 14 evaluable patients (7.1%) and one SD in 10 patients (71.4%). Disease stabilizations lasting z 6 months were recorded in 4 cases (28.6%) in thyroid, prostatic, pancreatic carcinoma and peritoneal mesothelioma, in 2 of them lasting 13.4 months (peritoneal mesothelioma) and 14.3 months (prostate cancer). The PR and 3 of the 4 long lasting disease stabilizations were obtained at the recommended Phase 2 dose (RP2D) of 80 mg/m2/day plus 1000 mg/m2/day gemcitabine, supporting development of combination therapies with Milciclib in advanced cancer patients. Results of trial CDKO-125a-004 were published: S. Aspeslagh et.al. Cancer Chemother. Pharmacol (2017) 79: 1257-1265

Phase 2 Development

Trial	Patient Population	Treatment Schedule / Dosing	Key Findings
CDKO-125a-005	Malignant pleural mesothelioma 38 patients	150 mg/day orally administered for 7 consecutive days every 14 days in 2-week cycles	*Pharmacokinetics:* Plasma levels of Milciclib were comparable to those previously obtained in the Phase 1 study CDK0-125a-001 at the same dosage and with the same schedule, confirming the reliability of the pharmacokinetic profile of the compound. *Clinical observations:* No objective responses were reported; prolonged SDs were observed in 2 patients, lasting 8.9 months and 8.7 months, respectively.
CDKO-125a-006 Trial cutoff: 1/9/2017	Malignant B3 thymoma / thymic carcinoma 72 patients	Single agent (flat dose) 150 mg once daily 7days on/7days off q2wks	*Clinical Observations:* Treatment with Milciclib met the primary endpoint of PFS at 3 months (PFS-3). 56 of 72 treated patients had median PFS of 5.78 months with upper and lower 95% confidence limits of 3.48 months and 7.89 months, respectively. The secondary endpoint, OS, was also met in this trial. 36 of 72 patients (50%) had median OS of 24.44 months with upper and lower 95% confidence limits of 22.05 and 54.55 months, respectively. Five patients from this study are continuing treatment with Milciclib.
CDKO-125a-007 Trial cutoff: 1/9/2017	Malignant B3 thymoma / thymic carcinoma 30 patients	Single agent (flat dose) 150 mg once daily 7days on/7days off q2wks	*Clinical Observations:* Treatment with Milciclib met the primary endpoint of PFS-3. 18 of 30 patients had median PFS of 5.65 months with upper and lower 95% confidence limits of 3.94 months and 17.45 months, respectively. The secondary endpoint, OS, was met in this trial. 3 of 30 treated patients (54.5%) had median OS of 21 months. Upper 95% confidence limits could not be calculated.
CDKO-125a-010	Recurrent or metastatic unresectable HCC	Single agent (flat dose) 100 mg once daily 4days on/3days off x 4 wks q4 wks	*Clinical Observations:* 28 out of 31 treated patients were evaluable, 14 completed the 6-month duration study. The most frequent adverse events such as diarrhea, ascites, nausea, fatigue, asthenia, fever, ataxia, headache, and rash were manageable. No drug-related deaths were recorded.

Source: Milciclib Investigators Brochure version 14 and Clinical Study reports for CDKO-125a-006-and CDKO-125a-007

Safety

Overall, Milciclib has indicated a similar pattern of toxicity across studies. Consistent with preclinical findings, the safety profile of the compound in humans is characterized by a dose-limiting neurological toxicity and, to a lesser extent, by GI toxicity. Asthenia (weakness) and fatigue have also been observed, as well as effects on liver,

especially with prolonged schedules of administration. Mild/moderate tremors are a common finding, reported also at recommended Phase 2 doses (RP2Ds) (only one case of grade 3), whereas ataxia (loss of muscle control and balance) was observed primarily during the first dose-escalation study (one case of grade 3 ataxia occurred also at the RP2D in the combination study CDKO-125a-004 and one in CDKO-125a-006 trial). Both tremor and ataxia were generally reversible in all cases in up to 7-9 days, upon drug discontinuation or dose reduction in some cases. Grade 1-2 dizziness was also reported, with only one grade 3 occurrence, overall. Mild dysgeusia (disorder of sense of taste) is another event that was reported across studies, as well as headache and anorexia (loss of appetite). Grade 3 myasthenia (muscle weakness) was also reported in two patients. Nausea and/or vomiting and/or diarrhea were mostly of grade 1-2 in severity and were manageable with appropriate therapy. Diarrhea was occasionally severe, leading to dehydration in several instances. Skin disorders were also reported across studies; the events were mainly of grade 1-2 in severity except for one case of grade 3 rash maculopapular and one case grade 3 of erythema multiforme. Hematological toxicity was mainly represented by lymphocytes (white blood cells) decrease and, to a lesser extent by all the other hematological parameters. Severe thrombocytopenia (decrease in number of platelets in blood) was sporadically observed, especially at the highest doses tested and in combination with gemcitabine. Effects on liver were dose-dependent and mainly represented by transient transaminase elevation (with bilirubin slightly less affected). ALT/AST (liver enzymes measured to monitor liver damage) elevations were usually mild using the 7 days on / 7 days off schedule (even if prolonged transaminases (liver enzymes) were occasionally observed). The more prolonged administrations were associated with a more frequent and pronounced effect on liver function tests. Asymptomatic grade 3-4 lipase (a pancreatic enzyme that breaks down fats, measured to monitor pancreatic function) elevations were sometimes reported, without clinical manifestation. No important effects on renal function were noted.

Monitoring of visual function was performed through visual acuity, funduscopy (ophthalmic examination of the back of the eye) and, in a subset of studies, electroretinography examinations, or ERG. Overall, no clinically relevant abnormalities for these parameters emerged during treatment across studies, except for ERG worsening, compared to baseline, observed in three patients, who for this reason discontinued study treatment as per protocol, and one case of retinal detachment reported as a serious event in one patient (CDKO-125a-006 trial) and assessed as probably related to Milciclib maleate.

Our interim review in trial CDKD-125A-010, as noted above, found Milciclib to be well-tolerated with no drug-related serious adverse events in 6 patients with unresectable or metastatic HCC who had concluded a first cycle of treatment with Milciclib.

Phase 2 Data in Thymoma and Thymic Carcinoma

Thymomas and thymic carcinomas are tumors that originate in epithelial cells of the thymus gland. Generally, thymoma does not spread beyond the thymus, while thymic carcinoma, represents an aggressive cancer that metastasizes rapidly and poses treatment challenges. Both cancers are rare, and it is estimated that together they account for ~400 cases per year in the US, or about 1.5 persons per million diagnosed with thymoma/thymic carcinoma. Patients more often present with advanced disease, with a 5-year survival of 30% to 50%. Standard primary treatment for patients with these types of tumors is surgical resection. Depending on tumor stage, treatment options include the use of radiation therapy and chemotherapy with or without surgery. First line of chemotherapy treatment is the combination of cisplatin, doxorubicin and cyclophosphamide for thymoma. For thymic carcinoma the first line of treatment is the combination of paclitaxel and carboplatin. Milciclib has Orphan Drug Designation (ODD) in the U.S. and EU for thymic cancer (thymic epithelial tumor or TET).

Milciclib met its primary endpoints in two Phase 2 clinical trials in patients with thymic carcinoma and thymoma. Clinical trials, CDKO-125A-006 (72 patients) and CDKO-125A-007 (30 patients) in patients with thymic carcinoma and thymoma, respectively, were conducted in the US, France and Italy. Monotherapy treatment regimen with Milciclib (150mg/day; 7 days on / 7 days off) was well-tolerated. Seven patients (5 patients in the CDKO-125A-006 study and 2 patients in the CDKO-125A-007) have been continuing treatment with Milciclib for more than 2 years with excellent tolerance profile. Among these, 2 patients have been treated with Milciclib for approximately 5 years, demonstrating tolerability of the drug for long term treatment.

In trial CDKO-125A-006, 56 of 72 treated patients had median PFS of 5.78 months with upper and lower 95% confidence limits of 3.48 and months, respectively. In trial CDKO-125A-007, 18 of 30 treated patients had median PFS of 5.65 months with upper and lower 95% confidence limits of 3.94 and 17.45 months, respectively. These results materially exceeded the median PFS> 10.2 weeks established for monotherapy with pemetrexed. The OS secondary endpoint was also met in both trials. In trial CDKO-125A-006, 36 of 72 (50%) treated patients had median OS of 24.44 months with upper and lower 95% confidence limits of 22.05 and 53.55 months, respectively. In trial CDKO-125A-007, 18 of 30 patients had an OS (54.5%) of 48 months. As a median was not reached, the 95% confidence limits could not be calculated.

Both clinical studies demonstrated that treatment with Milciclib met PFS as the primary endpoint and OS as a secondary endpoint.

Preclinical Data

The pharmacokinetics of Milciclib were investigated in mouse, rat, dog and monkey models after single intravenous and oral administration of the compound. Since the compound is intended for the oral administration route, the pharmacokinetics were further characterized after single and repeated oral administrations. These preclinical studies were performed with Milciclib formulated as maleate or mono/di/tri-hydrochloride salt. Following intravenous administration, Milciclib was characterized by a moderate clearance in mice, rats and monkeys and a high clearance in dogs. The volume of distribution was higher than the total body water in all tested species, suggesting an extensive tissue distribution. Following oral administration to rats and monkeys, Milciclib crossed the blood-brain barrier and distributed in the brain. In all species, Milciclib plasma levels increased largely in direct proportion with the dose.

Preclinical toxicology studies conducted with Milciclib have shown that the hemolymphopoietic system, the GI tract and the male reproductive organs are the major target organs considered related to the pharmacological activity of the compound in all species. The effects on the hemolymphopoietic system and GI tract were reversible after drug withdrawal. Reversibility could not be demonstrated in the male reproductive organs at the end of the 2-3-week recovery period because of the longtime of maturation of the seminiferous epithelium. Additional toxicities, that are considered not related to the mechanism of action of the compound, were Central Nervous System, or CNS, ocular and renal toxicities. In addition, hemorrhages in different organs were observed in dogs and monkeys. Clinical signs of CNS toxicity were observed at high doses given as single or repeated administrations in all species.

Our Preclinical Programs

Anti-IL6R Fully Human mAb TZLS-501 (formerly known as NI-1201)

TZLS-501 is a fully human mAb targeting the IL-6R. We licensed the intellectual property from Novimmune in January 2017. This fully human mAb has a novel mechanism of action, binding to both the membrane-bound and soluble forms of the IL-6R and depleting circulating levels of the IL-6 in the blood. An excessive production of IL-6 is regarded as a key driver of chronic inflammation, associated with autoimmune diseases such as multiple myeloma, oncology indications and rheumatoid arthritis, and we believe that TZLS-501 may have potential therapeutic value for these indications.

In preclinical studies, TZLS-501 demonstrated the potential for overcoming the limitations of other IL-6 blocking pathway drugs. Compared to tocilizumab and sarilumab, while binding to the membrane-bound IL-6R complex, TZLS-501 has been observed to have a higher affinity for the soluble IL-6 receptor from antibody binding studies conducted in cell culture. TZLS-501 also demonstrated the potential to block or reduce IL-6 signaling in mouse models of inflammation. The soluble form of IL-6 has been implicated to have a larger role in disease progression compared to the membrane- bound form (Kallen, K.J. (2002). “The role of transsignaling via the agonistic soluble IL-6 receptor in human diseases.” Biochimica et Biophysica Acta. 1592 (3): 323—343.).

StemPrintER™

StemPrintER is a multi-gene signature assay intended for use in patients diagnosed with estrogen-receptor positive ER+/HER2 negative breast cancers. We believe this in-vitro prognostic test will be used in conjunction with clinical evaluation to identify those patients at increased risk for early and/or late metastasis. StemPrintER is designed to help physicians distinguish ER+/HER2 negative patients:

- with an elevated risk of early recurrence (<5 years) who could benefit from chemotherapy in addition to hormonal therapy;
- with a high risk of late recurrence who could benefit from prolonged endocrine treatment up to 10 years; and
- with a low risk of early recurrence who might be spared chemotherapy or be eligible for less aggressive treatments.

Our diagnostic has a novel biological basis, being based on the detection of cancer stem cell markers, uses a reliable platform (qRT-PCR, FFPE), and has been evaluated in an initial retrospective validation study using a consecutive cohort of approximately 2400 patients with breast cancer. Our development team is preparing for a retrospective validation study using an independent cohort and has conducted a pre-submission meeting with the FDA, and it is our intention to proceed with the study in the event that we are able to procure a collaboration partner or grant funding but it is not a project of primary focus at the current time.

Manufacturing

We believe our current CMOs will be able to fully meet our current clinical trial needs and anticipated future commercial demand for Foralumab and Milciclib in a cost-effective manner.

A large-scale cGMP manufacturing of Foralumab drug substance has been accomplished and we have produced sufficient purified material for completing all clinical studies up to Phase 3. This material was produced by Lonza Group AG using a proprietary cell culture technology. The Foralumab material is highly stable when stored at -80ºC for several years. A novel and proprietary formulation suitable for oral administration of Foralumab has been developed. We have completed cGMP manufacturing of formulated drug product for nasal and oral routes of administration for Phase I clinical studies.

We have also achieved cGMP manufacturing of Milciclib at pilot scale. The chemical scheme for manufacturing is simple with reproducible yields. This method has been used for producing drug substance to supply the ongoing clinical studies. The chemical process is very cost-effective and can be scaled-up for much larger scale needed for commercialization.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

We are aware of a number of companies focused on developing therapies in various indications. Any advances made by a competitor may be used to develop therapies that could compete against any of our product candidates.

For our specific product candidates, the main competitors include:

- Sorafenib and Lenvatinib are currently the standards of use therapy for HCC but the drugs exhibit severe toxicities and patients often develop resistance to the treatment with Sorafenib. As a result, there is an immediate need for improvement in treatment for HCC.
- We believe that Foralumab is currently the only fully human anti-CD3 mAb in clinical development for treatment of NASH and Crohn’s disease.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger R&D, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA or other regulatory 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. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Intellectual Property

We strive to protect and enhance the proprietary technologies, inventions and improvements that we believe are important to our business, including seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. Our policy is to seek to protect our proprietary position by, among other methods,

pursuing and obtaining patent protection in the United States and in jurisdictions outside of the United States related to our proprietary technology, inventions, improvements, platforms and our product candidates that are important to the development and implementation of our business.

As of June 27, 2019, we have 255 patents and 30 patents pending and our intellectual property portfolio was made up as follows:

Family	Subject	Priority	Status	Expires	Jurisdiction
Foralumab TZLS-401	Methods of Use (Autoimmune or Inflammatory diseases and disorders)	2004	Issued	2025	Australia, Canada, China, Hong Kong, Israel, Japan, Mexico, Norway, Singapore, South Africa, Ukraine, Armenia, Austria, Azerbaijan, Belgium, Belarus, Switzerland, Germany, Denmark, Spain, France, United Kingdom, Ireland, Italy, Kyrgyzstan, Kazakhstan, Luxembourg, Moldova, Netherlands, Portugal, Russian Federation, Sweden, Tajikistan, Turkmenistan,
	Composition and methods of use	2004	Issued/ Pending	2025	US, Armenia, Australia, Austria, Azerbaijan, Belarus, Canada, China, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Netherlands, Norway, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Switzerland, Tajikistan, Turkmenistan, and Ukraine Pending: Brazil, Japan (divisional), Singapore (divisional), US (divisional)
	Methods of Use (In combination with anti-IL-6/IL-6R antibodies)	2011	Pending	2032	US
	Formulations and dosing regimen	2016	Pending	2037	US, Australia, Canada, China, Europe, Israel, Japan
	Methods of Use (CNS disorders)	2017	Pending	2038	PCT
	Methods of Use (gastrointestinal/autoimmune/inflammatory)	2018	Pending	2039	Provisional
Milciclib TZLS-201	Composition of matter, methods of use, process of manufacturing	2003	Issued/ Pending	2024	US, Europe, Eurasia, Africa, Algeria, Antigua & Barbuda, Argentina, Australia, Barbados, Bosnia & Herzegovina, Brazil, Canada, Colombia, Costa Rica, Croatia, Cuba, Ecuador, Egypt, Georgia, Iceland, India, Indonesia, Israel, Japan, Korea, Kosovo, Malaysia, Mexico, Mongolia, Montenegro, New Zealand, Nicaragua, Norway, Pakistan, Philippines, Serbia, Singapore, South Africa, Sri Lanka, Taiwan, Thailand, Trinidad & Tobago, Tunisia, Ukraine, Uzbekistan, Venezuela, Vietnam Pending: Several in US and other countries
	Methods of use (multiple indications)	2008; 2009	Issued	2029; 2030	US, EU, China, Hong Kong, Japan
	Methods of use (combination therapies with cytotoxics)	2008; 2009	Issued	2029; 2030	US, EU, China, Hong Kong, Japan
	Compositions of related entities, formulations and methods of treatment	2009	Issued	2030	US, EU, China, Hong Kong, Japan
	Methods of use (combination therapies with therapeutic antibodies)	2006	Issued	2027	US, EU, China, Japan
	Formulations of milciclib and therapeutic combinations of the same for use in the treatment of cancer	2017	Pending	2038	US, PCT
Anti IL-6/IL-6R Antibody TZLS-501	Composition of Matter and Methods of use	2009	Issued	2029	US, Austria, Australia, Belgium, Canada, China, Denmark, France, Germany, Ireland, Italy, Japan Luxembourg, Mexico, Netherland, Spain, Sweden, Switzerland and UK Pending: US (divisional), Japan (divisional), India
StemPrinter	Methods and Kits Comprising Gene Signature for Stratifying Breast Cancer Patients	2016	Pending	2037	US, EU, Canada
	Methods and Kits Comprising Gene Signature for Stratifying Breast Cancer Patients	2018	Pending	2038	PCT

We have rights to a patent family that discloses the Milciclib compound, methods of using the compound, and processes for making the compound under license from Nerviano (which is further described below). This patent family includes six granted U.S. patents, one granted European patent, and one granted Eurasian patent. This patent family also includes granted patents in Africa (African Intellectual Property Organization, African Regional Intellectual Property Organization), Algeria, Argentina, Australia, Barbados, Bosnia & Herzegovina, Canada, Colombia, Costa Rica, Croatia, Cuba, Ecuador, Georgia, Iceland, India, Indonesia, Israel, Japan, Korea, Kosovo, Malaysia, Mexico, Mongolia, Montenegro, New Zealand, Nicaragua, Norway, Pakistan, Philippines, Serbia, Singapore, South Africa, Sri Lanka, Taiwan, Tunisia, Ukraine, Uzbekistan, and Vietnam. Several applications are pending in the U.S. and other countries in this family. The patents in this family will expire in April 2024, excluding any patent term adjustment and patent term extension in the U.S. and similar regulatory extensions available in several other jurisdictions, such as Europe.

We also have rights to a second patent family which covers related entities, such as salts and crystal forms, of Milciclib, and methods of using the salts and crystal forms. This patent family comprises one granted U.S. patent and one granted patent in each of Europe, China, Japan, and Hong Kong. The patents in this family will expire in April 2030, excluding any patent term adjustment and patent term extension in the U.S. and several other jurisdictions, such as Europe.

In addition, we have rights to five patent families which cover methods of using Milciclib in the treatment of multiple indications. These patent families comprise five granted U.S. patents, and granted patents in Europe, China, Hong Kong, and Japan, and one pending patent application in Europe. The patents in these families will expire between February 2027 and March 2030, excluding any patent term adjustment and patent term extension in the U.S. and similar regulatory extensions available in several other jurisdictions, such as Europe.

Among the above five patent families, two families also cover combination therapies of Milciclib with cytotoxic agents. These families comprise two granted U.S. patents, and granted patents in Europe, China, Hong Kong, and Japan. The patents in these families will expire between November 2029 and March 2030, excluding any patent term adjustment and patent term extension in the U.S. and similar regulatory extensions available in several other jurisdictions, such as Europe.

One family of the above five patent families also covers combination therapies of Milciclib with therapeutic antibodies. This patent family includes one granted U.S. patent, and granted patents in Europe, China, and Japan. The patents in this family will expire in February 2027, excluding any patent term adjustment and patent term extension in the U.S. and similar regulatory extensions available in several other jurisdictions, such as Europe.

In addition, we have rights to a patent family which covers methods of using Milciclib together with a second anti-cancer agent in the treatment of cancer. This patent family includes one pending application in the U.S and one pending international application. The patent applications in this family, if issued as patents, will expire in December 2038, excluding any patent term adjustment and patent term extension in the U.S. and similar regulatory extensions available in several other jurisdictions, such as Europe.

We have rights to a first patent family that disclose methods of using Foralumab, licensed from Novimmune (which is further described below). This patent family includes, one granted European patent, and one granted Eurasian patent. This patent family also includes granted patents in Australia, Canada, China, Hong Kong, Israel, Japan, Mexico, Norway, Singapore, South Africa, Ukraine, and Portugal. The patents in this family will expire in April 2025, excluding any patent term extensions available in several jurisdictions, such as Europe.

We also have rights to a second patent family that discloses the Foralumab compound and methods of using the compound also licensed from Novimmune. This patent family comprises three granted U.S. patent one granted European patent, and one granted Eurasian patent. This patent family also includes granted patents in Australia, Canada, China, Hong Kong, India, Israel, Japan, Mexico, Norway, Republic of Korea, Singapore, South Africa, and Ukraine. Applications are pending in Brazil, Japan, Singapore and U.S. The patents in these families will expire in June 2025, excluding any patent term adjustment in the U.S. and patent term extensions available in the U.S. and several other jurisdictions, such as Europe.

In addition, we have rights to a third patent family that discloses combination therapies of Foralumab with Il-6 or IL-6R antibodies licensed from Novimmune. This patent family has one pending U.S. application. The patents in these families will expire in January 2032, excluding any patent term adjustment and patent term extensions available in the U.S.

We own and have right to a fourth patent family that discloses formulations of Foralumab and dosing regimens for treating various disorders. This patent family has applications pending in the U.S, Australia, Canada, China, Europe, Israel and Japan. The patents in these families will expire in August 2037, excluding any patent term adjustment and patent term extensions available in the U.S and several other jurisdictions.

We have rights to a patent family that discloses methods of using TZLS-501 to treat various disorders, licensed from Novimmune. This patent family includes, four granted U.S. patents and one granted European patent. This patent family also includes granted patents in Australia, Canada, China, Japan and Mexico. Applications are pending in U.S. and India. The patents in this family will expire in May 2029, excluding any patent term extensions available in several jurisdictions, such as Europe.

Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued for regularly filed applications in the United States are granted a term of 20 years from the earliest effective non-provisional filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the USPTO delay in issuing the patent as well as a portion of the term effectively lost as a result of the FDA regulatory review period. However, as to the FDA component, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product by product basis, from country to country and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Furthermore, we rely upon trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention assignment agreements with our collaborators and selected consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements 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 collaborators, employees and consultants 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.

Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our product candidates or processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize our future product candidates may have an adverse impact on us. If third parties have prepared and filed patent applications prior to March 16, 2013 in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the USPTO, to determine priority of invention. For more information, see “Risk Factors — Risks Related to Our Intellectual Property.”

Material Agreements

Nerviano Agreement

In January 2015, we entered into an agreement with Nerviano, or the Nerviano Agreement, pursuant to which we obtained a worldwide, exclusive license to patents owned or controlled by Nerviano, or the Nerviano License to develop and commercialize products and services incorporating Milciclib as an active ingredient, and any product or service controlled or owned by Nerviano that is used to diagnose or assess responsiveness to Milciclib therapy or dosage. The Nerviano License confers the right on us grant sub-licenses, and otherwise to employ third party manufacturers and distributors to produce and sell licensed products and services.

Each party to the Nerviano Agreement agreed to a development plan, or the Nerviano Development Plan, approved by a joint development committee, or the JDC. The JDC is comprised of at least two members of each party, meets at least twice a year and endeavors to make decisions by consensus, save that where there is a disagreement with respect to any aspect of the licensed products or services we shall have a deciding vote.

Under the Nerviano Development Plan, we (or, as the case may be, our sub-licensee(s)) are obliged to use commercially reasonable efforts to develop and commercialize a licensed product or service in at least one therapeutic indication that arises out of the Nerviano Development Plan, and Nerviano is obliged to use commercially reasonable efforts to manufacture such product(s) or service(s). Pursuant to the Nerviano Development Plan, we have sole responsibility for costs for further clinical development and Nerviano is obliged to perform Phase 2 studies of licensed products and services, save that the amounts to be invoiced by Nerviano to us for Phase 2 studies shall be commercially reasonable and not be greater than a low-double-digit percentage in excess than amounts estimated to be invoiced by another reputable clinical research organization.

During the term of the Nerviano Development Plan, or the Nerviano Exclusivity Period, we and our affiliates may not, directly or indirectly, develop, make, use, sell, offer for sale or import any small molecule compound or other biological or chemical molecule other than Milciclib that directly binds to, with an affinity indicated by an IC50 of 100nM or less, and modulates the following specified pharmacological targets hit by Milciclib: Cdk-2, Cdc-4 and Cdc6.

Upon entry into the Nerviano Agreement, we paid an upfront, non-refundable initial license fee of $3,500,000 to Nerviano. We issued 4,233,616 of ordinary shares, fully paid with a nominal value of three pence each, or the Consideration Shares, to Nerviano at an issue price of 50.5 pence each (equivalent to an aggregate value of £2,137,976.08).

Nerviano granted us an option, or the Nerviano Option, to buy-back all the Consideration Shares for a de minimis aggregate consideration exercisable on written notice at any time after the earlier of:

(i) an unsuccessful Phase 2 trial for HCC or breast cancer with a licensed product or service and the concomitant decision of the company, our affiliates or sub-licensees to discontinue development of a licensed product or service;

(ii) the fifth anniversary of the Nerviano Agreement, (provided that if on such date a Phase 2 trial has commenced but has not been completed our ability to exercise the Nerviano Option shall be delayed until the outcome of the Phase 2 trial has become clear); or

(iii) our abandonment of any licensed product or service for bona fide scientific reasons.

The Nerviano Option cannot be exercised if any of the following events (each, a Release Event), occurs:

(i) a successful completion of a Phase 2 trial for HCC or breast cancer with a licensed product or service, where such successful conclusion renders the licensed product or service eligible for entry into a Phase 3 trial with no further clinical study; or

(ii) our abandonment of the development of, or failure to exercise commercially reasonable efforts develop any, licensed product or service, save for where we have bona fide scientific reasons.

The Nerviano Option effectively allows us to recover the Consideration Shares if it transpires that Milciclib proves to be unsuccessful in the indications for which we licensed it or we fail to see satisfactory results in a period of 5 years from the date of the license agreement.

Prior to a Release Event, Nerviano has agreed to not transfer, dispose of, or grant options or other rights over directly or indirectly any interests in the Consideration Shares nor to derive any financial benefit from the Shares, but is entitled to exercise all voting rights arising from the Consideration Shares.

Following a Release Event, Nerviano has agreed to a 12 month lock-up, or the Nerviano Lock-Up, in respect of the Consideration Shares, subject to customary exceptions, including the prior written consent of the company and our nominated adviser from time to time (which consent may be approved, provided or provided subject to conditions as each may determine in its absolute discretion), acceptance of takeover bids, share buy-backs by the company, or where required by law.

Following the lapse of the term of the Nerviano Lock-Up, Nerviano has agreed to not directly or indirectly, transfer, sell, mortgage, charge or otherwise dispose of more than 10% of the Consideration Shares (i.e. 423,362 ordinary shares) per calendar month, and to utilize the company's broker from time to time to execute those transactions in respect of the legal and or beneficial ownership or any other interest in the Consideration Shares so as to ensure an orderly market.

We are obligated to pay Nerviano the following additional amounts in respect of the first licensed product or service which achieves the stated development milestones:

(a) $100,000 upon initiation, first patient dosed, or FPD, of the first Phase 3 registration trial in thymic carcinoma.

(b) $4,000,000 upon FPD of the first Phase 3 registration trial in HCC.

(c) $6,000,000 upon FPD of the first Phase 3 registration trial in breast cancer.

(d) Upon the first NDA equivalent in: thymic carcinoma, $900,000; HCC, $9,000,000; breast cancer, $15,000,000.

We are obliged to pay Nerviano a low-single-digit percentage royalty fee of the annual net sales of licensed products or services, subject to certain royalty off-sets on a country-by-country basis and, subject to certain exclusions, a low-double-digit percentage of sub-licensing revenues from the sale of licensed products or services for the life of the licensed patents.

During the Nerviano Exclusivity Period, we have the right to terminate activities and funding to Nerviano after 24 months from the beginning of the Nerviano Exclusivity Period but not prior thereto. If we exercise our termination right, we are obliged to transfer to Nerviano all relevant data, licensed products and services and an exclusive license pertaining to the licensed product or services, and Nerviano shall pay us a low-single-digit percentage royalty on annual net sales of licensed products and services, subject to certain exceptions.

Following the expiry of the Nerviano Exclusivity Period, we may terminate the Nerviano Agreement at any time on 90 days' written notice, and either party may terminate the Nerviano Agreement for material breach by the other party of any material obligation or condition of the Nerviano Agreement by written notice, subject to a 45 day cure period for a payment breach, and a 120 day cure period for any other breach.

Absent early termination, the Nerviano Agreement shall remain in force until the later of, in all countries in which licensed products and services are marketed pursuant to the Nerviano Agreement, (a) the expiration of the last claim in an issued, unexpired patent within the licensed patents, subject to certain exceptions, which covers the sale of such licensed products or services, or (b) five years from the date of first commercial sale of such licensed product or service in such country.

Novimmune CD3 Agreement

In December 2014, we entered into a license and sublicense agreement with Novimmune, or the Novimmune CD3 Agreement, pursuant to which we obtained a worldwide, exclusive license to certain patents owned or controlled by Novimmune, or the Novimmune CD3 License, together with a sublicense to certain patent licenses from Bristol-Myers Squibb Company, or BMS, or the BMS CD3 Sublicense, and any associated know-how, biologic materials, clinical data or other technology relating to CD3 receptor mAbs and their use in order to research, develop and commercialize products and services. The Novimmune CD3 License and BMS CD3 Sublicense both confer the right to us to grant sublicenses, and otherwise to employ third party manufacturers and distributors to produce and sell licensed products and services, respectively.

Pursuant to the Novimmune CD3 Agreement, Novimmune granted the BMS CD3 Sub-License to us. Novimmune effected such grant pursuant to a research and commercialization agreement between Novimmune and BMS dated September 20, 2014, or the BMS R&C Agreement, and the agreement for the exclusive commercial license for the CD3 licensed product (NI-0401) between Novimmune and BMS dated February 2005.

Under the Novimmune CD3 Agreement, we have full control and authority over the research, development and commercialization of licensed products and services, and are required to exercise commercially reasonable efforts to commercialize such licensed products and services at all times.

Upon our entry into the Novimmune CD3 Agreement we paid an upfront fee of $750,000 to Novimmune (to be on paid by Novimmune to BMS pursuant to the terms of the BMS R&C Agreement), and a further upfront fee of $500,000 to Novimmune. We are required to pay Novimmune installments of $250,000 on each of the 14 month, 26 month and 38 month anniversaries of the date of the Novimmune CD3 Agreement. For the term of the Novimmune Agreement, we are obligated to pay to Novimmune a royalty of a low-single-digit percentage on net sales of licensed products and services, together with any amounts owed to BMS incurred pursuant to the BMS CD3 Sub-License.

We may terminate the Novimmune CD3 Agreement at any time on 90 days' written notice, and either party may terminate the Novimmune CD3 Agreement by written notice for a payment breach or any other breach, subject to 45 day and 120 day cure periods, respectively. Absent early termination, the Novimmune CD3 Agreement will continue until the later of, in all countries in which licensed products are marketed pursuant to the Novimmune CD3 Agreement, (a) the expiration of the last claim in an issued, unexpired patent within the licensed patents or a claim that has not been pending more than five years, subject to certain exceptions, which covers the sale of such licensed product or service, or (b) the end of any market exclusivity period granted by the relevant governmental authority in a country that prevents another party from marketing the same licensed product or service.

Novimmune IL-6r Agreement

In December 2016, we entered into a license and sublicense agreement with Novimmune, or the Novimmune IL-6r Agreement, pursuant to which we obtained a worldwide, exclusive license to certain patents owned or controlled by Novimmune, or the Novimmune IL-6r License, together with a sub-license to certain patent licenses from BMS, or the BMS IL-6r Sub-License, and any associated know-how, biologic materials, clinical data or other technology relating to IL-6r mAbs and their use in order to research, develop, commercialize products and services. The Novimmune IL-6r License and BMS IL-6r Sub-License both confer the right to us to grant sub-licenses, and otherwise to employ third party manufacturers and distributors to produce and sell licensed products and services, respectively.

Pursuant to the Novimmune IL-6r Agreement, Novimmune granted the BMS IL-6r Sub-License. Novimmune effected such grant pursuant to the BMS R&C Agreement and the agreement for the IL-6r exclusive commercial license for the IL-6r antibody licensed product (NI-1201) between Novimmune and BMS dated September 20, 2009, or the IL-6r Commercial License Agreement.

Under the Novimmune IL-6r Agreement, we have full control and authority over the research, development and commercialization of licensed products and services, and are required to exercise commercially reasonable efforts to commercialize such licensed products and services at all times.

Upon our entry into the Novimmune IL-6r Agreement we paid an upfront fee of $100,000 to Novimmune. For the term of the Novimmune IL-6r Agreement, we are obligated to pay to Novimmune a royalty of a low-single-digit percentage on net sales of licensed products and services, or low-double-digit percentage of any sub-license royalty revenue which we receive that arises from sales of licensed products and services, together with any amounts owed to BMS incurred pursuant to the BMS IL-6r Sub-License.

The BMS R&C Agreement and the IL-6r Commercial License Agreement were amended pursuant to an agreement between Novimmune and BMS dated December 2016, or the Novimmune Amendment Agreement. Pursuant to the Novimmune Amendment Agreement, in the event that Novimmune (or, as the case may be, a sublicensee) commercializes a combination product comprising NI-1201 and NI-0401, then such product shall be subject to a single royalty.

We may terminate the Novimmune IL-6r Agreement at any time on 90 days' written notice, and either party may terminate the Novimmune IL-6r Agreement by written notice for a payment breach or any other breach, subject to 45 day and 120 day cure periods, respectively. Absent early termination, the Novimmune IL-6r Agreement will continue until the later of, in all countries in which licensed products are marketed pursuant to the Novimmune IL-6r Agreement, (a) the expiration of the last claim in an issued, unexpired patent within the licensed patents or a claim that has not been pending more than five years, subject to certain exceptions, which covers the sale of such licensed product or service, or (b) the end of any market exclusivity period granted by the relevant governmental authority in a country that prevents another party from marketing the same licensed product or service.

Brigham and Women's Hospital License

On May 29, 2018, we entered into a license agreement, or the BWH License, with BWH pursuant to which we obtained a worldwide exclusive license to a patent owned by BWH for a novel technology discovered by Dr. Howard Weiner. The patent relates to a formulation of Foralumab in a medical device developed for nasal administration of Foralumab. The BWH License extends to any associated know-how, clinical data and use in order to research, develop and commercialize products and services. The BWH License confers on us the right to grant sub-licenses, and otherwise to employ third party manufacturers and distributors to sell licensed products and services.

Under the BWH License we have full control and amnesty over the research, development and commercialization of licensed products and services and are required to exercise commercially reasonable efforts to commercialize such licensed products and services at all times.

Upon our entry into the BWH License we paid an upfront fee of $10,000 to BWH. We are required to pay annual maintenance fees, all ongoing patent maintenance and prosecution costs and a low single-digit royalty on annual net sales (and a 12% royalty of non-royalty sub-license revenues for the life of the intellectual property). We are also obliged to make certain milestone payments of: (a) US$300,000 within 60 days of first patient enrolled in a Phase 1 human clinical trial; (b) US$600,000 within 60 days of first patient enrolled in a Phase 2 human clinical trial; (c) US$1,500,000 within 60 days of first patient enrolled in a Phase 3 clinical trial; and (d) US$3,000,000 within 60 days of first commercial sale of a licensed product.

We may terminate the BWH License at any time on 90 days' written notice, and either party may terminate the BWH License by written notice for payment or other breach, subject to a 60 day cure period. Absent early termination the BWH License will remain in effect until the date on which all patents and filed patent applications have expired or been abandoned.

Organizational Structure

The following table sets out details of our significant subsidiaries:

Name	Principal activity	Registered address	Percentage shareholding	Country of incorporation
Tiziana Pharma Limited	Clinical stage biotechnology company	3rd Floor, 11–12 St James's Square, London, SW1Y 4LB	100%	England & Wales
Tiziana Therapeutics Inc.	Clinical stage biotechnology company	420 Lexington Avenue Suite 2525 New York, NY 10170	100%	USA
Longevia Genomics S.r.l.	Biotechnology discovery company	Via Constantinopli 42 09100–Cagliria (CA)	100%	Italy

Government Regulation

Overview

Government authorities in most jurisdictions extensively regulate the research, development, clinical testing, manufacture, distribution and marketing of pharmaceutical products such as those that the company is developing. Obtaining regulatory approvals and ensuring subsequent compliance with applicable laws and regulations requires the expenditure of substantial time and financial and managerial resources. Regulatory requirements in different jurisdictions vary, and the timing and success of efforts to obtain regulatory approvals can be highly uncertain. Development of a successful drug candidate, from identification of a candidate drug compound, through preclinical and clinical testing, to registration, typically takes more than ten years.

Drug development is a highly structured process divided into two major stages, preclinical and clinical. In the preclinical stage, the toxicology and mode of action of an active compound is evaluated. The clinical stage is designed to prove the safety of any new pharmaceutical, determine dosage requirements and, predominantly in the later phases, prove its therapeutic utility. This stage is carried out in three phases, which, as a developer moves through the phases, require increasingly large, complex, expensive and time-consuming clinical studies. During Phase 1, the product candidate is initially given to a small number of healthy human subjects or patients and tested for safety, tolerance, absorption, metabolism, distribution and excretion. During Phase 2, additional trials are conducted in a larger, but still relatively limited, patient population to verify that the product candidate has the desired effect and to identify optimal dosage levels. Furthermore, possible adverse effects and safety risks are identified. The therapeutic utility of the product candidate for specific targeted diseases is also studied in more depth. During Phase 3, trials are undertaken to further evaluate dosage, to provide statistically significant evidence of clinical effectiveness and to further study the safety in an expanded patient population at multiple clinical trial sites. Phase 3 trials may require several hundreds or thousands of patients and are therefore the most expensive and time-consuming to conduct. At any time during one of the phases, a trial may produce a negative result, in which case the developer may choose to end the development project.

Following completion of the Phase 3 trials, the developer submits all the preclinical and clinical trial documentation as well as extensive data characterizing the manufacturing process to the regulator to seek regulatory approval to market the formulation as a pharmaceutical product. The regulator reviews all the information related to the safety of the active compound, and whether the pharmacological effect claimed by the developer on the proposed label can be substantiated by the results of the clinical trials. The regulator has the option to decide to approve the application as requested, ask for changes to the claims made by the developer, ask for more information, require that further clinical trials are undertaken, or refuse to approve the formulation for sale.

Even after initial regulatory approval has been obtained, further studies, including Phase 4 post-approval safety studies, may be required to provide additional data on safety and will be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested. There are also continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data. In addition, regulatory authorities require post-marketing reporting to monitor the adverse effects of the product. Results of post-approval programs may limit or expand the further marketing of the products. Further, if there are any modifications to the product, including changes in indication, manufacturing process or labeling, or a change in the manufacturing facility, an application seeking approval of such changes or, as the case may be, notification, must be submitted to the relevant regulatory authorities before the modified product can be commercialized. Moreover, an approved drug product may be subject to a REMS, which could impose a number of post-approval obligations, including (among other things) a communication plan for physicians regarding safe use of the drug, distribution and use restrictions, and/or periodic assessments of the effectiveness of the REMS. Finally, studies may be required as a contingency of regulatory approval (post-approval commitments), and completion of these studies within a regulator mandated time frame may be required.

European Union

The development, marketing and sale of medicinal products in the EU is subject to extensive pre and post marketing regulation by regulatory authorities at both the EU and national levels. The requirements, regulatory approvals and processes governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country, although there is some degree of EU wide harmonization.

Clinical Trials

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. If the sponsor of the clinical trial is not established within the EU, it must appoint an entity within the EU to act as its legal representative. The sponsor must take out a clinical trial insurance policy and, in most EU countries, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the relevant regulatory authority, and a positive opinion from an independent ethics committee. The application for a clinical trial authorization must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, clinical trial authorization applications must be submitted to the regulatory authority in each Member State in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is currently expected to take effect in 2019, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with cGMP.

Marketing Approval

In the EU medicinal products can only be commercialized after obtaining an MA. There are three procedures for obtaining marketing approvals: the centralized procedure, the decentralized procedure and the mutual recognition procedure/national procedure.

The Community marketing authorization, which is issued by the European Commission through the centralized procedure, based on the opinion of the CHMP of the EMA, is valid throughout the entire territory of the EU. The centralized procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EU, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

Marketing approvals obtained using the decentralized procedure are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the regulatory authorities of each of the Member States in which the marketing approval is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics and a draft of the labeling and package leaflet, which are sent to the other the concerned Member States, or CMSs, for their approval. A CMS can raise an objection, based on the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health. If no such objections are raised the product will be granted a national marketing authorization in the RMS and all of the selected CMSs. Where a product has already been authorized for marketing in a Member State, this decentralized procedure approval can be recognized in other Member States through the mutual recognition procedure.

Marketing approvals obtained using the national procedure are issued by a single regulatory authority of one of the Member States and only apply to the territory covered by the relevant regulatory authority. They are available for products not falling within the mandatory scope of the centralized procedure. Once a product has been authorized for marketing in a Member State through the national procedure, any application in another Member State must be by the mutual recognition procedure whereby the marketing approval can also be recognized in other Member States through the mutual recognition procedure.

Under the procedures described above, before granting the MA, the EMA or the relevant regulatory authority of the Member States of the EU makes an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and therapeutic utility.

The holder of a marketing authorization in any Member State of the EU is subject to various obligations under applicable EU regulations, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports to the regulatory authorities. The holder must also ensure that the manufacturing and batch release of its product is in compliance

with the applicable requirements. The marketing approval holder is further obligated to ensure that the advertising and promotion of its products complies with applicable laws, which can differ from Member State to Member State of the EU.

Data Exclusivity

MAAs for generic medicinal products in the EU do not need to include the results of preclinical and clinical trials, but instead can refer to the data included in the marketing approval of a reference product for which regulatory data exclusivity has expired. If a marketing approval is granted for a medicinal product containing a new active substance, that product benefits from eight years of data exclusivity, during which generic MAAs referring to the data of that product may not be accepted by the regulatory authorities, and a further two years of market exclusivity, during which such generic products may not be placed on the market. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved.

There is a special regime for biosimilars, or biological medicinal products that are similar to a reference medicinal product but that do not meet the definition of a generic medicinal product, for example, because of differences in raw materials or manufacturing processes. For such products, the results of appropriate preclinical or clinical trials must be provided, and guidelines from the EMA detail the type of quantity of supplementary data to be provided for different types of biological product. There are no such guidelines for complex biological products, such as gene or cell therapy medicinal products, and so it is unlikely that biosimilars of those products will currently be approved in the EU. However, guidance from the EMA states that they will be considered in the future in light of the scientific knowledge and regulatory experience gained at the time.

Orphan Medicinal Products

The EMA's Committee for Orphan Medicinal Products, or COMP, may recommend orphan medicinal product designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the product in the EU would be sufficient to justify the necessary investment in developing the medicinal product. The COMP may only recommend orphan medicinal product designation when the product in question offers a significant clinical benefit over existing approved products for the relevant indication. Following a positive opinion by the COMP, the European Commission adopts a decision granting orphan status. The COMP will reassess orphan status in parallel with EMA review of a marketing authorization application and orphan status may be withdrawn at that stage if it no longer fulfills the orphan criteria (for instance because in the meantime a new product was approved for the indication and no convincing data are available to demonstrate a significant benefit over that product). Orphan medicinal product designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following marketing authorization. During this period, the competent authorities may not accept or approve any similar medicinal product, unless it offers a significant clinical benefit. This period may be redacted to six years if the orphan medicinal product designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

United States

Standard Procedure

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act of 1938 and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory studies, animal studies and formulation studies in compliance with the FDA's good laboratory practice regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by the institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as GCPs to establish the safety and clinical utility of the proposed product candidate for its proposed indication;
- submission to the FDA of a BLA or NDA;
- satisfactory completion of an FDA pre-approval inspection of the production facility or facilities where the product is produced to assess compliance with the FDA's cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality, purity and potency;
- potential FDA audit of the preclinical and/or clinical trial sites that generated the data in support of the NDA; and
- FDA review and approval of the BLA or NDA prior to any commercial marketing or sale of the product in the United States.

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. 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 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.

Clinical Trials

Clinical trials involve the administration of the IND to human patients under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research patients provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, 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. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their website. Regulatory authorities, IRBs or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research patients are being exposed to an unacceptable health risk.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls, or CMC, and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act guidelines that are currently in effect, the FDA has a goal of ten months from the date of filing of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a filing decision.

In addition, under the Pediatric Research Equity Act of 2003**,** certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug 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. 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.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are 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 reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. 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.

Before approving a BLA or NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. 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 may inspect one or more clinical trial sites to assure compliance with GCP requirements.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a CR letter. A CR letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may

decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a 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-marketing studies or surveillance programs. After approval, some 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.

Orphan Drug Designation

Under the Orphan Drug Act of 1983, the FDA may designate a biologic 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 biologic product available in the United States for treatment of the disease or condition will be recovered from sales of the product).

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, meaning that the FDA may not approve any other applications to market the same drug or biologic product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or if the party holding the exclusivity fails to assure the availability of sufficient quantities of the drug to meet the needs of patients with the disease or condition for which the drug was designated. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity.

Post-Approval Requirements for the EU and United States

The FDA and the relevant regulatory authorities in the EU strictly regulate marketing, labeling, advertising and promotion of products that are placed on the market in their respective territories. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The regulatory authorities 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, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the relevant regulatory authorities, and are subject to periodic unannounced inspections by them to confirm compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior approval of the relevant regulatory authorities before being implemented. Regulations laid down by the FDA and the regulatory authorities in the EU also require investigation and correction of any deviations from the requirements of cGMP and impose reporting and documentation requirements upon the marketing approval holder and any third party manufacturers that the marketing approval holder may decide to use.

Other Healthcare Laws in the EU and United States

The company will also be subject to healthcare regulation and enforcement by the U.S. federal government and the states and governments in the EU and any other countries in which the company conducts its business, including its research, and the marketing and distribution of its product candidates and products once they have obtained an MA. Failure to comply with these laws, where applicable, can result in the imposition of significant civil penalties, criminal penalties, exclusion from participating in health care programs, additional reporting requirements and oversight if the company becomes subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws and other sanctions. The healthcare laws and regulations that may affect the company's ability to operate in the United States include: the federal fraud and abuse laws, including the federal anti-kickback and

false claims laws; federal data privacy and security laws; and federal transparency laws related to payments and/or other transfers of value made to physicians and other healthcare professionals and teaching hospitals. Many US states have similar laws and regulations that may differ from each other and federal law in significant ways. Moreover, several US states have enacted legislation requiring pharmaceutical manufacturers to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. Rules and legislation covering more or less the same subject matter as those in the United States apply to in countries in the EU and to other countries. These can differ between jurisdictions and can sometimes result in lower or higher exposure in those countries than in the United States. Where a product is sold in a number of countries compliance efforts can therefore be complicated.

Coverage and Reimbursement in the EU and United States

Sales of products developed from the company's product candidates, if approved, will depend, in part, on the extent to which such products will be covered by third party payors, such as government health care authorities, government health care programs, commercial insurance and managed healthcare organizations. These third party payors are increasingly limiting coverage or reducing reimbursements for medical products and services. In the United States, no uniform policy of coverage and reimbursement for products exists among third party payors. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products.

Governments influence the price of medicinal products in the EU through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general in the EU governments influence the price of medicinal products through their pricing and reimbursement.

The adoption of price controls and cost-containment measures, and the adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit the company's net revenue and results. Decreases in third party reimbursement for the company's product candidates or a decision by a third party payor to not cover the company's product candidates could reduce physician usage of the company's product candidates, once approved, and have a material adverse effect on the company's sales, results of operations and financial condition.

Privacy and Data Protection Laws in Europe

We are subject to European laws relating to our and our suppliers', partners' and subcontractors' collection, control, processing and other use of personal data (i.e. any data relating to an identifiable living individual, whether that individual can be identified directly or indirectly). We are subject to the supervision of local data protection authorities in those jurisdictions where we are established, where we offer goods or services to EU residents and where we monitor the behavior of individuals in the EU (i.e. undertaking clinical trials). We and our suppliers, partners and subcontractors process personal data including in relation to our employees, employees of customers, clinical trial patients, healthcare professionals and employees of suppliers including health and medical information. The data privacy regime in the EU includes the General Data Protection Regulation, or GDPR, the e-Privacy Directive (2002/58/EC) and the e-Privacy Regulation (once in force) and the national laws and regulations implementing or supplementing each of them.

The GDPR requires that personal data is only collected for specified, explicit and legal purposes as set out in the GDPR or local laws, and the data may then only be processed in a manner consistent with those purposes. The personal data collected and processed must be adequate, relevant and not excessive in relation to the purposes for which it is collected and processed, it must be held securely, not transferred outside of the European Economic Area, or EEA, (unless certain steps are taken to ensure an adequate level of protection), and must not be retained for longer than necessary for the purposes for which it was collected. In addition, the GDPR requires companies processing personal data to take certain organizational steps to ensure that they have adequate records, policies, security, training and governance frameworks in place to ensure the protection of data subject rights, including as required to respond

to complaints and requests from data subjects. For example, the GDPR requires us to make more detailed disclosures to data subjects, requires disclosure of the legal basis on which we can process personal data, makes it harder for us to obtain valid consent for processing, will require the appointment of a data protection officer where sensitive personal data (i.e. health data) is processed on a large scale, introduces mandatory data breach notification throughout the EU and imposes additional obligations on us when we are contracting with service providers.

In addition, to the extent a company processes, controls or otherwise uses "special category" personal data (including patients' health or medical information, genetic information and biometric information), more stringent rules apply, further limiting the circumstances and the manner in which a company is legally permitted to process that data. Finally, the GDPR provides a broad right for Member State to create supplemental national laws which may result in divergence across Europe making it harder to maintain a consistent operating model or standard operating procedures. Such laws, for example, may relate to the processing of health, genetic and biometric data, which could further limit our ability to use and share such data or could cause our costs to increase, and harm our business and financial condition.

We depend on a number of third parties in relation to the provision of our services, a number of which process personal data on our behalf. With each such provider we enter into contractual arrangements to ensure that they only process personal data according to our instructions, and that they have sufficient technical and organizational security measures in place. Where we transfer personal data outside the EU, we do so in compliance with the relevant data export requirements from time to time. We take our data protection obligations seriously, as any improper, unlawful or accidental disclosure, loss, alteration or access to, personal data, particularly sensitive personal data (i.e. special category), could negatively impact our business and/or our reputation.

We are also subject to EU laws on personal data export, as we may transfer personal data from the EU to other jurisdictions which are not considered by the European Commission to offer adequate protection of personal data. Such transfers need to be legitimized by a valid transfer mechanism under the GDPR. There is currently ongoing litigation challenging the commonly used transfer mechanisms, the EU Commission approved model clauses. In addition, the U.S. Privacy Shield is currently under review by the European Commission. As such, it is uncertain whether the Privacy Shield framework and/or model clauses will be invalidated in the near future. These changes may require us to find alternative bases for the compliant transfer of personal data from the EU to the United States and we are monitoring developments in this area. Invalidation of any mechanism on which we rely could require operational changes and increased costs and may lead to governmental enforcement actions, litigation, fines and penalties or adverse publicity that could have an adverse effect on our business.

The EU is in the process of replacing the e-Privacy Directive with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each Member State, without the need for further enactment. The draft e-Privacy Regulation imposes strict opt-in marketing rules with limited exceptions for business-to-business communications and alters rules on third-party cookies, web beacons and similar technology. Regulation of cookies and web beacons may lead to broader restrictions on online research activities, including efforts to understand users' internet usage. The current draft also significantly increases fining powers to the same levels as GDPR (i.e. the greater of 20 million Euros or 4% of total global annual revenue). While no official timeframe has been provided, commentators have stated that the e-Privacy Regulation is likely to be agreed in 2019 and to come into force during the second half of 2020 or during 2021 following a transition period.

There are costs and administrative burdens associated with compliance with the GDPR and the resultant changes in the EU and EEA member states' national laws and the introduction of the e-Privacy Regulation once it takes effect. Any failure or perceived failure to comply with global privacy laws carries with it the risk of significant penalties and sanctions of up to €20 million or 4% of global turnover. These laws or new interpretations, enactments or supplementary forms of these laws, could create liability for us, could impose additional operational requirements on our business, could affect the manner in which we use and transmit patient information and could increase our cost of doing business. Claims of violations of privacy rights or contractual breaches, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

Property, Plant and Equipment

The below table contains information regarding existing or planned material tangible fixed assets owned or leased by us and our subsidiaries. We believe that suitable additional or substitute space will be available as needed to accommodate any future expansion of our operations.

Location	Tenure	Principal Use	Size
55 Park Lane, Suite 14a, London W1K 1NA, United Kingdom	Annual Lease	Principal Office	652 square feet
420 Lexington Avenue Suite 2525 New York, United States	Five year lease	Principal Office	3,011 square feet
3805 Old Easton Road, Doylestown, PA, United States	Annual lease	Research & Development Centre	408 square feet

DIRECTORS, SENIOR MANAGEMENT AND EMPLOYEES

The following table sets forth information regarding our directors as of June 30, 2019:

Name	Age	Position
Gabriele Marco Antonio Cerrone MBA[(2)]	47	Executive Chairman
Willy Simon[(3)]	67	Non-Executive Director
Dr. Kunwar Shailubhai MBA[(1)(2)]	61	Chief Executive Officer, Chief Scientific Officer and Executive Director
Leopoldo Zambeletti[(1)(2)(3)]	50	Non-Executive Director

(1) Remuneration Committee member
(2) Nominating Committee member
(3) Audit Committee member

The following table sets forth information regarding our senior managers as of June 30, 2019:

Name	Position
Tiziano Lazzaretti	Chief Financial Officer
Jules S. Jacob	Senior Director, CMC & Non-Clinical Development
Dr. Evangeline Priya Eddy DABT	Senior Director, Safety and Toxicology
Dr. Vaseem A. Palejwala	Director, Clinical Operations

Gabriele Marco Antonio Cerrone — *Executive Chairman*

Mr. Gabriele Marco Antonio Cerrone, is the Founder of the company and has been its Executive Chairman since April 2014. Mr. Cerrone has founded nine biotechnology companies in oncology, infectious diseases and molecular diagnostics, and has listed six of these companies on Nasdaq and one on AIM. Mr. Cerrone co-founded Trovagene, Inc. a molecular diagnostic company and served as its co-chairman. Mr. Cerrone was a co-founder and served as chairman of both Synergy Pharmaceuticals, Inc. and Callisto Pharmaceuticals, Inc., and was a director of and led the restructuring of Siga Technologies, Inc. Mr. Cerrone co-founded FermaVir Pharmaceuticals, Inc. and served as chairman until its merger in September 2007 with Inhibitex, Inc. Mr. Cerrone served as a director of Inhibitex, Inc. until its US$2.5bn sale to Bristol Myer Squibb in 2012. Mr. Cerrone graduated from New York University's Stern School of Business with a master in business administration (MBA).

Willy Simon — *Non-Executive Director*

Willy Jules Simon has served as a Non-Executive Director of the company since November 2015. Mr. Simon has served as non-executive chairman of Bever Holding B.V. a Dutch listed public company focused on real estate development since August 2007. Mr. Simon served as the Chief Executive Officer of Fortis Investment Management from January 2000 to July 2002. Mr. Simon worked in banking at Kredietbank N.V. from August 1975 to December 1983 and at Citibank London from January 1984 to December 1996 before serving as an executive member of the board of Generale Bank NL from January 1997 to December 1999. From July 2004 until April 2012, he served as a non-executive director of Redi & Partners Ltd., a fund of funds. Mr. Simon was previously chairman of AIM-traded Velox3 plc (formerly 24/7 Gaming Group Holdings plc), a company focused on publishing and developing gaming software for the mobile gaming industry, from April 2012 until April 2014. Mr. Simon was a director of Playlogic Entertainment Inc., a Nasdaq listed company focused on developing, publishing, and selling interactive software games, from December 2003 to September 2011. Mr. Simon acted as chairman of Bank Oyens & van Eeghen from September 2102 to December 2004. Mr. Simon holds a law degree from the University of Louvain and a post-graduate degree in European law and economics from Institut des Hautes Etudes Européennes, Strasbourg.

Leopoldo Zambeletti — *Non-Executive Director*

Mr. Zambeletti joined our board of directors on April 19, 2018. During a 19 year career as an investment banker, Mr. Zambeletti led the European Healthcare Investment Banking team at JPMorgan for eight years from April 1999 to April 2007 before taking up the same position at Credit Suisse for a further five years from September 2012 to November 2012. Since 2013 he has been an independent strategic advisor to life science companies on merger

and acquisitions, out-licensing deals and financing strategy. He is a non-executive director of, Qardio Inc., Summit Therapeutics plc, Nogra Pharma Limited, Faron Pharmaceuticals OY and DS Biopharma Limited. Mr. Zambeletti started his career at KPMG as an auditor. Mr. Zambeletti received a B.A. in Business from Bocconi University in Milan, Italy. He serves as a trustee to Barts and the London Charity, which helps to fund the hospitals of the Barts NHS Trust including St Bartholomew, the Royal London and the London Chest Hospitals. He is the founder of the cultural initiative 5x5 Italy.

Dr. Kunwar Shailubhai — *Chief Executive Officer, Chief Scientific Officer and Executive Director*

Dr. Kunwar Shalilubhai has served as Chief Executive Officer, Chief Scientific Officer and Executive Director of the company since 2008. Since April, 2017, Dr. Shailubhai has served as Chief Executive Officer of Rasna Therapeutics, Inc. Dr. Shailubhai was a co-founder of Synergy Pharmaceuticals Inc. and served as Chief Scientific Officer from July 2008 to May 2017. From March 2004 until July 2008, Dr. Shailubhai served as Senior Vice President, Drug Discovery of Synergy, which at that time was a subsidiary of Callisto Pharmaceuticals, Inc. ("Synergy DE"). From May 2003 until March 2004, Dr. Shailubhai served as executive vice president, R&D of Synergy DE. From 2001 to April 2003, Dr. Shailubhai held the position of Vice President, Drug Discovery at Synergy DE where he was chiefly responsible for the preclinical development of its GC-C agonist program for drugs to treat colon cancer and GI inflammation. Between 1993 and 2000, he was with Monsanto Company, serving as group leader of the cancer chemoprevention group. Dr. Shailubhai is a director of Rasna Therapeutics, Inc. and Okyo Pharma Ltd. Dr. Shailubhai previously served as a senior staff fellow at the National Institutes of Health, and as an assistant professor at the University of Maryland. Dr. Shailubhai received his Ph.D. in microbiology in 1984 from the University of Baroda, India, and his MBA in 2001 from the University of Missouri, St. Louis.

Tiziano Lazzaretti — *Chief Financial Officer*

Mr. Lazzaretti has served as Chief Financial Officer of the company since March 2016. Mr. Lazzaretti has extensive experience in the healthcare and pharmaceutical industries and joined the company from Pharmentis Srl, a spin-off from Teva Ratiopharm, where he served as group finance director from 2011 to 2016. Since 2016, Mr. Lazzaretti has been the chief financial officer of Rasna Therapeutics, Inc. and since 2017, he has been the chief financial officer of Okyo Pharma Ltd. Mr. Lazzaretti was executive director at Alliance Boots Healthcare, an international pharmacy-led health and beauty group. Mr. Lazzaretti held senior positions at SNIA Spa, Accenture, and Fiat Group. Mr. Lazzaretti received his bachelor of science (BSc Hons) in accounting and finance from the University of Turin, Italy, was awarded a master in business administration from Bocconi University, Milan and studied corporate finance at the London Business School.

Jules S. Jacob — *Senior Director, CMC & Non-Clinical Development*

Mr. Jules Jacob has served as Senior Director of CMC and Non-Clinical Development of the company since July 2017 and has over 25 years of drug development experience. Previously, Mr. Jacob was senior director of product development at Aprecia Pharmaceuticals Company, a drug delivery technology platform company, from March 2009 to July 2017, where he led the development of Spritam®, the first FDA-approved dosage form manufactured using 3-dimensional printing, and other 505(b)(2) pipeline products. Mr. Jacob was director of formulation development at Panacos Pharmaceuticals Inc., a drug company focused on human immunodeficiency virus, or HIV, and other major human viral diseases, from March 2007 to December 2008, where he worked on the development of first-in-class maturation inhibitors for the treatment of HIV. Mr. Jacob was a founding scientist, director of R&D and director of technology development at Spherics, Inc., a pharmaceutical company that engaged in developing and manufacturing oral pharmaceutical products for CNS conditions, GI disorders, and cancer, from February 2000 to February 2007. Mr. Jacob worked on the development of bioadhesive dosage forms for treatment of CNS disorders, through the 505(b)(2) regulatory pathway at Spherics Inc. Mr. Jacob completed his undergraduate degree and graduate education in biological and medical sciences at Brown University and has an active visiting faculty appointment in the Department of Molecular Pharmacology, Physiology and Biotechnology at Brown University.

Dr. Evangeline Priya Eddy — *Senior Director, Safety & Toxicology*

Dr. Eddy has served as Senior Director, Safety & Toxicology of the company and of Rasna Therapeutics, Inc., respectively, since January 2017 and has over 20 years of experience in drug discovery and development.

Dr. Eddy served as senior director, toxicology and safety pharmacology at Synergy Pharmaceuticals Inc. from September 2013 to January 2017, where she was responsible for toxicology, ADME/PK and safety pharmacology studies. Dr. Eddy contributed to the NDA for Trulance® and her work at Synergy also included the development of a delayed release formulation for dolcanatide, as well as involvement in the supply of API for GLP and feasibility studies. Dr. Eddy worked at Endo Pharmaceuticals as an associate director, toxicology and safety pharmacology from February 2011 to October 2012 and as senior director, preclinical development at Zelos Therapeutics from April 2008 to February 2011. Dr. Eddy worked at Millennium Pharmaceuticals (now a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited) 2000 to 2003 and at SmithKline Beecham Pharmaceuticals (now GlaxoSmithKline) from August 1992 to February 1999 in the areas of drug discovery and development including early clinical development. Dr. Eddy received her Ph.D. degree in biochemistry from Osmania University, Hyderabad India and is a board-certified toxicologist of the American Board of Toxicology. Before joining the pharmaceutical industry, Dr. Eddy worked at Case Western Reserve University in Cleveland, OH in the area of chemical carcinogenesis and environmental health sciences.

Dr. Vaseem A. Palejwala — *Director, Clinical Operations*

Dr. Palejwala is Director, Clinical Operations and has served in this position since January 2019. Between January 2017 to 2019 he served as Director of Non-Clinical Studies of the company. He has 18 years of experience in drug discovery and development. From January 2015 to January 2017, Dr. Palejwala served as director of discovery and preclinical research, and from December 2012 to December 2014 served as associate director of discovery and preclinical research, at Synergy Pharmaceuticals Inc. where he actively contributed to establishing GI tract-related preclinical animal models for testing the efficacy and validating the mechanism of action for both plecanatide and dolcanatide. Dr. Palejwala also actively participated in preparation of the nonclinical pharmacology section of the NDA for Trulance®. From 2001 to 2012, Dr. Palejwala served as discovery scientist/manager at Sanofi S.A., *a* multinational pharmaceutical company, where he advanced both small molecule and biologic programs in immunology, inflammation, oncology, CNS and metabolic disorders and also contributed to establishing and managing high-throughput gene expression profiling platform capabilities. Dr. Palejwala holds a degree in microbiology and chemistry from Bombay University, as well as a master of science degree in microbiology and a Ph.D. in microbiology from the Maharaja Sayajirao University of Baroda.

Family Relationships

There are no family relationships among any of our executive officers or directors.

Compensation

Total Compensation for the Chairman and Non-Executive Directors

The table below sets out the total remuneration received by the Chairman and the Non-Executive Directors for the year ended December 31, 2018.

Name	Position	Fees earned or paid in cash ($)	Options awarded ($)[1]	Total ($)
Gabriele Cerrone	Chairman	124,008	528,036	652,044
Riccardo Dalla-Favera[2]	Non – Executive Director	26,668	—	26,668
Willy Simon	Non – Executive Director	50,670	—	50,670

(1) Represents the fair value of incentive stock options granted during the year to December 31, 2018 using the Black-Scholes model for computing stock-based compensation expense as of the date of grant.

(2) Dr. Dalla-Favera resigned from the board of directors on February 7, 2019.

Compensation of Executive Directors and Senior Managers

The table below sets the remuneration of each of the Executive Directors and Senior Managers for the financial year ended December 31, 2018.

Name	Position	Fees earned or paid in cash ($)	Options awarded ($)[1]	Total ($)
Kunwar Shailubhai	Executive Director	300,000	1,275,754	1,561,579
Tiziano Lazzaretti	Chief Financial Officer	141,343	—	141,343

(1) Represents the fair value of incentive stock options granted during the year to December 31, 2018 using the Black-Scholes model for computing stock-based compensation expense as of the date of grant.

The Tiziana Life Sciences plc Employee Share Option Plan with Non-Employee Sub-Plan and US Sub-Plan

The Tiziana Life Sciences plc Employee Share Option Plan with Non-Employee Sub-Plan and US Sub-Plan, or the 2016 Plan, was adopted by the Board on March 23, 2016 and approved by shareholders on June 30, 2016 and allows for the grant of options to eligible service providers. The material terms of the 2016 Plan are summarized below.

Eligibility and Administration

Our employees, consultants and directors, and employees and consultants of our subsidiaries are eligible to receive options under the 2016 Plan. The 2016 Plan is administered by our board of directors, which may delegate its duties and responsibilities to one or more committees of our directors and/or officers (referred to collectively as the plan administrator below), subject to the limitations imposed under the 2016 Plan, stock exchange rules and other applicable laws. The plan administrator has the authority to take all actions and make all determinations under the 2016 Plan, to interpret the 2016 Plan and option agreements and to adopt, amend and repeal rules for the administration of the 2016 Plan as it deems advisable. The plan administrator also has the authority to determine which eligible service providers receive options, to grant options and to set the terms and conditions of all options granted under the 2016 Plan, including any vesting and vesting acceleration provisions, subject to the conditions and limitations in the 2016 Plan.

Shares Available for Options

An aggregate of 10% of the company’s ordinary share capital from time to time may be placed under options granted under the 2016 Plan. Shares issued to satisfy the exercise of options granted under the 2016 Plan may be newly issued shares or shares purchased on the open market

If an option granted under the 2016 Plan, expires, lapses or is terminated, exchanged for cash, surrendered, canceled without having been fully exercised or forfeited, any unused shares subject to the option will, as applicable, become or again be available for new grants under the 2016 Plan.

Options

The 2016 Plan provides for the grant of options. All options granted under the 2016 Plan will be set forth in option agreements, which will detail the terms and conditions of the options.

Options provide for the purchase of our ordinary shares in the future at an exercise price set on the grant date. The plan administrator will determine the number of shares covered by each option, the exercise price of each option and the conditions and limitations applicable to the exercise of each option

If a holder of options dies, options may be exercised by the personal representative with 12 months following death in respect of all or such proportion of the option as the plan administrator may specify to take account of the extent to which any exercise conditions have been achieved at the relevant date. If a holder of options leaves as a good leaver or the plan administrator allows, options may be exercised within 90 days in respect of all or such proportion of the option as the plan administrator may specify to take account of the extent to which any exercise conditions have been achieved at the relevant date

Exercise Conditions

The plan administrator may specify one or more appropriate exercise conditions that must be satisfied before options may be exercised.

Change of Control and Variation of Share Capital

In the event of a change of control, the plan administrator may specify whether all or a proportion of options will be exercisable to take account of the extent to which any exercise conditions have been achieved at the relevant date. Alternatively, holders of options may agree to accept an offer to exchange options for options to acquire shares in an acquiring company.

If there is a variation of our ordinary shares the plan administrator may adjust the number of shares under options and/or the exercise price.

Plan Amendment and Termination

Our board of directors may amend the 2016 Plan at any time; however, the provisions governing eligibility requirements, equity dilution, the basis for determining the rights of holders of options and the adjustment of options cannot be altered to the advantage of existing or new holders of options without the prior approval of our shareholders in general meeting. No options may be granted under the 2016 Plan after the tenth anniversary of the date of adoption by our board of directors.

Transferability

Options granted under the 2016 Plan are generally non-transferrable, except on death. With regard to tax withholding and exercise price obligations arising in connection with the exercise of options under the 2016 Plan, the plan administrator may, in its discretion, accept cash, wire transfer or cheque,

Non-Employee Sub-Plan

Under the Non-Employee Sub-Plan, options may be granted to advisers, consultants and non-executive directors on terms comparable to those described above.

US Sub-Plan

The US Sub-Plan permits the grant of options to employees, directors and consultants who are US residents and US taxpayers, including potentially tax efficient Incentive Stock Options (as defined in Section 422 of the Internal Revenue Code). A maximum of 9,233,392 ordinary shares may be issued under the US Sub-Plan (which number shall be the maximum number that may be granted as Incentive Stock Options).

The following table summarizes: (i) the outstanding number of options and awards under the equity incentive plans; and (ii) the number of ordinary shares granted to directors, executive officers, and non-executive directors, as of April 1, 2019:

Name	Ordinary Shares	Ordinary Shares Underlying Options	Exercise Price Per Ordinary Share (£)	Grant Date	Expiration Date
Gabriele Cerrone	—	1,200,000	0.15	06/25/2014	06/25/2024
		2,000,000	0.35	06/25/2014	06/25/2024
		3,259,403	1.50	06/09/2016	06/09/2026
		550,000	0.8175	04/30/2018	04/30/2028
Willy Simon	—				
Kunwar Shailubhai	—	300,000	0.50	06/25/2014	06/25/2024
		400,000	1.595	08/30/2017	08/30/2027
		2,500,000	0.8175	04/30/2018	04/30/2028
		4,000,000	0.8175	04/30/2018	04/30/2028
Leopoldo Zambeletti	—	550,000	0.8175	04/30/2018	04/30/2028
Tiziano Lazzaretti	—	200,000	1.26	03/23/2016	03/23/2026
		100,000	1.86	11/05/2016	11/05/2026
Fayez Hamzeh	—	600,000	0.8175	04/30/2018	04/30/2028
Jules Jacob	—	50,000	1.595	08/30/2017	08/30/2027
Evangeline Priya-Eddy	—	50,000	1.595	08/30/2017	08/30/2027
Vaseem Palejwala	—	40,000	1.595	08/30/2017	08/30/2027

Board Practices

Corporate Governance Practices

We are a “foreign private issuer,” as defined by the SEC. As a result, in accordance with Nasdaq listing requirements, we may rely on home country governance requirements and certain exemptions thereunder rather than complying with Nasdaq corporate governance standards. While we voluntarily follow most Nasdaq corporate governance rules, we may choose to take advantage of the following limited exemptions:

- Exemption from filing quarterly reports on Form 10-Q containing unaudited financial and other specified information or current reports on Form 8-K upon the occurrence of specified significant events.
- Exemption from Section 16 rules requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades in a short period of time, which will provide less data in this regard than shareholders of U.S. companies that are subject to the Exchange Act.
- Exemption from the Nasdaq requirement requiring disclosure of any waivers of the code of business conduct and ethics for directors and officers.
- Exemption from the requirement that our board have a compensation committee that is composed entirely of independent directors with a written charter addressing the committee’s purpose and responsibilities.
- Exemption from the requirement to have independent director oversight of director nominations.

We intend to follow U.K. corporate governance practices in lieu of Nasdaq corporate governance requirements as follows:

- We do not intend to follow Nasdaq Rule 5620(c) regarding quorum requirements applicable to meetings of shareholders. Such quorum requirements are not required under English law. In accordance with generally accepted business practice, our Articles of Association will provide alternative quorum requirements that are generally applicable to meetings of shareholders.

- We do not intend to follow Nasdaq Rule 5605(b)(2), which requires that independent directors regularly meet in executive sessions where only independent directors are present. Our independent directors may choose to meet in executive sessions at their discretion.

Although we may rely on certain home country corporate governance practices, we must comply with Nasdaq's Notification of Noncompliance requirement (Nasdaq Rule 5625) and the Voting Rights requirement (Nasdaq Rule 5640). Further, we must have an audit committee that satisfies Nasdaq Rule 5605(c)(3), which addresses audit committee responsibilities and authority and requires that the audit committee consist of members who meet the independence requirements of Nasdaq Rule 5605(c)(2)(A)(ii).

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act, the rules adopted by the SEC and Nasdaq listing rules. Accordingly, our shareholders will not have the same protections afforded to shareholders of companies that are subject to all of the corporate governance requirements of Nasdaq. For an overview of our corporate governance principles, see the section titled "Description of Share Capital and Articles of Association — Differences in Corporate Law."

Compliance with the Quoted Companies Alliance Corporate Governance Code

All companies with securities admitted to trading on AIM are required to include on their website details of a recognized corporate governance code that the board of directors of the company has decided to apply, how the company complies with that code, and where it departs from its chosen corporate governance code an explanation of the reasons for doing so. This information is required to be reviewed annually.

The company has decided to apply the Corporate Governance Code published by the Quoted Companies Alliance, or the QCA Code. The QCA Code sets out a standard of minimum best practice for small and midsize quoted companies.

Composition of Our Board of Directors

Our board of directors is currently composed of four members and the Board has determined that two of the directors, Mr. Zambeletti and Mr. Simon, are considered to be "independent" as that term is defined under Nasdaq rules.

In accordance with our Articles, each of our directors for whom it is the third annual general meeting following the annual general meeting at which they were elected or last re-elected, or who was appointed by the board since the previous annual general meeting, shall retire from office but shall be eligible to stand for re-election. See "Description of Share Capital and Articles of Association — Articles of Association — Board of Directors."

The expiration of the current terms of the members of the board of directors and the period each member has served in that term are as follows:

Name	Year Current Term Began	Year Current Term Expires
Gabriele Cerrone	2017	2020
Kunwar Shailubhai	2018	2021
Willy Simon	2016	2019
Leopoldo Zambeletti	2018	2021

Committees of Our Board of Directors

Our board of directors has three standing committees: an audit committee, a remuneration committee and a nominating committee.

Audit Committee

The audit committee, which consists of, Mr. Zambeletti and Mr. Simon, assists the board of directors in overseeing our accounting and financial reporting processes. Mr. Simon serves as chairman of the audit committee. The audit committee consists exclusively of members of our board who are financially literate, and Mr. Simon is considered an "audit committee financial expert" as defined by applicable SEC rules and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations.

Our board has determined that all of the members of the audit committee satisfy the "independence" requirements set forth in Rule 10A-3 under the Exchange Act. The audit committee will be governed by a charter that complies with Nasdaq rules.

The audit committee's responsibilities include:

- recommending the appointment of the independent auditor to the general meeting of shareholders;
- the appointment, compensation, retention and oversight of any accounting firm engaged for the purpose of preparing or issuing an audit report or performing other audit services;
- pre-approving the audit services and non-audit services to be provided by our independent auditor before the auditor is engaged to render such services;
- evaluating the independent auditor's qualifications, performance and independence, and presenting its conclusions to the full board of directors on at least an annual basis;
- reviewing and discussing with management and our independent registered public accounting firm our financial statements and our financial reporting process;
- reviewing, approving or ratifying any related party transactions.
- recommending the appointment of the independent auditor to the general meeting of shareholders; and
- the appointment, compensation, retention and oversight of any accounting firm engaged for the purpose of preparing or issuing an audit report or performing other audit services;

Remuneration Committee

The remuneration committee consists of Mr. Zambeletti and Mr. Simon. Mr. Simon serves as chairman of the remuneration committee. Under SEC and Nasdaq rules, there are heightened independence standards for members of the remuneration committee, including a prohibition against the receipt of any compensation from us other than standard board member fees.

The remuneration committee's responsibilities include:

- identifying, reviewing and proposing policies relevant to the compensation and benefits of our directors and executive officers;
- evaluating each executive officer's performance in light of such policies and reporting to the board; and
- overseeing and administering our employee share option scheme or equity incentive plans in operation from time to time.

Nominating Committee

The nominating committee consists of Mr. Cerrone, Mr. Simon and Mr. Zambeletti. Mr. Zambeletti serves as chairman of the nominating committee. The nominating committee's responsibilities include:

- drawing up selection criteria and appointment procedures for directors;

- recommending nominees for election to our board of directors and its corresponding committees;
- assessing the functioning of individual members of our board of directors and executive officers and reporting the results of such assessment to the board of directors; and
- developing corporate governance guidelines.

Code of Business Conduct and Ethics

Our Code of Business Conduct and Ethics is applicable to all of our employees, officers and directors and is available on our website at *https://www.tizianalifesciences.com*. Our Code of Business Conduct and Ethics provides that our directors and officers are expected to avoid any action, position or interest that conflicts with the interests of our company or gives the appearance of a conflict. Our directors and officers have an obligation under our Code of Business Conduct and Ethics to advance our company's interests when the opportunity to do so arises. We expect that any amendment to this code, or any waivers of its requirements, will be disclosed on our website.

Compensation of Executive Officers and Directors

For the year ended December 31, 2018, the aggregate compensation accrued or paid to the members of our board of directors and our executive officers for services in all capacities was $0.5 million.

Executive Director Service Agreement

Dr. Kunwar Shailubhai

We entered into an employment agreement with Dr. Kunwar Shailubhai in May 2017, which was amended by way of a letter agreement in January 2019. The employment agreement requires Dr. Shailubhai to work for the company for 100% of his time and pursuant to it he is entitled to receive an initial annual base salary of $600,000 per year. Dr. Shailubhai is eligible to receive an annual cash bonus of up to 35% of his base salary, such bonus amount to be determined in the company's absolute discretion and subject to such conditions (including, but not limited to, with respect to his performance and that of the company, and related to the timing of payment).

Dr. Shailubhai is also entitled to the same fringe benefits as we provide to our other executives from time to time and is eligible to receive employee share incentives. The vesting of any unvested employee share incentives held by Dr. Shailubhai will accelerate in the event his employment is terminated without cause (as such term is defined in his employment agreement), or if he resigns for good reason (as such term is defined in the employment agreement) and, in each case, such termination is upon the consummation of or within 12 months following a change of control of the company. If Dr. Shailubhai's employment with the company is terminated without cause, or if he resigns for good reason, Dr. Shailubhai will also be entitled to receive severance equal to continuation of his base salary as then currently in effect for 12 months following his date of termination and will be eligible for reimbursement for medical coverage premiums for up to the same period. Dr. Shailubhai, his spouse and eligible dependents are entitled to stay on our health insurance plans for a period of 12 months following his termination for any reason. Dr. Shailubhai's severance benefits are conditioned on, *inter alia*, his execution of our standard separation agreement and a general release of claims in our favor.

The employment agreement provides that Dr. Shailubhai's employment with us is at-will. If required by the company, the employment agreement further provides that Dr. Shailubhai will resign from his position on our board of directors effective as of the date of his termination for any reason. The employment agreement further contains a six-month non-competition covenant and a 12-month non-solicitation covenant by Dr. Shailubhai.

Non-Executive Director Service Contracts

The remuneration of our non-executive directors is determined by our board as a whole, based on a review of current practices in other companies. We intend to enter into service contracts with our directors for their services or amend and restate any prior service contracts in place prior to, or as soon as practicable, following the filing of this registration statement.

Employees

As of December 31, 2018, 2017 and 2016, we had 9, 5 and 9 employees, respectively. All of our employees were based in the United Kingdom, except that, as of December 31, 2017, we had 3 employees based outside of the United Kingdom in the US. All of our employees were engaged in either administrative or R&D functions. None of our employees are covered by a collective bargaining agreement.

Insurance and Indemnification

To the extent permitted by the Companies Act, we are empowered to indemnify our directors against any liability they incur by reason of their directorship. We maintain directors' and officers' insurance to insure such persons against certain liabilities. We expect to enter into a deed of indemnity with each of our directors and executive officers prior to, or as soon as practicable, following the filing of this registration statement.

In addition to such indemnification, we provide our directors and executive officers with directors' and officers' liability insurance.

Insofar as indemnification of liabilities arising under the Securities Act may be permitted to our board of directors, executive officers, or persons controlling us pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

The following is a description of related party transactions we have entered into since January 1, 2018, with the beneficial owners of 5% or more of our ordinary shares, which are our only voting securities, and senior management and members of our board of directors.

Tiziana Pharma Limited is a wholly-owned subsidiary of our company. During the year ended December 31, 2018, we transferred $3.9 million to Tiziana Pharma Limited.

Tiziana Therapeutics Inc. is a wholly-owned subsidiary of our company. During the year ended December 31, 2018, we transferred $1.5 million to Tiziana Therapeutics Inc.

Kunwar Shailubhai, a director of our company, is also a director of Rasna Therapeutics, Inc., or Rasna. In addition, Tiziano Lazzaretti, CFO of our company, is also CFO of Rasna. Rasna is a party to a Shared Services Agreement with us whereby we are charged for shared services such as payroll and rent. As of December 31, 2018, $130,000 was as owed to us by Rasna.

Indemnity Agreements

We have entered into deeds of indemnity with each of our directors.

Related Person Transaction Policy

Our board of directors has adopted a written related person transaction policy, effective as of November 9, 2018. This policy covers, any transaction or proposed transactions between us and a related person that are material to us or the related person, including without limitation, purchases of goods or services by or from the related person or entities in which the related person has a material interest, indebtedness, guarantees of indebtedness and employment by us of a related person. In reviewing and approving any such transactions, our audit and risk committee is tasked to consider all relevant facts and circumstances, including, but not limited to, whether the transaction is on terms comparable to those that could be obtained in an arm’s length transaction and the extent of the related person’s interest in the transaction. All of the transactions described in this section occurred prior to the adoption of this policy.

PRINCIPAL SHAREHOLDERS

The following table sets forth information relating to the beneficial ownership of our ordinary shares as of September 19, 2019 by:

- each person, or group of affiliated persons, known by us to own beneficially 5% or more of our outstanding ordinary shares; and
- each member of our board of directors and each of our executive officers.

The number of ordinary shares beneficially owned by each entity, person, board member, or executive officer is determined in accordance with the rules of the SEC, and the information is not necessarily indicative of beneficial ownership for any other purpose. Under such rules, beneficial ownership includes any ordinary shares over which the individual has sole or shared voting power or investment power as well as any ordinary shares that the individual has the right to acquire within 60 days of September 19, 2019 through the exercise of any option, warrant or other right. Percentage of ownership is based on 136,463,818 ordinary shares issued as of September 19, 2019. Except as otherwise indicated, and subject to applicable community property laws, the persons named in the table have sole voting and investment power with respect to all ordinary shares held by that person.

	Number of Ordinary Shares Beneficially Owned	
Name and address of beneficial owner	**Shares**	**%**
5% or Greater Shareholders:		
Gabriele Cerrone[1]	67,455,925	48.3
Executive Officers and Directors:		
Gabriele Cerrone[1]	67,455,925	48.3
Willy Simon	—	—
Leopoldo Zambeletti[4]	137,500	*
Kunwar Shailubhai[2]	1,505,000	1.1
Tiziano Lazzaretti[3]	252,000	*
All directors and executive officers as a group (5 persons)[5]	69,350,425	49.0

* Indicates beneficial ownership of less than 1% of the total outstanding ordinary shares.

(1) Mr. Gabriele Cerrone is the ultimate beneficial owner of ordinary shares through Planwise Group Limited and Panetta Partners Limited.
Includes 3,200,000 stock options which are currently exercisable or exercisable within 60 days of September 19, 2019.

(2) Includes of 1,500,000 stock options which are currently exercisable or exercisable within 60 days of September 19, 2019.

(3) Includes of 250,000 stock options which are currently exercisable or exercisable within 60 days of September 19, 2019.

(4) Includes 137,500 stock options which are currently exercisable or exercisable within 60 days of September 19, 2019.

(5) Includes 5,087,500 stock options which are currently exercisable or exercisable within 60 days of September 19, 2019.

DESCRIPTION OF SHARE CAPITAL AND ARTICLES OF ASSOCIATION

We were originally incorporated under the laws of England and Wales on February 11, 1998 under the name of Bigboom plc, with the goal of leveraging the expertise of our management team as well as Dr. Napoleone Ferrara, Dr. Arun Sanyal, Dr. Howard Weiner and Dr. Kevan Herold, and to acquire and exploit certain intellectual property in biotechnology. We subsequently changed our name to Tiziana Life Sciences plc in April 2014 as a result of the acquisition of Tiziana Pharma Limited in April 2014.

Our registered office is located at 3rd Floor, 11-12 St James's Square, London SW1Y 4LB and our telephone number is +44 20 7495 2379. Our website address is *www.tizianalifesciences.com*. The reference to our website is an inactive textual reference only and the information contained in, or that can be accessed through, our website is not a part of this registration statement.

Current authorized share capital

Not applicable.

Current issued share capital

As of June 30, 2019, our issued share capital was 136,463,818 ordinary shares with a nominal value of £0.03 per share. Each issued ordinary share is fully paid.

Information about the Ordinary Shares

In accordance with our Articles to be in effect upon the filing of this registration statement, the following summarizes the rights of holders of our ordinary shares:

- each holder of our ordinary shares is entitled to one vote per ordinary share on all matters to be voted on by shareholders generally;
- the holders of the ordinary shares shall be entitled to receive notice of, attend, speak and vote at our general meetings; and
- holders of our ordinary shares are entitled to receive such dividends as are recommended by our directors and declared by our shareholders.

Registered Shares

We are required by the Companies Act to keep a register of our shareholders. Under English law, the ordinary shares are deemed to be issued when the name of the shareholder is entered in our share register. The share register therefore is prima facie evidence of the identity of our shareholders, and the shares that they hold. The share register generally provides limited, or no, information regarding the ultimate beneficial owners of our ordinary shares. Our share register is maintained by our registrar, Link Asset Services.

Potential future holders of our ADSs will not be treated as one of our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the shares underlying our ADSs. Potential future holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see "Description of the American Depositary Shares" in this prospectus.

Under the Companies Act, we must enter an allotment of shares in our share register as soon as practicable and in any event within two months of the allotment. We will perform all procedures necessary to update the share register to reflect any ordinary shares being sold in any potential offering, including updating the share register with the number of ordinary shares to be issued to the depositary upon the closing of any such offering in the future. We also are required by the Companies Act to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

We, any of our shareholders, or any other affected person may apply to the court for rectification of the share register if:

- the name of any person, without sufficient cause, is entered in or omitted from our register of members; or
- default is made or unnecessary delay takes place in entering on the register the fact of any person having ceased to be a member or on which we have a lien, provided that such delay does not prevent dealings in the shares taking place on an open and proper basis.

Pre-emptive Rights

English law generally provides shareholders with pre-emptive rights when new shares are issued for cash; however, it is possible for the Articles, or shareholders by special resolution, to exclude pre-emptive rights. Such an exclusion of pre-emptive rights may be for a maximum period of up to five years from the date of adoption of the Articles, if the exclusion is contained in the Articles, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). Typically U.K. public companies renew the disapplication of pre-emption rights on an annual basis or their annual general meeting. On June 25, 2018, our shareholders approved the exclusion of pre-emptive rights for a period of 15 months or the date of the next annual general meeting, which exclusion is for a number of shares equal to 20% of the issued share capital at the time of passing of the resolution and which will need to be renewed upon expiration (i.e., the earlier of 15 months from the date of passing the resolution on the date of the next annual general meeting) to remain effective.

Articles of Association

Our Articles were adopted by a special resolution of the founder shareholder passed at a general meeting on June 30, 2016. A summary of the terms of the Articles is set out below. The summary below is not a complete copy of the terms of the Articles.

The Articles contain no specific restrictions on our purpose and therefore, by virtue of section 31(1) of the Companies Act, our purpose is unrestricted.

The Articles contain, among other things, provisions to the following effect:

Share Capital

Our share capital currently consists of ordinary shares. Subject to the Companies Act and to any rights attached to existing shares, we may issue shares with such rights or restrictions as may be determined by ordinary resolution or if no ordinary resolution has been passed or so far as such ordinary resolution does not make specific provision, as the board may determine. In addition, shares which are to be redeemed, or are liable to be redeemed at our option or the holder of such shares may be issued with the board determining the terms and conditions of such redemption.

Voting

The shareholders have the right to receive notice of, and to vote at, our general meetings. Each shareholder who is present in person (or, being a corporation, by representative) at a general meeting on a show of hands has one vote and, on a poll, every such holder who is present in person (or, being a corporation, by representative) or by proxy has one vote in respect of every share held by him.

Variation of Rights

Subject to the Companies Act, whenever our share capital is divided into different classes of shares, the special rights attached to any class may be varied or abrogated either with the consent in writing of the holders of three-fourths in nominal value of the issued shares of that class (excluding any shares held as treasury shares) or with the sanction of a special resolution passed at a separate general meeting of the holders of the shares of that class, held in accordance with the Articles.

Dividends

We may, subject to the provisions of the Companies Act and the Articles, by ordinary resolution from time to time declare dividends to be paid to shareholders not exceeding the amount recommended by our board of directors.

Subject to the provisions of the Companies Act, in so far as, in the board of directors' opinions, our profits justify such payments, the board of directors may pay interim dividends on any class of our shares.

Any dividend unclaimed after a period of 12 years from the date such dividend was declared or became payable shall, if the board of directors resolve, be forfeited and shall cease to remain owing by us. No dividend or other moneys payable on or in respect of a share shall bear interest as against us.

Transfer of Ordinary Shares

Each member may transfer all or any of his shares which are in certificated form by means of an instrument of transfer in any usual form or in any other form which the board of directors may approve. Each member may transfer all or any of his shares which are in uncertificated form by means of a "relevant system" (i.e., the CREST System) in such manner provided for, and subject as provided in, the CREST Regulations.

The Board may, in its absolute discretion, refuse to register a transfer of certificated shares unless:

(i) it is for a share which is fully paid up;

(ii) it is for a share upon which the company has no lien;

(iii) it is only for one class of share;

(iv) it is in favor of a single transferee or no more than four joint transferees;

(v) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the board of directors to be exempt from stamp duty; and

(vi) it is delivered for registration to the registered office of the company (or such other place as the board of directors may determine), accompanied (except in the case of a transfer by a person to whom the company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the board of directors may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

The board of directors may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the CREST Regulations and the CREST System.

Allotment of Shares and Pre-emption Rights

Subject to the Companies Act and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the board of directors may determine (including shares which are to be redeemed, or are liable to be redeemed at the option of the company or the holder of such shares).

In accordance with section 551 of the Companies Act, the board of directors may be generally and unconditionally authorized to exercise all the powers of the company to allot shares up to an aggregate nominal amount equal to the amount stated in the relevant ordinary resolution authorizing such allotment.

The provisions of section 561 of the Companies Act (which confer on shareholders rights of pre-emption in respect of the allotment of equity securities which are paid up in cash) apply to the company except to the extent disapplied by special resolution of the company. Such pre-emption rights have been disapplied, in part, pursuant to the special resolution passed on June 25, 2018.

Alteration of Share Capital

The company may by ordinary resolution consolidate or divide all of its share capital into shares of larger nominal value than its existing shares, or cancel any shares which, at the date of the ordinary resolution, have not been taken or agreed to be taken by any person and diminish the amount of its share capital by the nominal amount of shares so cancelled or sub-divide its shares, or any of them, into shares of smaller nominal value.

The company may, in accordance with the Companies Act, reduce or cancel its share capital or any capital redemption reserve or share premium account in any manner and with and subject to any conditions, authorities and consents required by law.

Board of Directors

Unless otherwise determined by the company by ordinary resolution, the number of directors (other than any alternate directors) shall not be less than two, but there shall be no maximum number of directors.

Subject to the Articles and the Companies Act, the company may by ordinary resolution appoint a person who is willing to act as a director and the board of directors shall have power at any time to appoint any person who is willing to act as a director, in both cases either to fill a vacancy or as an addition to the existing board of directors.

At every annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not elected or re-elected at one of the preceding two annual general meetings, must retire from office and may offer themselves for re-election by the shareholders by ordinary resolution.

Subject to the provisions of the Articles, the board of directors may regulate their proceedings as they deem appropriate. A director may, and the secretary at the request of a director shall, call a meeting of the directors.

The quorum for a meeting of the board of directors shall be fixed from time to time by a decision of the board of directors, but it must never be less than two and unless otherwise fixed, it is two.

Questions and matters requiring resolution arising at a meeting shall be decided by a majority of votes of the participating directors, with each director having one vote. In the case of an equality of votes, the chairman will only have a casting vote or second vote (unless he is not entitled to vote on the resolution in question).

Directors shall be entitled to receive such remuneration as the board shall determine for their services to the company as directors, and for any other service which they undertake for the company provided that the aggregate fees payable to the directors must not exceed £250,000 per annum or such higher amount as decided by ordinary resolution. The directors shall also be entitled to be paid all reasonable expenses properly incurred by them in connection with their attendance at meetings of shareholders or class meetings, board of director or committee meetings or otherwise in connection with the exercise of their powers and the discharge of their responsibilities in relation to the company.

The board of directors may, in accordance with the requirements in the Articles, authorize any matter proposed to them by any director which would, if not authorized, involve a director breaching his duty under the Companies Act, to avoid conflicts of interests.

A director seeking authorization in respect of such conflict shall declare to the board of directors the nature and extent of his interest in a conflict as soon as is reasonably practicable. The director shall provide the board with such details of the matter as are necessary for the board to decide how to address the conflict together with such additional information as may be requested by the board.

Any authorization by the board of directors will be effective only if:

(i) to the extent permitted by the Companies Act, the matter in question shall have been proposed by any director for consideration in the same way that any other matter may be proposed to the directors under the provisions of the Articles;

(ii) any requirement as to the quorum for consideration of the relevant matter is met without counting the conflicted director and any other conflicted director; and

(iii) the matter is agreed to without the conflicted director voting or would be agreed to if the conflicted director's and any other interested director's vote is not counted.

Subject to the provisions of the Companies Act, every director, secretary or other officer of the company (other than an auditor) is entitled to be indemnified against all costs, charges, losses, damages and liabilities incurred by him in the actual purported exercise or discharge of his duties or exercise of his powers or otherwise in relation to them.

General Meetings

The company must convene and hold annual general meetings in accordance with the Companies Act. Under the Companies Act, an annual general meeting must be called by notice of at least 21 days.

No business shall be transacted at any general meeting unless a quorum is present when the meeting proceeds to business, but the absence of a quorum shall not preclude the choice or appointment of a chairman of the meeting which shall not be treated as part of the business of the meeting. Save as otherwise provided by the Articles, two shareholders present in person or by proxy and entitled to vote shall be a quorum for all purposes.

Borrowing Powers

Subject to the Articles and the Companies Act, the board of directors may exercise all of the powers of the company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the company or of any third party.

The borrowing powers are restricted to the sum of £25,000,000 but this limit may be increased by ordinary resolution of shareholders.

Capitalization of profits

The directors may, if they are so authorized by an ordinary resolution of the shareholders, decide to capitalize any undivided profits of the company (whether or not they are available for distribution), or any sum standing to the credit of the company's share premium account or capital redemption reserve. The directors may also, subject to the aforementioned ordinary resolution, appropriate any sum which they so decide to capitalize to the persons who would have been entitled to it if it were distributed by way of dividend and in the same proportions.

Uncertificated Shares

Subject to the Companies Act, the board of directors may permit title to shares of any class to be issued or held otherwise than by a certificate and to be transferred by means of a "relevant system" (i.e., the CREST System) without a certificate.

The board of directors may take such steps as it sees fit in relation to the evidencing of and transfer of title to uncertificated shares, any records relating to the holding of uncertificated shares and the conversion of uncertificated shares to certificated shares, or vice-versa.

The board of directors may by notice to the holder of an uncertificated share, require that share to be converted into certificated form.

The board of directors may take such other action that the board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of an uncertified share or otherwise to enforce a lien in respect of it.

Mandatory Bid

The U.K. City Code on Takeovers and Mergers, or Takeover Code, applies to the company. Under the Takeover Code, where:

(a) any person, together with persons acting in concert with him, acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares in which he is already interested, and in which persons acting in concert with him are interested) carry 30% or more of the voting rights of a company; or

(b) any person who, together with persons acting in concert with him, is interested in shares which in the aggregate carry not less than 30% of the voting rights of a company but does not hold shares carrying more than 50% of such voting rights and such person, or any person acting in concert with him, acquires an interest in any other shares which increases the percentage of shares carrying voting rights in which he is interested, such person shall, except in limited circumstances, be obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights. Offers for different classes of equity share capital must be comparable; the U.K. Panel on Takeovers and Mergers, or Takeover Panel, should be consulted in advance in such cases.

An offer under Rule 9 of the Takeover Code must be in cash and at the highest price paid for any interest in the shares by the person required to make an offer or any person acting in concert with him during the 12 months prior to the announcement of the offer.

Under the Takeover Code, a "concert party" arises where persons acting together pursuant to an agreement or understanding (whether formal or informal and whether or not in writing) cooperate, through the acquisition by them of an interest in shares in a company, to obtain or consolidate control of the company. "Control" means holding, or aggregate holdings, of an interest in shares carrying 30% or more of the voting rights of the company, irrespective of whether the holding or holdings give *de facto* control.

Panetta Partners Limited, Planwise Group Limited and Gabriele Cerrone are considered to be a "concert party" for the purposes of the Takeover Code, or the Cerrone Concert Party. Following the offering the Cerrone Concert Party will hold shares carrying voting rights equal to approximately 42.6%. Accordingly following the offering the Cerrone Concert Party will not, save in limited circumstances, be able to acquire further interests in shares carrying voting rights without being obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights.

Squeeze-out

Under the Companies Act, if a takeover offer (as defined in Section 974 of the Companies Act) is made for the shares of a company and the offeror were to acquire, or unconditionally contract to acquire:

(i) not less than 90% in value of the shares to which the takeover offer relates, or the Takeover Offer Shares; and

(ii) where those shares are voting shares, not less than 90% of the voting rights attached to the Takeover Offer Shares,

the offeror could acquire compulsorily the remaining 10%. It would do so by sending a notice to outstanding shareholders within three months of the last day on which its offer can be accepted telling them that it will acquire compulsorily their shares, or Takeover Offer Shares, and then, six weeks later, it would send a copy of the notice to the company with an executed instrument of transfer of the outstanding Takeover Offer Shares in its favor and pay the consideration to the company, which would hold the consideration on trust for outstanding shareholders. The consideration offered to the shareholders whose Takeover Offer Shares are acquired compulsorily under the Companies Act must, in general, be the same as the consideration that was available under the takeover offer.

Sell-out

The Companies Act also gives minority shareholders a right to be bought out in certain circumstances by an offeror who has made a takeover offer (as defined in Section 974 of the Companies Act). If a takeover offer related to all the shares of a company and, at any time before the end of the period within which the offer could be accepted, the offeror held or had agreed to acquire not less than 90% of the shares to which the offer relates, any holder of the shares to which the offer related who had not accepted the offer could by a written communication to the offeror require it to acquire those shares. The offeror is required to give any shareholder notice of his or her right to be bought out within one month of that right arising. The offeror may impose a time limit on the rights of the minority shareholders to be bought out, but that period cannot end less than three months after the end of the acceptance period. If a shareholder exercises his or her rights, the offeror is bound to acquire those shares on the terms of the offer or on such other terms as may be agreed.

Shareholder Notification and Disclosure Requirements

Shareholders are obliged to comply with the shareholding notification and disclosure requirements set out in Chapter 5 of the Disclosure Guidance and Transparency Rules, or DTRs. A shareholder is required pursuant to Rule 5 of the DTRs to notify the company if, as a result of an acquisition or disposal of shares or financial instruments, the shareholder's percentage of voting rights of the company reaches, exceeds or falls below 3% of the nominal value of the company's share capital or any 1% threshold above that.

The DTRs can be accessed and downloaded from the Financial Conduct Authority's website at *www.fshandbook.info/FS/html/FCA/DTR*. Shareholders are urged to consider their notification and disclosure obligations carefully as a failure to make a required disclosure to the company may result in disenfranchisement.

U.K. City Code on Takeovers and Mergers

As a U.K. public company whose shares are traded on a multi-lateral trading facility in the United Kingdom, we are subject to the Takeover Code, which is issued and administered by the Takeover Panel. The Takeover Code provides a framework within which takeovers are regulated and conducted. Under the Takeover Code, where:

(i) any person, together with persons acting in concert with him, acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares in which he is already interested, and in which persons acting in concert with him are interested) carry 30% or more of the voting rights of a company; or

(ii) any person who, together with persons acting in concert with him, is interested in shares which in the aggregate carry not less than 30% of the voting rights of a company but does not hold shares carrying more than 50% of such voting rights and such person, or any person acting in concert with him, acquires an interest in any other shares which increases the percentage of shares carrying voting rights in which he is interested;

such person shall, except in limited circumstances, be obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights. Offers for different classes of equity share capital must be comparable; the Takeover Panel should be consulted in advance in such cases.

An offer under Rule 9 of the Takeover Code must be in cash and at the highest price paid for any interest in the shares by the person required to make an offer or any person acting in concert with him during the 12 months prior to the announcement of the offer.

Under the Takeover Code, a "concert party" arises where persons acting together pursuant to an agreement or understanding (whether formal or informal and whether or not in writing) cooperate, through the acquisition by them of an interest in shares in a company, to obtain or consolidate control of the company. "Control" means holding, or aggregate holdings, of an interest in shares carrying 30% or more of the voting rights of the company, irrespective of whether the holding or holdings give de facto control.

Panetta Partners Limited, Planwise Group Limited and Gabriele Cerrone, together the Cerrone Concert Party are considered to be a "concert party" for the purposes of the Takeover Code. Following the offering the Cerrone Concert

Party will hold shares carrying voting rights equal to approximately 42%. Accordingly following the offering the Cerrone Concert Party will not, save in limited circumstances, be able to acquire further interests in shares carrying voting rights without being obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights.

Differences in Corporate Law

The applicable provisions of the Companies Act differ from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of certain differences between the provisions of the Companies Act applicable to us and the Delaware General Corporation Law relating to shareholders' rights and protections. This summary is not intended to be a complete discussion of the respective rights and it is qualified in its entirety by reference to Delaware law and English law.

	England and Wales	**Delaware**
Number of Directors	Under the Companies Act, a public limited company must have at least two directors and the number of directors may be fixed by or in the manner provided in a company's Articles.	Under Delaware law, a corporation must have at least one director and the number of directors shall be fixed by or in the manner provided in the bylaws.
Removal of Directors	Under the Companies Act, shareholders may remove a director without cause by an ordinary resolution (which is passed by a simple majority of those voting in person or by proxy at a general meeting) irrespective of any provisions of any service contract the director has with the company, provided 28 clear days' notice of the resolution has been given to the company and its shareholders. On receipt of notice of an intended resolution to remove a director, the company must forthwith send a copy of the notice to the director concerned. Certain other procedural requirements under the Companies Act must also be followed, such as allowing the director to make representations against his or her removal either at the meeting or in writing.	Under Delaware law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (i) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board of directors is classified, stockholders may effect such removal only for cause, or (ii) in the case of a corporation having cumulative voting, if less than the entire board of directors is to be removed, no director may be removed without cause if the votes cast against his removal would be sufficient to elect him if then cumulatively voted at an election of the entire board of directors, or, if there are classes of directors, at an election of the class of directors of which he is a part.
Vacancies on the Board of Directors	Under English law, the procedure by which directors, other than a company's initial directors, are appointed is generally set out in a company's Articles, provided that where two or more persons are appointed as directors of a public limited company by a single resolution of the shareholders, such resolution must not be put to shareholders unless a resolution that it should so be made has first been agreed to by the shareholders without any vote being given against it.	Under Delaware law, vacancies and newly created directorships may be filled by a majority of the directors then in office (even though less than a quorum) or by a sole remaining director unless (i) otherwise provided in the certificate of incorporation or bylaws of the corporation or (ii) the certificate of incorporation directs that a particular class of stock is to elect such director, in which case a majority of the other directors elected by such class, or a sole remaining director elected by such class, will fill such vacancy.

	England and Wales	Delaware
Annual General Meeting	Under the Companies Act, a public limited company must hold an annual general meeting in each six-month period beginning with the day following the company's annual accounting reference date.	Under Delaware law, the annual meeting of stockholders shall be held at such place, on such date and at such time as may be designated from time to time by the board of directors or as provided in the certificate of incorporation or by the bylaws.
General Meeting	Under the Companies Act, a general meeting of the shareholders of a public limited company may be called by the directors. Shareholders holding at least 5% of the paid-up capital of the company carrying voting rights at general meetings (excluding any paid up capital held as treasury shares) can require the directors to call a general meeting and, if the directors fail to do so within a certain period, may themselves or any of them representing more than one half of the total voting rights of all of them convene a general meeting.	Under Delaware law, special meetings of the stockholders may be called by the board of directors or by such person or persons as may be authorized by the certificate of incorporation or by the bylaws.
Notice of General Meetings	Under the Companies Act, at least 21 days' notice must be given for an annual general meeting and any resolutions to be proposed at the meeting, subject to a company's Articles providing for a longer period. Subject to a company's Articles providing for a longer period, at least 14 days' notice is required for other general meetings of a public limited company which fulfill certain conditions. In addition, certain matters, such as the removal of directors or auditors, require special notice, which is 28 days' notice. The shareholders of a company may in all cases consent to a shorter notice period, the proportion of shareholders' consent required being 100% of those entitled to attend and vote in the case of an annual general meeting and, in the case of any other general meeting, a majority in number of the members having a right to attend and vote at the meeting, being a majority who together hold not less than 95% in nominal value of the shares giving a right to attend and vote at the meeting.	Under Delaware law, unless otherwise provided in the certificate of incorporation or bylaws, written notice of any meeting of the stockholders must be given to each stockholder entitled to vote at the meeting not less than ten nor more than 60 days before the date of the meeting and shall specify the place, date, hour and purpose or purposes of the meeting.

	England and Wales	Delaware
Quorum	Subject to the provisions of a company's Articles, the Companies Act provides that two shareholders present at a meeting (in person, by proxy or authorised under the Companies Act) shall constitute a quorum for companies with more than one shareholder.	The certificate of incorporation or bylaws may specify the number of shares, the holders of which shall be present or represented by proxy at any meeting in order to constitute a quorum, but in no event shall a quorum consist of less than one third of the shares entitled to vote at the meeting. In the absence of such specification in the certificate of incorporation or bylaws, a majority of the shares entitled to vote, present in person or represented by proxy, shall constitute a quorum at a meeting of stockholders.
Proxy	Under the Companies Act, at any meeting of shareholders, a shareholder may designate another person to attend, speak and vote at the meeting on their behalf by proxy.	Under Delaware law, at any meeting of stockholders, a stockholder may designate another person to act for such stockholder by proxy, but no such proxy shall be voted or acted upon after three years from its date, unless the proxy provides for a longer period. A director of a Delaware corporation may not issue a proxy representing the director's voting rights as a director.
Issue of New Shares	Under the Companies Act, the directors of a company must not exercise any power to allot shares or grant rights to subscribe for, or to convert any security into, shares unless they are authorized to do so by the company's Articles or by an ordinary resolution of the shareholders. Any authorization given must state the maximum amount of shares that may be allotted under it and specify the date on which it will expire, which must be not more than five years from the date the authorization was given. The authority can be renewed by a further resolution of the shareholders.	Under Delaware law, if the company's certificate of incorporation so provides, the directors have the power to authorize additional stock. The directors may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the company or any combination thereof.
Pre-emptive Rights	Under the Companies Act, "equity securities," being (i) shares in the company other than shares that, with respect to dividends and capital, carry a right to participate only up to a specified amount in a distribution, referred to as "ordinary shares," or (ii) rights to subscribe for, or to convert securities into, ordinary shares, proposed to be allotted for cash must be offered first to the existing equity shareholders in the company in proportion to the respective nominal value of their holdings, unless the period during which any such offer	Under Delaware law, shareholders have no pre-emptive rights to subscribe to additional issues of stock or to any security convertible into such stock unless, and except to the extent that, such rights are expressly provided for in the certificate of incorporation.

	England and Wales	Delaware
	may be accepted has expired or the company has received notice of acceptance or refusal, or an exception applies or a special resolution to the contrary has been passed by shareholders in a general meeting or the Articles provide otherwise in each case in accordance with the provisions of the Companies Act.	
Authority to Allot	Under the Companies Act, the directors of a company must not allot shares or grant rights to subscribe for or convert any security into shares unless an ordinary resolution to the contrary has been passed by shareholders in a general meeting or the Articles provide otherwise, in each case in accordance with the provisions of the Companies Act.	Under Delaware law, if the corporation's charter or certificate of incorporation so provides, the board of directors has the power to authorize the issuance of stock. The board of directors may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the corporation or any combination thereof. It may determine the amount of such consideration by approving a formula. In the absence of actual fraud in the transaction, the judgment of the directors as to the value of such consideration is conclusive.
Liability of Directors and Officers	Under the Companies Act, any provision, whether contained in a company's Articles or any contract or otherwise, that purports to exempt a director of a company, to any extent, from any liability that would otherwise attach to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company, is void. Any provision by which a company directly or indirectly provides an indemnity, to any extent, for a director of the company or of an associated company against any liability attaching to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act, which provides exceptions for the company to: (i) purchase and maintain insurance against such liability; (ii) provide a "qualifying third party indemnity," or an indemnity against liability incurred by the director to a person other than the company or an associated company; and (iii) provide a "qualifying pension scheme indemnity," or an indemnity against liability incurred in connection with the company's activities as trustee of an occupational pension plan.	Under Delaware law, a corporation's certificate of incorporation may include a provision eliminating or limiting the personal liability of a director to the corporation and its stockholders for damages arising from a breach of fiduciary duty as a director. However, no provision can limit the liability of a director for: • any breach of the director's duty of loyalty to the corporation or its stockholders; • acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law; • intentional or negligent payment of unlawful dividends or stock purchases or redemptions; or • any transaction from which the director derives an improper personal benefit.

	England and Wales	Delaware
Voting Rights	Under the model articles for public companies, unless a poll is demanded by the shareholders of a company or is required by the chairman of the meeting or the company's Articles, shareholders shall vote on all resolutions on a show of hands. Under the Companies Act, a poll may be demanded by: (i) not fewer than five shareholders having the right to vote on the resolution; (ii) any shareholder(s) representing not less than 10% of the total voting rights of all the shareholders having the right to vote on the resolution (excluding any voting rights attaching to treasury shares); or (iii) any shareholder(s) holding shares in the company conferring a right to vote on the resolution (excluding any voting rights attaching to treasury shares) being shares on which an aggregate sum has been paid up equal to not less than 10% of the total sum paid up on all the shares conferring that right. A company's Articles may provide more extensive rights for shareholders to call a poll. Under English law, an ordinary resolution is passed on a show of hands if it is approved by a simple majority (more than 50%) of the votes cast by shareholders present (in person or by proxy) and entitled to vote. If a poll is demanded, an ordinary resolution is passed if it is approved by holders representing a simple majority of the total voting rights of shareholders present, in person or by proxy, who, being entitled to vote, vote on the resolution. Special resolutions require the affirmative vote of not less than 75% of the votes cast by shareholders present, in person or by proxy, at the meeting.	Delaware law provides that, unless otherwise provided in the certificate of incorporation, each stockholder is entitled to one vote for each share of capital stock held by such stockholder.
Shareholder Vote on Certain Transactions	The Companies Act provides for schemes of arrangement, which are arrangements or compromises between a company and any class of shareholders or creditors and used in certain types of reconstructions, amalgamations, capital reorganizations or takeovers. These arrangements require: • the approval at a shareholders' or creditors' meeting convened by order of the court, of a majority in number of shareholders	Generally, under Delaware law, unless the certificate of incorporation provides for the vote of a larger portion of the stock, completion of a merger, consolidation, sale, lease or exchange of all or substantially all of a corporation's assets or dissolution requires: • the approval of the board of directors; and

	England and Wales	Delaware
	or creditors or class thereof representing 75% in value, the class of shareholders or creditors, or class thereof present and voting, either in person or by proxy; and • the approval of the court.	• the approval by the vote of the holders of a majority of the outstanding stock or, if the certificate of incorporation provides for more or less than one vote per share, a majority of the votes of the outstanding stock of the corporation entitled to vote on the matter.
Standard of Conduct for Directors	Under English law, a director owes various statutory and fiduciary duties to the company, including: • to act in the way he considers, in good faith, would be most likely to promote the success of the company for the benefit of its members as a whole; • to avoid a situation in which he has, or can have, a direct or indirect interest that conflicts, or possibly conflicts, with the interests of the company; • to act in accordance with the company's constitution and only exercise his powers for the purposes for which they are conferred; • to exercise independent judgment; • to exercise reasonable care, skill and diligence; • not to accept benefits from a third party conferred by reason of his being a director or doing, or not doing, anything as a director; and • to declare any interest that he has, whether directly or indirectly, in a proposed or existing transaction or arrangement with the company.	Delaware law does not contain specific provisions setting forth the standard of conduct of a director. The scope of the fiduciary duties of directors is generally determined by the courts of the State of Delaware. In general, directors have a duty to act without self-interest, on a well-informed basis and in a manner they reasonably believe to be in the best interest of the stockholders. Directors of a Delaware corporation owe fiduciary duties of care and loyalty to the corporation and to its shareholders. The duty of care generally requires that a director act in good faith, with the care that an ordinarily prudent person would exercise under similar circumstances. Under this duty, a director must inform himself of all material information reasonably available regarding a significant transaction. The duty of loyalty requires that a director act in a manner he reasonably believes to be in the best interests of the corporation. He must not use his corporate position for personal gain or advantage. In general, but subject to certain exceptions, actions of a director are presumed to have been made on an informed basis, in good faith and in the honest belief that the action taken was in the best interests of the corporation. However, this presumption may be rebutted by evidence of a breach of one of the fiduciary duties. Delaware courts have also imposed a heightened standard of conduct upon directors of a Delaware corporation who take any action designed to defeat a threatened change in control of the corporation.

	England and Wales	Delaware
		In addition, under Delaware law, when the board of directors of a Delaware corporation approves the sale or break-up of a corporation, the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the shareholders.
Shareholder Suits	Under English law, generally, the company, rather than its shareholders, is the proper claimant in an action in respect of a wrong done to the company or where there is an irregularity in the company's internal management. Notwithstanding this general position, the Companies Act provides that (i) a court may allow a shareholder to bring a derivative claim (that is, an action in respect of and on behalf of the company) in respect of a cause of action arising from a director's negligence, default, breach of duty or breach of trust and (ii) a shareholder may bring a claim for a court order where the company's affairs have been or are being conducted in a manner that is unfairly prejudicial to some of its shareholders.	Under Delaware law, a stockholder may initiate a derivative action to enforce a right of a corporation if the corporation fails to enforce the right itself. The complaint must: • state that the plaintiff was a stockholder at the time of the transaction of which the plaintiff complains or that the plaintiffs shares thereafter devolved on the plaintiff by operation of law; and • allege with particularity the efforts made by the plaintiff to obtain the action the plaintiff desires from the directors and the reasons for the plaintiff's failure to obtain the action; or • state the reasons for not making the effort. Additionally, the plaintiff must remain a stockholder through the duration of the derivative suit. The action will not be dismissed or compromised without the approval of the Delaware Court of Chancery.

Other U.K. Law Considerations

Registered Shares

We are required by the Companies Act to keep a register of our shareholders. Under English law, shares are deemed to be issued when the name of the shareholder is entered in our register of members. The register of members therefore is prima facie evidence of the identity of our shareholders, and the shares that they hold. The register of members generally provides limited, or no, information regarding the ultimate beneficial owners of our shares. Our register of members is maintained by our registrar, LINK Asset Services Limited.

Under the Companies Act, we must enter an allotment of shares in our register of members as soon as practicable and in any event within two months of the allotment. We will perform all procedures necessary to update the register of members to reflect the ordinary shares and the ADSs being allotted and issued in this offering. We also are required by the Companies Act to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

We, any of our shareholders or any other affected person may apply to the court for rectification of the register of members if:

- the name of any person, without sufficient cause, is entered in or omitted from our register of members; or
- default is made or unnecessary delay takes place in entering on the register the fact of any person having ceased to be a member.

Distributions and Dividends

Under the Companies Act, before a company can lawfully make a distribution or dividend, it must ensure that it has sufficient distributable reserves, as determined on a non-consolidated basis. The basic rule is that a company's profits available for the purpose of making a distribution are its accumulated, realized profits, so far as not previously utilized by distribution or capitalization, less its accumulated, realized losses, so far as not previously written off in a reduction or reorganization of capital duly made. The requirement to have sufficient distributable reserves before a distribution or dividend can be paid applies to us and to each of our subsidiaries that has been incorporated under English law.

As a public company, it is also not sufficient that we have made a distributable profit for the purpose of making a distribution. An additional capital maintenance requirement is imposed on us to ensure that the net worth of the company is at least equal to the amount of its capital. A public company can only make a distribution:

- if, at the time that the distribution is made, the amount of its net assets (that is, the total excess of assets over liabilities) is not less than the total of its called up share capital and undistributable reserves; and
- if, and to the extent that, the distribution itself, at the time that it is made, does not reduce the amount of its net assets to less than that total.

Limitation on Owning Securities

Our Articles do not restrict in any way the ownership or voting of our shares by non-residents.

Purchase of Own Shares

English law permits a public limited company to purchase its own shares out of the distributable profits of the company or the proceeds of a fresh issue of shares made for the purpose of financing the purchase, subject to complying with procedural requirements under the Companies Act and provided that its Articles do not prohibit it from doing so. Our Articles, a summary of which is provided above, do not prohibit us from purchasing our own shares. A public limited company must not purchase its own shares if, as a result of the purchase, there would no longer be any issued shares of the company other than redeemable shares or shares held as treasury shares.

Any such purchase will be either a "market purchase" or "off market purchase," each as defined in the Companies Act. A "market purchase" is a purchase made on a "recognized investment exchange" (other than an overseas exchange) as defined in the U.K. Financial Services and Markets Act 2000, or FSMA and is not an "off-market purchase." An "off market purchase" is a purchase that is not made on a "recognized investment exchange" or purchased on a "recognized investment exchange" but not subject to a marketing arrangement on such "recognized investment exchange." Both "market purchases" and "off market purchases" require prior shareholder approval by way of an ordinary resolution. In the case of an "off market purchase," a company's shareholders, other than the shareholders from whom the company is purchasing shares, must approve the terms of the contract to purchase shares and in the case of a "market purchase," the shareholders must approve the maximum number of shares that can be purchased and the maximum and minimum prices to be paid by the company.

Nasdaq Global Market is an "overseas exchange" for the purposes of the Companies Act and does not fall within the definition of a "recognized investment exchange" for the purposes of FSMA and any purchase made by us would need to comply with the procedural requirements under the Companies Act that regulate "off market purchases."

A share buyback by a company of its shares will give rise to U.K. stamp duty at the rate of 0.5% of the amount or value of the consideration payable by the company, and such stamp duty will be paid by the company.

Our Articles do not have conditions governing changes to our capital which are more stringent that those required by law.

Shareholder Rights

Certain rights granted under the Companies Act, including the right to requisition a general meeting or require a resolution to be put to shareholders at the annual general meeting, are only available to our members. For English law purposes, our members are the persons who are registered as the owners of the legal title to the shares and whose names are recorded in our register of members. In the case of shares held in a settlement system operated by the Depository Trust Company, or DTC, the registered member will be DTC's nominee, Cede & Co. If a person who holds their ADSs in DTC wishes to exercise certain of the rights granted under the Companies Act, they may be required to first take steps to withdraw their ADSs from the settlement system operated by DTC and become the registered holder of the shares in our register of members. A withdrawal of shares from DTC may have tax implications, for additional information on the potential tax implications of withdrawing your shares from the settlement system operated by DTC, see "Material Tax Considerations — United Kingdom Taxation."

DESCRIPTION OF THE AMERICAN DEPOSITARY SHARES

JPMorgan Chase Bank, N.A., as depositary will issue the ADSs which you will be entitled to receive in this offering. Each ADS will represent an ownership interest in a designated number of ordinary shares which we will deposit with the custodian, as agent of the depositary, under the deposit agreement among ourselves, the depositary and yourself as an ADR holder. In the future, each ADS will also represent any securities, cash or other property deposited with the depositary but which they have not distributed directly to you. Unless certificated ADRs are specifically requested by you, all ADSs will be issued on the books of our depositary in book-entry form and periodic statements will be mailed to you which reflect your ownership interest in such ADSs. In our description, references to American depositary receipts, or ADRs, shall include the statements you will receive which reflect your ownership of ADSs.

The depositary's office is located at 383 Madison Avenue, Floor 11, New York, NY, 10179.

You may hold ADSs either directly or indirectly through your broker or other financial institution. If you hold ADSs directly, by having an ADS registered in your name on the books of the depositary, you are an ADR holder. This description assumes you hold your ADSs directly. If you hold the ADSs through your broker or financial institution nominee, you must rely on the procedures of such broker or financial institution to assert the rights of an ADR holder described in this section. You should consult with your broker or financial institution to find out what those procedures are.

As an ADR holder, we will not treat you as a shareholder of ours and you will not have any shareholder rights. The law of England and Wales governs shareholder rights. Because the depositary or its nominee will be the shareholder of record for the ordinary shares represented by all outstanding ADSs, shareholder rights rest with such record holder. Your rights are those of an ADR holder. Such rights derive from the terms of the deposit agreement to be entered into among us, the depositary and all registered holders from time to time of ADRs issued under the deposit agreement. The obligations of our company, the depositary and its agents are also set out in the deposit agreement. Because the depositary or its nominee will actually be the registered owner of the ordinary shares, you must rely on it to exercise the rights of a shareholder on your behalf. The deposit agreement and the ADSs are governed by New York law. Under the deposit agreement, as an ADR holder, you agree that any legal suit, action or proceeding against or involving us or the depositary, arising out of or based upon the deposit agreement, the ADSs or the transactions contemplated thereby, may only be instituted in a state or federal court in New York, New York, and you irrevocably waive any objection which you may have to the laying of venue of any such proceeding and irrevocably submit to the exclusive jurisdiction of such courts in any such suit, action or proceeding.

The following is a summary of what we believe to be the material terms of the deposit agreement. Notwithstanding this, because it is a summary, it may not contain all the information that you may otherwise deem important. For more complete information, you should read the entire deposit agreement and the form of ADR which contains the terms of your ADSs. You can read a copy of the deposit agreement which is filed as an exhibit to the registration statement of which this prospectus forms a part. You may also obtain a copy of the deposit agreement at the SEC's Public Reference Room which is located at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-732-0330. You may also find the registration statement and the attached deposit agreement on the SEC's website at *www.sec.gov*.

Share Dividends and Other Distributions

How will I receive dividends and other distributions on the ordinary shares underlying my ADSs?

We may make various types of distributions with respect to our securities. The depositary has agreed that, to the extent practicable, it will pay to you the cash dividends or other distributions it or the custodian receives on ordinary shares or other deposited securities, after converting any cash received into U.S. dollars (if it determines such conversion may be made on a reasonable basis) and, in all cases, making any necessary deductions provided for in the deposit agreement. The depositary may utilize a division, branch or affiliate of JPMorgan Chase Bank, N.A. to direct, manage and/or execute any public and/or private sale of securities under the deposit agreement. Such division, branch and/or affiliate may charge the depositary a fee in connection with such sales, which fee is considered an expense of the depositary. You will receive these distributions in proportion to the number of underlying securities that your ADSs represent.

Except as stated below, the depositary will deliver such distributions to ADR holders in proportion to their interests in the following manner:

- *Cash.* The depositary will distribute any U.S. dollars available to it resulting from a cash dividend or other cash distribution or the net proceeds of sales of any other distribution or portion thereof (to the extent applicable), on an averaged or other practicable basis, subject to (i) appropriate adjustments for taxes withheld, (ii) such distribution being impermissible or impracticable with respect to certain registered ADR holders, and (iii) deduction of the depositary's and/or its agents' expenses in (1) converting any foreign currency to U.S. dollars to the extent that it determines that such conversion may be made on a reasonable basis, (2) transferring foreign currency or U.S. dollars to the United States by such means as the depositary may determine to the extent that it determines that such transfer may be made on a reasonable basis, (3) obtaining any approval or license of any governmental authority required for such conversion or transfer, which is obtainable at a reasonable cost and within a reasonable time and (4) making any sale by public or private means in any commercially reasonable manner. *If exchange rates fluctuate during a time when the depositary cannot convert a foreign currency, you may lose some or all of the value of the distribution.*

- *Ordinary Shares*. In the case of a distribution in ordinary shares, the depositary will issue additional ADRs to evidence the number of ADSs representing such ordinary shares. Only whole ADSs will be issued. Any ordinary shares which would result in fractional ADSs will be sold and the net proceeds will be distributed in the same manner as cash to the ADR holders entitled thereto.

- *Rights to receive additional ordinary shares.* In the case of a distribution of rights to subscribe for additional ordinary shares or other rights, if we timely provide evidence satisfactory to the depositary that it may lawfully distribute such rights, the depositary will distribute warrants or other instruments in the discretion of the depositary representing rights to acquire additional ADRs. However, if we do not timely furnish such evidence, the depositary may:

  (i) sell such rights if practicable and distribute the net proceeds in the same manner as cash to the ADR holders entitled thereto; or

  (ii) if it is not practicable to sell such rights by reason of the non-transferability of the rights, limited markets therefor, their short duration or otherwise, do nothing and allow such rights to lapse, in which case ADR holders will receive nothing and the rights may lapse.

- *Other Distributions.* In the case of a distribution of securities or property other than those described above, the depositary may either (i) distribute such securities or property in any manner it deems equitable and practicable or (ii) to the extent the depositary deems distribution of such securities or property not to be equitable and practicable, sell such securities or property and distribute any net proceeds in the same way it distributes cash.

- *Elective Distributions.* In the case of a dividend payable at the election of our shareholders in cash or in additional ordinary shares, we will notify the depositary at least 30 days prior to the proposed distribution stating whether or not we wish such elective distribution to be made available to ADR holders. The depositary shall make such elective distribution available to ADR holders only if (i) we shall have timely requested that the elective distribution is available to ADR holders, (ii) the depositary shall have determined that such distribution is reasonably practicable and (iii) the depositary shall have received satisfactory documentation within the terms of the deposit agreement including any legal opinions of counsel that the depositary in its reasonable discretion may request. If the above conditions are not satisfied, the depositary shall, to the extent permitted by law, distribute to the ADR holders, on the basis of the same determination as is made in the local market in respect of the ordinary shares for which no election is made, either (x) cash or (y) additional ADSs representing such additional ordinary shares. If the above conditions are satisfied, the depositary shall establish procedures to enable ADR holders to elect the receipt of the proposed dividend in cash or in additional ADSs. There can be no assurance that ADR holders generally, or any ADR holder in particular, will be given the opportunity to receive elective distributions on the same terms and conditions as the holders of ordinary shares.

If the depositary determines in its discretion that any distribution described above is not practicable with respect to any specific registered ADR holder, the depositary may choose any method of distribution that it deems practicable for such ADR holder, including the distribution of foreign currency, securities or property, or it may retain such items, without paying interest on or investing them, on behalf of the ADR holder as deposited securities, in which case the ADSs will also represent the retained items.

Any U.S. dollars will be distributed by checks drawn on a bank in the United States for whole dollars and cents. Fractional cents will be withheld without liability and dealt with by the depositary in accordance with its then current practices.

The depositary is not responsible if it fails to determine that any distribution or action is lawful or reasonably practicable.

There can be no assurance that the depositary will be able to convert any currency at a specified exchange rate or sell any property, rights, shares or other securities at a specified price, nor that any of such transactions can be completed within a specified time period. All purchases and sales of securities will be handled by the Depositary in accordance with its then current policies, which are currently set forth in the "Depositary Receipt Sale and Purchase of Security" section of www.adr.com/Investors/FindOutAboutDRs, the location and contents of which the Depositary shall be solely responsible for.

Deposit, withdrawal and Cancellation

How does the depositary issue ADSs?

The depositary will issue ADSs if you or your broker deposit ordinary shares or evidence of rights to receive ordinary shares with the custodian and pay the fees and expenses owing to the depositary in connection with such issuance. In the case of the ADSs to be issued under this prospectus, we will arrange with the underwriters named herein to deposit such ordinary shares.

Ordinary shares deposited in the future with the custodian must be accompanied by certain delivery documentation and shall, at the time of such deposit, be registered in the name of the depositary, the custodian or a nominee of either.

The custodian will hold all deposited ordinary shares (including those being deposited by or on our behalf in connection with this offering to which this prospectus relates) for the account and to the order of the depositary for the benefit of registered holders of ADRs, to the extent not prohibited by law. ADR holders thus have no direct ownership interest in the ordinary shares and only have such rights as are contained in the deposit agreement. The custodian will also hold any additional securities, property and cash received on or in substitution for the deposited ordinary shares. The deposited ordinary shares and any such additional items are referred to as "deposited securities."

Upon each deposit of ordinary shares, receipt of related delivery documentation and compliance with the other provisions of the deposit agreement, including the payment of the fees and charges of the depositary and any taxes or other fees or charges owing, the depositary will issue an ADR or ADRs in the name or upon the order of the person entitled thereto evidencing the number of ADSs to which such person is entitled. All of the ADSs issued will, unless specifically requested to the contrary, be part of the depositary's direct registration system, and a registered holder will receive periodic statements from the depositary which will show the number of ADSs registered in such holder's name. An ADR holder can request that the ADSs not be held through the depositary's direct registration system and that a certificated ADR be issued.

How do ADR holders cancel an ADS and obtain deposited securities?

When you turn in your ADR certificate at the depositary's office, or when you provide proper instructions and documentation in the case of direct registration ADSs, the depositary will, upon payment of certain applicable fees, charges and taxes, deliver the underlying ordinary shares to you or upon your written order. Delivery of deposited securities in certificated form will be made at the custodian's office. At your risk, expense and request, the depositary may deliver deposited securities at such other place as you may request.

The depositary may only restrict the withdrawal of deposited securities in connection with:

- temporary delays caused by closing our transfer books or those of the depositary or the deposit of ordinary shares in connection with voting at a shareholders meeting, or the payment of dividends;
- the payment of fees, taxes and similar charges; or
- compliance with any U.S. or foreign laws or governmental regulations relating to the ADRs or to the withdrawal of deposited securities.

This right of withdrawal may not be limited by any other provision of the deposit agreement.

Record Dates

The depositary may, after consultation with us if practicable, fix record dates (which, to the extent applicable, shall be as near as practicable to any corresponding record dates set by us) for the determination of the registered ADR holders who will be entitled (or obligated, as the case may be):

- to receive any distribution on or in respect of deposited securities;
- to give instructions for the exercise of voting rights;
- to pay the fee assessed by the depositary for administration of the ADR program and for any expenses as provided for in the ADR; or
- to receive any notice or to act in respect of other matters,
- all subject to the provisions of the deposit agreement.

Voting Rights

How do I vote?

If you are an ADR holder and the depositary asks you to provide it with voting instructions, you may instruct the depositary how to exercise the voting rights for the ordinary shares which underlie your ADSs. Subject to the next sentence, as soon as practicable after receipt from us of notice of any meeting at which the holders of ordinary shares are entitled to vote, or of our solicitation of consents or proxies from holders of ordinary shares, the depositary shall fix the ADS record date in accordance with the provisions of the deposit agreement in respect of such meeting or solicitation of consent or proxy. The depositary shall, if we request in writing in a timely manner (the depositary having no obligation to take any further action if our request shall not have been received by the depositary at least 30 days prior to the date of such vote or meeting) and at our expense and provided no legal prohibitions exist, distribute to the registered ADR holders a notice stating such information as is contained in the voting materials received by the depositary, stating that that each registered holder of ADRs on the ADS record date will, subject to any applicable provisions of the law of England and Wales, be entitled to instruct the depositary as to the exercise of any voting rights pertaining to ordinary shares underlying such holder's ADSs, and describing how you may instruct the depositary to exercise the voting rights for the ordinary shares which underlie your ADSs, including instructions for giving a discretionary proxy to a person designated by us. For instructions to be valid, the depositary must receive them in the manner and on or before the date specified. The depositary will try, as far as is practical, subject to the provisions of or governing the underlying ordinary shares or other deposited securities, to vote or cause to be voted the ordinary shares or other deposited securities as you instruct. The depositary will only vote or attempt to vote as you instruct. Holders are strongly encouraged to forward their voting instructions to the depositary as soon as possible. Voting instructions will not be deemed to be received until such time as the ADR department responsible for proxies and voting has received such instructions notwithstanding that such instructions may have been physically received by the depositary prior to such time. The depositary will not itself exercise any voting discretion. Furthermore, neither the depositary nor its agents are responsible for any failure to carry out any voting instructions, for the manner in which any vote is cast or for the effect of any vote. Notwithstanding anything contained in the deposit agreement or any ADR, the depositary may, to the extent not prohibited by law or regulations, or by the requirements of the stock exchange on which the ADSs are listed, in lieu of distribution of the materials provided to the depositary in connection with any meeting of, or solicitation of consents or proxies from, holders of deposited securities, distribute to the registered holders of ADRs

a notice that provides such holders with, or otherwise publicizes to such holders, instructions on how to retrieve such materials or receive such materials upon request (*i.e.*, by reference to a website containing the materials for retrieval or a contact for requesting copies of the materials).

There is no guarantee that you will receive voting materials in time to instruct the depositary to vote and it is possible that you, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote.

Reports and Other Communications

Will ADR holders be able to view our reports?

The depositary will make available for inspection by ADR holders at the offices of the depositary and the custodian the deposit agreement, the provisions of or governing deposited securities, and any written communications from us which are both received by the custodian or its nominee as a holder of deposited securities and made generally available to the holders of deposited securities.

Additionally, if we make any written communications generally available to holders of our ordinary shares, and we furnish copies thereof (or English translations or summaries) to the depositary, it will distribute the same to registered ADR holders.

Fees and Expenses

What fees and expenses will I be responsible for paying?

The depositary may charge each person to whom ADSs are issued, including, without limitation, issuances against deposits of ordinary shares, issuances in respect of share distributions, rights and other distributions, issuances pursuant to a stock dividend or stock split declared by us or issuances pursuant to a merger, exchange of securities or any other transaction or event affecting the ADSs or deposited securities, and each person surrendering ADSs for withdrawal of deposited securities or whose ADSs are cancelled or reduced for any other reason, $5.00 for each 100 ADSs (or any portion thereof) issued, delivered, reduced, cancelled or surrendered, as the case may be. The depositary may sell (by public or private sale) sufficient securities and property received in respect of a share distribution, rights and/or other distribution prior to such deposit to pay such charge.

The following additional charges shall be incurred by the ADR holders, by any party depositing or withdrawing ordinary shares or by any party surrendering ADSs and/or to whom ADSs are issued (including, without limitation, issuance pursuant to a stock dividend or stock split declared by us or an exchange of stock regarding the ADSs or the deposited securities or a distribution of ADSs), whichever is applicable:

- a fee of U.S.$1.50 per ADR or ADRs for transfers of certificated or direct registration ADRs;
- a fee of up to U.S.$0.05 per ADS for any cash distribution made pursuant to the deposit agreement;
- an aggregate fee of up to U.S.$0.05 per ADS per calendar year (or portion thereof) for services performed by the depositary in administering the ADRs (which fee may be charged on a periodic basis during each calendar year and shall be assessed against holders of ADRs as of the record date or record dates set by the depositary during each calendar year and shall be payable in the manner described in the next succeeding provision);
- a fee for the reimbursement of such fees, charges and expenses as are incurred by the depositary and/or any of its agents (including, without limitation, the custodian and expenses incurred on behalf of holders in connection with compliance with foreign exchange control regulations or any law or regulation relating to foreign investment) in connection with the servicing of the ordinary shares or other deposited securities, the sale of securities (including, without limitation, deposited securities), the delivery of deposited securities or otherwise in connection with the depositary's or its custodian's compliance with applicable law, rule or regulation (which fees and charges shall be assessed on a proportionate basis against holders as of the record date or dates set by the depositary and shall be payable at the sole discretion of the depositary by billing such holders or by deducting such charge from one or more cash dividends or other cash distributions);

- a fee for the distribution of securities (or the sale of securities in connection with a distribution), such fee being in an amount equal to the $0.05 per ADS issuance fee for the execution and delivery of ADSs which would have been charged as a result of the deposit of such securities (treating all such securities as if they were ordinary shares) but which securities or the net cash proceeds from the sale thereof are instead distributed by the depositary to those holders entitled thereto;
- stock transfer or other taxes and other governmental charges;
- SWIFT, cable, telex and facsimile transmission and delivery charges incurred at your request in connection with the deposit or delivery of ordinary shares, ADRs or deposited securities;
- transfer or registration fees for the registration or transfer of deposited securities on any applicable register in connection with the deposit or withdrawal of deposited securities;
- in connection with the conversion of foreign currency into U.S. dollars, JPMorgan Chase Bank, N.A. shall deduct out of such foreign currency the fees, expenses and other charges charged by it and/or its agent (which may be a division, branch or affiliate) so appointed in connection with such conversion; and
- fees of any division, branch or affiliate of the depositary utilized by the depositary to direct, manage and/or execute any public and/or private sale of securities under the deposit agreement.

JPMorgan Chase Bank, N.A. and/or its agent may act as principal for such conversion of foreign currency. For further details see *www.adr.com*.

We will pay all other charges and expenses of the depositary and any agent of the depositary (except the custodian) pursuant to agreements from time to time between us and the depositary. The charges described above may be amended from time to time by agreement between us and the depositary. The right of the depositary to receive payment of fees, charges and expenses as provided above shall survive the termination of the deposit agreement.

The depositary may make available to us a set amount or a portion of the depositary fees charged in respect of the ADR program or otherwise upon such terms and conditions as we and the depositary may agree from time to time. The depositary collects its fees for issuance and cancellation of ADSs directly from investors depositing ordinary shares or surrendering ADSs for the purpose of withdrawal or from intermediaries acting for them. The depositary collects fees for making distributions to investors by deducting those fees from the amounts distributed or by selling a portion of distributable property to pay the fees. The depositary may collect its annual fee for depositary services by deduction from cash distributions, or by directly billing investors, or by charging the book-entry system accounts of participants acting for them. The depositary will generally set off the amounts owing from distributions made to holders of ADSs. If, however, no distribution exists and payment owing is not timely received by the depositary, the depositary may refuse to provide any further services to holders that have not paid those fees and expenses owing until such fees and expenses have been paid. At the discretion of the depositary, all fees and charges owing under the deposit agreement are due in advance and/or when declared owing by the depositary.

Payment of Taxes

If any taxes or other governmental charges (including any penalties and/or interest) shall become payable by or on behalf of the custodian or the depositary with respect to any ADR, any deposited securities represented by the ADSs evidenced thereby or any distribution thereon, such tax or other governmental charge shall be paid by the holder thereof to the depositary and by holding or having held an ADR the holder and all prior holders thereof, jointly and severally, agree to indemnify, defend and save harmless each of the depositary and its agents in respect thereof. If an ADR holder owes any tax or other governmental charge, the depositary may (i) deduct the amount thereof from any cash distributions, or (ii) sell deposited securities by public or private sale (after attempting by reasonable means to notify the ADR holder hereof prior to such sale) and deduct the amount owing from the net proceeds of such sale. In either case the ADR holder remains liable for any shortfall. If any tax or governmental charge is unpaid, the depositary may also refuse to effect any registration, registration of transfer, split-up or combination of deposited securities or withdrawal of deposited securities until such payment is made. If any tax or governmental charge is required to be withheld on any cash distribution, the depositary may deduct the amount required to be withheld from any cash distribution or, in the case of a non-cash distribution, sell the distributed property or securities (by public or private sale) in such amounts and in such manner as the depositary deems necessary and practicable to pay such taxes and distribute any remaining net proceeds or the balance of any such property after deduction of such taxes to the ADR holders entitled thereto.

By holding an ADR or an interest therein, you will be agreeing to indemnify us, the depositary, its custodian and any of our or their respective officers, directors, employees, agents and affiliates against, and hold each of them harmless from, any claims by any governmental authority with respect to taxes, additions to tax, penalties or interest arising out of any refund of taxes, reduced rate of withholding at source or other tax benefit obtained.

Reclassifications, Recapitalizations and Mergers

If we take certain actions that affect the deposited securities, including (i) any change in nominal value, split-up, consolidation, cancellation or other reclassification of deposited securities or (ii) any distributions of ordinary shares or other property not made to holders of ADRs or (iii) any recapitalization, reorganization, merger, consolidation, liquidation, receivership, bankruptcy or sale of all or substantially all of our assets, then the depositary may choose to, and shall if reasonably requested by us:

(1) amend the form of ADR;

(2) distribute additional or amended ADRs;

(3) distribute cash, securities or other property it has received in connection with such actions;

(4) sell any securities or property received and distribute the proceeds as cash; or

(5) none of the above.

If the depositary does not choose any of the above options, any of the cash, securities or other property it receives will constitute part of the deposited securities and each ADS will then represent a proportionate interest in such property.

Amendment and Termination

How may the deposit agreement be amended?

We may agree with the depositary to amend the deposit agreement and the ADSs without your consent for any reason. ADR holders must be given at least 30 days' notice of any amendment that imposes or increases any fees or charges (other than stock transfer or other taxes and other governmental charges, transfer or registration fees, SWIFT, cable, telex or facsimile transmission costs, delivery costs or other such expenses), or otherwise prejudices any substantial existing right of ADR holders. Such notice need not describe in detail the specific amendments effectuated thereby, but must identify to ADR holders a means to access the text of such amendment. If an ADR holder continues to hold an ADR or ADRs after being so notified, such ADR holder is deemed to agree to such amendment and to be bound by the deposit agreement as so amended. Any amendments or supplements which (i) are reasonably necessary (as agreed by us and the depositary) in order for (a) the ADSs to be registered on Form F-6 under the Securities Act or (b) the ADSs or ordinary shares to be traded solely in electronic book-entry form and (ii) do not in either such case impose or increase any fees or charges to be borne by ADR holders, shall be deemed not to prejudice any substantial rights of ADR holders. Notwithstanding the foregoing, if any governmental body or regulatory body should adopt new laws, rules or regulations which would require amendment or supplement of the deposit agreement or the form of ADR to ensure compliance therewith, we and the depositary may amend or supplement the deposit agreement and the ADR at any time in accordance with such changed laws, rules or regulations, which amendment or supplement may take effect before a notice is given or within any other period of time as required for compliance. No amendment, however, will impair your right to surrender your ADSs and receive the underlying securities, except in order to comply with mandatory provisions of applicable law.

How may the deposit agreement be terminated?

The depositary may, and shall at our written direction, terminate the deposit agreement and the ADRs by mailing notice of such termination to the registered holders of ADRs at least 30 days prior to the date fixed in such notice for such termination; provided, however, if the depositary shall have (i) resigned as depositary under the deposit agreement, notice of such termination by the depositary shall not be provided to registered holders unless a successor depositary shall not be operating under the deposit agreement within 60 days of the date of such resignation, and (ii) been removed as depositary under the deposit agreement, notice of such termination by the depositary shall not be provided to registered holders of ADRs unless a successor depositary shall not be operating under the deposit

agreement on the 120th day after our notice of removal was first provided to the depositary. After termination, the depositary's only responsibility will be (i) to deliver deposited securities to ADR holders who surrender their ADRs, and (ii) to hold or sell distributions received on deposited securities. As soon as practicable after the expiration of six months from the termination date, the depositary will sell the deposited securities which remain and hold the net proceeds of such sales (as long as it may lawfully do so), without liability for interest, in trust for the ADR holders who have not yet surrendered their ADRs. After making such sale, the depositary shall have no obligations except to account for such proceeds and other cash.

Limitations on Obligations and Liability to ADR holders

Limits on our obligations and the obligations of the depositary; limits on liability to ADR holders and holders of ADSs

Prior to the issue, registration, registration of transfer, split-up, combination, or cancellation of any ADRs, or the delivery of any distribution in respect thereof, and from time to time in the case of the production of proofs as described below, we or the depositary or its custodian may require:

- payment with respect thereto of (i) any stock transfer or other tax or other governmental charge, (ii) any stock transfer or registration fees in effect for the registration of transfers of ordinary shares or other deposited securities upon any applicable register and (iii) any applicable fees and expenses described in the deposit agreement;
- the production of proof satisfactory to it of (i) the identity of any signatory and genuineness of any signature and (ii) such other information, including without limitation, information as to citizenship, residence, exchange control approval, beneficial ownership of any securities, compliance with applicable law, regulations, provisions of or governing deposited securities and terms of the deposit agreement and the ADRs, as it may deem necessary or proper; and
- compliance with such regulations as the depositary may establish consistent with the deposit agreement.

The issuance of ADRs, the acceptance of deposits of ordinary shares, the registration, registration of transfer, split-up or combination of ADRs or the withdrawal of ordinary shares, may be suspended, generally or in particular instances, when the ADR register or any register for deposited securities is closed or when any such action is deemed advisable by the depositary; provided that the ability to withdraw ordinary shares may only be limited under the following circumstances: (i) temporary delays caused by closing transfer books of the depositary or our transfer books or the deposit of ordinary shares in connection with voting at a shareholders meeting, or the payment of dividends, (ii) the payment of fees, taxes, and similar charges, and (iii) compliance with any laws or governmental regulations relating to ADRs or to the withdrawal of deposited securities.

The deposit agreement expressly limits the obligations and liability of the depositary, ourselves and each of our and the depositary's respective agents, provided, however, that no disclaimer of liability under the Securities Act or the Exchange Act, to the extent applicable, is intended by any provision of the deposit agreement. In the deposit agreement it provides that neither we nor the depositary nor any such agent will be liable to registered holders or beneficial owners of ADSs if:

- any present or future law, rule, regulation, fiat, order or decree of the United States, England and Wales or any other country or jurisdiction, or of any governmental or regulatory authority or securities exchange or market or automated quotation system, the provisions of or governing any deposited securities, any present or future provision of our charter, any act of God, war, terrorism, nationalization, expropriation, currency restrictions, work stoppage, strike, civil unrest, revolutions, rebellions, explosions, computer failure or circumstance beyond our, the depositary's or our respective agents' direct and immediate control shall prevent or delay, or shall cause any of them to be subject to any civil or criminal penalty in connection with, any act which the deposit agreement or the ADRs provide shall be done or performed by us, the depositary or our respective agents (including, without limitation, voting);
- it exercises or fails to exercise discretion under the deposit agreement or the ADRs including, without limitation, any failure to determine that any distribution or action may be lawful or reasonably practicable;

- it performs its obligations under the deposit agreement and ADRs without gross negligence or willful misconduct; or
- it takes any action or refrains from taking any action in reliance upon the advice of or information from legal counsel, accountants, any person presenting ordinary shares for deposit, any registered holder of ADRs, or any other person believed by it to be competent to give such advice or information.

We, the depositary and its agents may rely and shall be protected in acting upon any written notice, request, direction, instruction or document believed by them to be genuine and to have been signed, presented or given by the proper party or parties.

Neither the depositary nor its agents have any obligation to appear in, prosecute or defend any action, suit or other proceeding in respect of any deposited securities or the ADRs. We and our agents shall only be obligated to appear in, prosecute or defend any action, suit or other proceeding in respect of any deposited securities or the ADRs, which in our opinion may involve us in expense or liability, if indemnity satisfactory to us against all expense (including fees and disbursements of counsel) and liability is furnished as often as may be required. The depositary and its agents may fully respond to any and all demands or requests for information maintained by or on its behalf in connection with the deposit agreement, any registered holder or holders of ADRs, any ADRs or otherwise related to the deposit agreement or ADRs to the extent such information is requested or required by or pursuant to any lawful authority, including without limitation laws, rules, regulations, administrative or judicial process, banking, securities or other regulators. The depositary shall not be liable for the acts or omissions made by, or the insolvency of, any securities depository, clearing agency or settlement system. Furthermore, the depositary shall not be responsible for, and shall incur no liability in connection with or arising from, the insolvency of any custodian that is not a branch or affiliate of JPMorgan Chase Bank, N.A. Notwithstanding anything to the contrary contained in the deposit agreement or any ADRs, the depositary shall not be responsible for, and shall incur no liability in connection with or arising from, any act or omission to act on the part of the custodian except to the extent that any registered holder of ADRs has incurred liability directly as a result of the custodian having (i) committed fraud or willful misconduct in the provision of custodial services to the depositary or (ii) failed to use reasonable care in the provision of custodial services to the depositary as determined in accordance with the standards prevailing in the jurisdiction in which the custodian is located. The depositary shall not have any liability for the price received in connection with any sale of securities, the timing thereof or any delay in action or omission to act nor shall it be responsible for any error or delay in action, omission to act, default or negligence on the part of the party so retained in connection with any such sale or proposed sale.

The depositary has no obligation to inform ADR holders or other holders of an interest in any ADSs about the requirements of the law of England and Wales, rules or regulations or any changes therein or thereto.

Neither the depositary nor its agents will be responsible for any failure to carry out any instructions to vote any of the deposited securities, for the manner in which any such vote is cast or for the effect of any such vote. The depositary may rely upon instructions from us or our counsel in respect of any approval or license required for any currency conversion, transfer or distribution. The depositary shall not incur any liability for the content of any information submitted to it by us or on our behalf for distribution to ADR holders or for any inaccuracy of any translation thereof, for any investment risk associated with acquiring an interest in the deposited securities, for the validity or worth of the deposited securities, for the credit-worthiness of any third party, for allowing any rights to lapse upon the terms of the deposit agreement or for the failure or timeliness of any notice from us. The depositary shall not be liable for any acts or omissions made by a successor depositary whether in connection with a previous act or omission of the depositary or in connection with any matter arising wholly after the removal or resignation of the depositary. Neither the depositary nor any of its agents shall be liable to registered holders or beneficial owners of interests in ADSs for any indirect, special, punitive or consequential damages (including, without limitation, legal fees and expenses) or lost profits, in each case of any form incurred by any person or entity, whether or not foreseeable and regardless of the type of action in which such a claim may be brought.

In the deposit agreement each party thereto (including, for avoidance of doubt, each holder and beneficial owner and/or holder of interests in ADRs) irrevocably waives, to the fullest extent permitted by applicable law, any right it may have to a trial by jury in any suit, action or proceeding against the depositary and/or us directly or indirectly arising out of or relating to the ordinary shares or other deposited securities, the ADSs or the ADRs, the deposit agreement or any transaction contemplated therein, or the breach thereof (whether based on contract, tort, common law or any other theory).

The depositary and its agents may own and deal in any class of securities of our company and our affiliates and in ADSs.

Disclosure of Interest in ADSs

To the extent that the provisions of or governing any deposited securities may require disclosure of or impose limits on beneficial or other ownership of deposited securities, other ordinary shares and other securities and may provide for blocking transfer, voting or other rights to enforce such disclosure or limits, you agree to comply with all such disclosure requirements and ownership limitations and to comply with any reasonable instructions we may provide in respect thereof. We reserve the right to instruct you to deliver your ADSs for cancellation and withdrawal of the deposited securities so as to permit us to deal with you directly as a holder of ordinary shares and, by holding an ADS or an interest therein, you will be agreeing to comply with such instructions.

Books of Depositary

The depositary or its agent will maintain a register for the registration, registration of transfer, combination and split-up of ADRs, which register shall include the depositary's direct registration system. Registered holders of ADRs may inspect such records at the depositary's office at all reasonable times, but solely for the purpose of communicating with other holders in the interest of the business of our company or a matter relating to the deposit agreement. Such register may be closed at any time or from time to time, when deemed expedient by the depositary.

The depositary will maintain facilities for the delivery and receipt of ADRs.

Appointment

In the deposit agreement, each registered holder of ADRs and each person holding an interest in ADSs, upon acceptance of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the deposit agreement will be deemed for all purposes to:

- be a party to and bound by the terms of the deposit agreement and the applicable ADR or ADRs; and
- appoint the depositary its attorney-in-fact, with full power to delegate, to act on its behalf and to take any and all actions contemplated in the deposit agreement and the applicable ADR or ADRs, to adopt any and all procedures necessary to comply with applicable laws and to take such action as the depositary in its sole discretion may deem necessary or appropriate to carry out the purposes of the deposit agreement and the applicable ADR and ADRs, the taking of such actions to be the conclusive determinant of the necessity and appropriateness thereof.

Governing Law

The deposit agreement and the ADRs shall be governed by and construed in accordance with the laws of the State of New York. In the deposit agreement, we have submitted to the jurisdiction of the courts of the State of New York and appointed an agent for service of process on our behalf. Notwithstanding the foregoing, any action based on the deposit agreement or the transactions contemplated thereby may be instituted by the depositary in any competent court in England and Wales.

By holding an ADS or an interest therein, registered holders of ADRs and owners of ADSs each irrevocably agree that any legal suit, action or proceeding against or involving us or the depositary, arising out of or based upon the deposit agreement, the ADSs or the transactions contemplated thereby, may only be instituted in a state or federal court in New York, New York, and each irrevocably waives any objection which it may have to the laying of venue of any such proceeding, and irrevocably submits to the exclusive jurisdiction of such courts in any such suit, action or proceeding.

Material U.S. Federal Income Tax Considerations for U.S. Holders

The following discussion describes certain material U.S. federal income tax consequences relating to the ownership and disposition of our ADSs by U.S. Holders. This discussion applies to U.S. Holders that purchase our ADSs pursuant to this offering and hold such ADSs as capital assets for tax purposes. This discussion is based on the Internal Revenue Code, U.S. Treasury regulations promulgated thereunder and administrative and judicial interpretations thereof, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as in effect on the date hereof and all of which are subject to change, possibly with retroactive effect. This discussion does not address all of the U.S. federal income tax consequences that may be relevant to specific U.S. Holders in light of their particular circumstances or to U.S. Holders subject to special treatment under U.S. federal income tax law (such as certain financial institutions, insurance companies, dealers or traders in securities or other persons that generally mark their securities to market for U.S. federal income tax purposes, tax-exempt entities or governmental organizations, retirement plans, regulated investment companies, real estate investment trusts, grantor trusts, brokers, dealers or traders in securities, commodities, currencies or notional principal contracts, certain former citizens or long-term residents of the United States, persons who hold our ADSs as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment, persons that have a "functional currency" other than the U.S. dollar, persons who are subject to the tax accounting rules of Section 451(b) of the Internal Revenue Code, persons that own directly, indirectly or through attribution 10% or more (by vote or value) of our equity, corporations that accumulate earnings to avoid U.S. federal income tax, partnerships and other pass-through entities, and investors in such pass-through entities). This discussion does not address any U.S. state or local or non-U.S. tax consequences or any U.S. federal estate, gift or alternative minimum tax consequences.

As used in this discussion, the term "U.S. Holder" means a beneficial owner of our ADSs that is, for U.S. federal income tax purposes, (1) an individual who is a citizen or resident of the United States, (2) a corporation (or entity treated as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States, any state thereof, or the District of Columbia, (3) an estate the income of which is subject to U.S. federal income tax regardless of its source or (4) a trust (x) with respect to which a court within the United States is able to exercise primary supervision over its administration and one or more United States persons have the authority to control all of its substantial decisions or (y) that has elected under applicable U.S. Treasury regulations to be treated as a domestic trust for U.S. federal income tax purposes.

If an entity treated as a partnership for U.S. federal income tax purposes holds our ADSs, the U.S. federal income tax consequences relating to an investment in such ADSs will depend upon the status and activities of such entity and the particular partner. Any such entity and a partner in any such entity should consult its own tax advisor regarding the U.S. federal income tax consequences applicable to it (and, as applicable, its partners) of the purchase, ownership and disposition of our ADSs.

We have not sought, nor will we seek, a ruling from the IRS with respect to the matters discussed below. There can be no assurance that the IRS will not take a different position concerning the tax consequences of the purchase, ownership or disposition of the ADSs or that any such position would not be sustained. Persons considering an investment in our ADSs should consult their own tax advisors as to the particular tax consequences applicable to them relating to the purchase, ownership and disposition of our ADSs, including the applicability of U.S. federal, state and local tax laws and non-U.S. tax laws.

Passive Foreign Investment Company Rules

In general, a corporation organized outside the United States will be treated as a PFIC for any taxable year in which either (1) at least 75% of its gross income is "passive income," or the PFIC income test, or (2) on average at least 50% of its assets, determined on a quarterly basis, are assets that produce passive income or are held for the production of passive income, or the PFIC asset test. Passive income for this purpose generally includes, among other things, dividends, interest, royalties, rents, and gains from the sale or exchange of property that give rise to passive income. Assets that produce or are held for the production of passive income generally include cash, even if held as working capital or raised in a public offering, marketable securities, and other assets that may produce passive income. Generally, in determining whether a non-U.S. corporation is a PFIC, a proportionate share of the income and assets of each corporation in which it owns, directly or indirectly, at least a 25% interest (by value) is taken into account.

Although PFIC status is determined on an annual basis and generally cannot be determined until the end of the taxable year, based on the nature of our current and expected income and the current and expected value and composition of our assets, we believe we were a PFIC for our 2018 tax year and we expect to be a PFIC for our current taxable year. There can be no assurance that we will not be a PFIC in future taxable years. Even if we determine that we are not a PFIC for a taxable year, there can be no assurance that the IRS will agree with our conclusion and that the IRS would not successfully challenge our position. Because of the uncertainties involved in establishing our PFIC status, our U.S. counsel expresses no opinion regarding our PFIC status, and also expresses no opinion with respect to our predictions or past determinations regarding our PFIC status.

If we are a PFIC in any taxable year during which a U.S. Holder owns our ADSs, the U.S. Holder could be liable for additional taxes and interest charges under the "PFIC excess distribution regime" upon (1) a distribution paid during a taxable year that is greater than 125% of the average annual distributions paid in the three preceding taxable years, or, if shorter, the U.S. Holder's holding period for our ADSs, and (2) any gain recognized on a sale, exchange or other disposition, including, under certain circumstances, a pledge, of our ADSs, whether or not we continue to be a PFIC in the year in which such U.S. Holder disposes of or is deemed to dispose of its ADSs. Under the PFIC excess distribution regime, the tax on such distribution or gain would be determined by allocating the distribution or gain ratably over the U.S. Holder's holding period for our ADSs. The amount allocated to the current taxable year (*i.e.*, the year in which the distribution occurs or the gain is recognized) and any year prior to the first taxable year in which we are a PFIC will be taxed as ordinary income earned in the current taxable year. The amount allocated to other taxable years will be taxed at the highest marginal rates in effect for individuals or corporations, as applicable, to ordinary income for each such taxable year, and an interest charge, generally applicable to underpayments of tax, will be added to the tax.

If we are a PFIC for any year during which a U.S. Holder holds our ADSs, we must generally continue to be treated as a PFIC by that U.S. Holder for all succeeding years during which the U.S. Holder holds such ADSs, unless we cease to meet the requirements for PFIC status and the U.S. Holder makes a "deemed sale" election with respect to our ADSs. If the election is made, the U.S. Holder will be deemed to sell our ADSs it holds at their fair market value on the last day of the last taxable year in which we qualified as a PFIC, and any gain recognized from such deemed sale would be taxed under the PFIC excess distribution regime. After the deemed sale election, the U.S. Holder's ADSs would not be treated as shares of a PFIC unless we subsequently become a PFIC.

If we are a PFIC for any taxable year during which a U.S. Holder holds our ADSs and one of our non-United States subsidiaries is also a PFIC (*i.e.*, a lower-tier PFIC), such U.S. Holder would be treated as owning a proportionate amount (by value) of the shares of the lower-tier PFIC and would be taxed under the PFIC excess distribution regime on distributions by the lower-tier PFIC and on gain from the disposition of shares of the lower-tier PFIC even though such U.S. Holder would not receive the proceeds of those distributions or dispositions. Any of our non-United States subsidiaries that have elected to be disregarded as entities separate from us or as partnerships for U.S. federal income tax purposes would not be corporations under U.S. federal income tax law and accordingly, cannot be classified as lower-tier PFICs. However, a non-United States subsidiary that has not made the election may be classified as a lower-tier PFIC if we are a PFIC during your holding period and the subsidiary meets the PFIC income test or PFIC asset test.

If we are a PFIC, a U.S. Holder will not be subject to tax under the PFIC excess distribution regime on distributions or gain recognized on our ADSs if a valid "mark-to-market" election is made by the U.S. Holder for our ADSs. An electing U.S. Holder generally would take into account as ordinary income each year, the excess of the fair market value of our ADSs held at the end of such taxable year over the adjusted tax basis of such ADSs. The U.S. Holder would also take into account, as an ordinary loss each year, the excess of the adjusted tax basis of such ADSs over their fair market value at the end of the taxable year, but only to the extent of the excess of amounts previously included in income over ordinary losses deducted as a result of the mark-to-market election. The U.S. Holder's tax basis in our ADSs would be adjusted annually to reflect any income or loss recognized as a result of the mark-to-market election. Any gain from a sale, exchange or other disposition of our ADSs in any taxable year in which we are a PFIC would be treated as ordinary income and any loss from such sale, exchange or other disposition would be treated first as ordinary loss (to the extent of any net mark-to-market gains previously included in income) and thereafter as capital loss. If, after having been a PFIC for a taxable year, we cease to be classified as a PFIC because we no longer meet the PFIC income or PFIC asset test, the U.S. Holder would not be required to take into account any latent gain or loss in the manner described above and any gain or loss recognized on the sale or exchange of the ADSs would be classified as a capital gain or loss.

A mark-to-market election is available to a U.S. Holder only for "marketable stock." Generally, stock will be considered marketable stock if it is "regularly traded" on a "qualified exchange" within the meaning of applicable U.S. Treasury regulations. A class of stock is regularly traded during any calendar year during which such class of stock is traded, other than in de minimis quantities, on at least 15 days during each calendar quarter.

Our ADSs will be marketable stock as long as they remain listed on Nasdaq and are regularly traded. A mark-to-market election will not apply to the ADSs for any taxable year during which we are not a PFIC, but will remain in effect with respect to any subsequent taxable year in which we become a PFIC. Such election will not apply to any of our non-U.S. subsidiaries. Accordingly, a U.S. Holder may continue to be subject to tax under the PFIC excess distribution regime with respect to any lower-tier PFICs notwithstanding the U.S. Holder's mark-to-market election for our ADSs.

The tax consequences that would apply if we are a PFIC would also be different from those described above if a U.S. Holder were able to make a valid QEF election. As we do not expect to provide U.S. Holders with the information necessary for a U.S. Holder to make a QEF election, prospective investors should assume that a QEF election will not be available.

The U.S. federal income tax rules relating to PFICs are very complex. Prospective U.S. investors are strongly urged to consult their own tax advisors with respect to the impact of PFIC status on the purchase, ownership and disposition of our ADSs, the consequences to them of an investment in a PFIC, any elections available with respect to the ADSs and the IRS information reporting obligations with respect to the purchase, ownership and disposition of ADSs of a PFIC.

Distributions

Subject to the discussion above under "— Passive Foreign Investment Company Rules," a U.S. Holder that receives a distribution with respect to our ADSs generally will be required to include the gross amount of such distribution in gross income as a dividend when actually or constructively received by the U.S. Holder to the extent of the U.S. Holder's pro rata share of our current and/or accumulated earnings and profits (as determined under U.S. federal income tax principles). To the extent a distribution received by a U.S. Holder is not a dividend because it exceeds the U.S. Holder's pro rata share of our current and accumulated earnings and profits, it will be treated first as a tax-free return of capital and reduce (but not below zero) the adjusted tax basis of the U.S. Holder's ADSs. To the extent the distribution exceeds the adjusted tax basis of the U.S. Holder's ADSs, the remainder will be taxed as capital gain. Because we may not account for our earnings and profits in accordance with U.S. federal income tax principles, U.S. Holders should expect all distributions to be reported to them as dividends. The amount of a dividend will include any amounts withheld by the company in respect of United Kingdom taxes.

Distributions on our ADSs that are treated as dividends generally will constitute income from sources outside the United States for foreign tax credit purposes and generally will constitute passive category income. Subject to applicable limitations, some of which vary depending upon the U.S. Holder's particular circumstances, any United Kingdom income taxes withheld from dividends on ADSs at a rate not exceeding the rate provided by the Treaty will be creditable against the U.S. Holder's U.S. federal income tax liability. The rules governing foreign tax credits are complex and U.S. Holders should consult their tax advisers regarding the creditability of foreign taxes in their particular circumstances. In lieu of claiming a foreign tax credit, U.S. Holders may, at their election, deduct foreign taxes, including any United Kingdom income tax, in computing their taxable income, subject to generally applicable limitations under U.S. law. An election to deduct foreign taxes instead of claiming foreign tax credits applies to all foreign taxes paid or accrued in the taxable year. The amount of any dividend income paid in a currency other than the U.S. dollar will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual or constructive receipt, regardless of whether the payment is in fact converted into U.S. dollars at that time. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. holder should not be required to recognize foreign currency gain or loss in respect of the dividend amount. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt.

Distributions paid on our ADSs will not be eligible for the "dividends received" deduction generally allowed to corporate shareholders with respect to dividends received from U.S. corporations under the Internal Revenue Code. Dividends paid by a "qualified foreign corporation'' to non-corporate U.S. Holders are eligible for taxation at a reduced capital gains rate rather than the marginal tax rates generally applicable to ordinary income provided that a holding period requirement (more than 60 days of ownership, without protection from the risk of loss, during

the 121-day period beginning 60 days before the ex-dividend date) and certain other requirements are met. Each U.S. Holder is advised to consult its tax advisors regarding the availability of the reduced tax rate on dividends to its particular circumstances. However, if we are a PFIC for the taxable year in which the dividend is paid or the preceding taxable year (see discussion above under "— Passive Foreign Investment Company Rules''), we will not be treated as a qualified foreign corporation, and therefore the reduced capital gains tax rate described above will not apply.

A non-United States corporation (other than a corporation that is classified as a PFIC for the taxable year in which the dividend is paid or the preceding taxable year) generally will be considered to be a qualified foreign corporation with respect to any dividend it pays on ADSs that are readily tradable on an established securities market in the United States.

The amount of any dividend income that is paid in Pounds Sterling will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt (actual or constructive), a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt (actual or constructive).

Sale, Exchange or Other Taxable Disposition of Our ADSs

Subject to the discussion above under "— Passive Foreign Investment Company Rules," a U.S. Holder generally will recognize capital gain or loss for U.S. federal income tax purposes upon the sale, exchange or other disposition of our ADSs in an amount equal to the difference, if any, between the amount realized (*i.e*., the amount of cash plus the fair market value of any property received) on the sale, exchange or other disposition and such U.S. Holder's adjusted tax basis in the ADSs. Such capital gain or loss generally will be long-term capital gain taxable at a reduced rate for non-corporate U.S. Holders or long-term capital loss if, on the date of sale, exchange or other disposition, the ADSs were held by the U.S. Holder for more than one year. Any capital gain of a non-corporate U.S. Holder that is not long-term capital gain is taxed at ordinary income rates. The deductibility of capital losses is subject to limitations. Any gain or loss recognized from the sale or other disposition of our ADSs will generally be gain or loss from sources within the United States for U.S. foreign tax credit purposes.

Medicare Tax

Certain U.S. Holders that are individuals, estates or trusts and whose income exceeds certain thresholds generally are subject to a 3.8% tax on all or a portion of their net investment income, which may include their gross dividend income and net gains from the disposition of our ADSs. If you are a U.S. Holder that is an individual, estate or trust, you are encouraged to consult your tax advisors regarding the applicability of this Medicare tax to your income and gains in respect of your investment in our ADSs.

Information Reporting and Backup Withholding

U.S. Holders may be required to file certain U.S. information reporting returns with the IRS with respect to an investment in our ADSs, including, among others, IRS Form 8938 (Statement of Specified Foreign Financial Assets). In addition, each U.S. Holder who is a shareholder of a PFIC must file an annual report containing certain information. U.S. Holders paying more than $100,000 for our ADSs may be required to file IRS Form 926 (Return by a U.S. Transferor of Property to a Foreign Corporation) reporting this payment. Substantial penalties and other adverse circumstances may be imposed upon a U.S. Holder that fails to comply with the required information reporting.

Dividends on and proceeds from the sale or other disposition of our ADSs generally have to be reported to the IRS unless the U.S. Holder establishes a basis for exemption. Backup withholding may apply to amounts subject to reporting if the holder (1) fails to provide an accurate U.S. taxpayer identification number or otherwise establish a basis for exemption, or (2) is described in certain other categories of persons. However, U.S. Holders that are corporations generally are excluded from these information reporting and backup withholding tax rules.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules generally will be allowed as a refund or a credit against a U.S. Holder's U.S. federal income tax liability if the required information is furnished by the U.S. Holder on a timely basis to the IRS.

U.S. Holders should consult their own tax advisors regarding the backup withholding tax and information reporting rules.

EACH PROSPECTIVE INVESTOR IS URGED TO CONSULT ITS OWN TAX ADVISOR ABOUT THE TAX CONSEQUENCES TO IT OF AN INVESTMENT IN OUR ADSs IN LIGHT OF THE INVESTOR'S OWN CIRCUMSTANCES. IN ADDITION, SIGNIFICANT CHANGES IN U.S. FEDERAL INCOME TAX LAWS WERE RECENTLY ENACTED. PROSPECTIVE INVESTORS SHOULD ALSO CONSULT WITH THEIR TAX ADVISORS WITH RESPECT TO SUCH CHANGES IN U.S. TAX LAW AS WELL AS POTENTIAL CONFORMING CHANGES IN STATE TAX LAWS.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HM Revenue and Customs, or HMRC, published practice applying as at the date of this prospectus (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs . It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from U.K. taxation. It is written on the basis that the company does not (and will not) directly or indirectly derive 75% or more of its qualifying asset value form U.K. land, and that the company is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under "U.S. Federal Income Taxation."

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and, in the case of individuals, domiciled or deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment or fixed base in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (where the ADSs are not held through an Individual Savings Account or a Self-Invested Personal Pension) and who hold the ADSs as investments.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- market makers, intermediaries, brokers or dealers in securities;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis.

The decision of the First-tier Tribunal (Tax Chamber) in *HSBC Holdings plc and The Bank of New York Mellon Corporation v HMRC* (2012) cast some doubt on whether a holder of a depositary receipt is the beneficial owner of the underlying shares. However, based on published HMRC guidance we would expect that HMRC will regard a holder of ADSs as holding the beneficial interest in the underlying shares and therefore these paragraphs assume that a holder of ADSs is the beneficial owner of the underlying ordinary shares and any dividends paid in respect of the underlying ordinary shares (where the dividends are regarded for U.K. purposes as that person's own income) for U.K. direct tax purposes.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN SPECIFIC CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax, irrespective of the residence or particular circumstances of the holders of ADSs.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a branch or agency to which the ADSs are attributable. There are certain exceptions for trading in the U.K. through independent agents, such as some brokers and investment managers.

All dividends received by an individual U.K. Holder from us or from other sources will form part of that U.K. Holder's total income for income tax purposes and will constitute the top slice of that income. A nil rate of income tax will apply to the first £2,000 of taxable dividend income received by the individual U.K. Holder in a tax year. Income within the nil-rate band will be taken into account in determining whether income in excess of the £2,000 tax-free allowance falls within the basic rate, higher rate or additional rate tax bands. Dividend income in excess of the tax-free allowance will (subject to the availability of any income tax personal allowance) be taxed at 7.5 per cent. to the extent that the excess amount falls within the basic rate tax band, 32.5 per cent. to the extent that the excess amount falls within the higher rate tax band and 38.1 per cent. to the extent that the excess amount falls within the additional rate tax band.

Corporation Tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate U.K. Holders should not be subject to U.K. corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, provided the dividends fall within an exempt class and certain conditions are met. If the conditions for the exemption are not satisfied, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19% reducing to 17% from April 1, 2020).

Chargeable Gains

A disposal or deemed disposal of ADSs by a U.K. Holder may, depending on the U.K. Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of U.K. capital gains tax and corporation tax on chargeable gains.

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the current applicable rate will be 20%. For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to capital gains tax on such disposal, the current applicable rate would be 10%, save to the extent that any capital gains when aggregated with the U.K. Holder's other taxable income and gains in the relevant tax year exceed the unused basic rate tax band. In that case, the rate currently applicable to the excess would be 20%.

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax (currently 19% reducing to 17% from April 1, 2020) would apply. Indexation allowance is not available in respect of disposals of ADSs acquired on or after January 1, 2018 (and only covers the movement in the retail prices index up until 31 December 2017, in respect of assets acquired prior to that date). A holder of ADSs which is not resident for tax purposes in the United Kingdom should not normally be liable to U.K. capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation in the United Kingdom through a branch or agency (or, in the case of a corporate holder of ADSs, through a permanent establishment) to which the ADSs are attributable. However, an individual holder of ADSs who is treated as resident outside the United Kingdom

for the purposes of a double tax treaty, or who has ceased to be resident for tax purposes in the United Kingdom for a period of less than five years and who disposes of ADSs during that period may be liable on his or her return to the United Kingdom to U.K. tax on any capital gain realized (subject to any available exemption or relief).

Stamp Duty and Stamp Duty Reserve Tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Shares

No U.K. stamp duty or stamp duty reserve tax, or SDRT, is payable on the issue of the underlying ordinary shares in the company.

Transfers of Shares

Neither U.K. stamp duty nor SDRT should arise on transfers of the underlying ordinary shares (including instruments transferring ordinary shares and agreements to transfer ordinary shares) on the basis that the ordinary shares are admitted to trading on AIM, provided the following requirements are (and continue to be) met:

- the ordinary shares are admitted to trading on AIM, but are not listed on any market (with the term "listed" being construed in accordance with section 99A of the Finance Act 1986), and this has been certified to Euroclear; and
- AIM continues to be accepted as a "recognized growth market" as construed in accordance with section 99A of the Finance Act 1986).

In the event that either of the above requirements is not met, stamp duty or SDRT will generally apply to transfers of, or agreements to transfer, ordinary shares. Where applicable, the purchaser normally pays the stamp duty or SDRT.

Issue and Transfers of ADSs

No U.K. stamp duty or SDRT is payable on the issue or transfer of (including an agreement to transfer) ADSs in the company.

UNDERWRITING

ThinkEquity, a division of Fordham Financial Management, Inc., is acting as the representative of the underwriters of this offering, or the Representative. We have entered into an underwriting agreement dated , 2019 with the Representative. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to each underwriter named below and each underwriter named below has severally and not jointly agreed to purchase from us, at the public offering price per share less the underwriting discounts set forth on the cover page of this prospectus, the number of ADSs listed next to its name in the following table:

Underwriter	Number of ADSs
ThinkEquity, a division of Fordham Financial Management, Inc.	
Total	

The underwriters are offering the ADSs subject to their acceptance of the ADSs from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the ADSs offered by this prospectus are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated, severally and not jointly, to take and pay for all of the ADSs offered by this prospectus if any such ADSs are taken, other than the ADSs covered by the underwriters' option to purchase additional ADSs described below. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may be increased or this offering may be terminated.

The underwriters initially propose to offer part of the ADSs directly to the public at the public offering price listed on the cover page of this prospectus and part of the ADSs to certain dealers at a price that represents a concession not in excess of $ per ADS from the initial public offering price. After the initial offering of the ADSs, this offering price and other selling terms may from time to time be varied by the underwriters.

Option to Purchase Additional ADSs

We have granted to the underwriters an option, exercisable for 45 days from the date of this prospectus, to purchase up to additional ADSs at the public offering price listed on the cover page of this prospectus, less underwriting discounts and commissions. The underwriters may exercise this over-allotment option solely for the purpose of covering over-allotments, if any, made in connection with this offering of the ADSs offered by this prospectus. To the extent the over-allotment option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional ADSs as the number listed next to the underwriter's name in the preceding table bears to the total number of ADSs listed next to the names of all underwriters in the preceding table.

Commissions and Expenses

The following table shows the per ADS and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' over-allotment option to purchase up to an additional ADSs:

	Per ADS	Total Without Over-allotment Option	Total With Over-allotment Option
Public offering price	$	$	$
Underwriting discounts and commissions (7.0%)	$	$	$
Non-accountable expense allowance (1.0%)[(1)]	$	$	$
Proceeds, before expenses, to us	$	$	$

(1) We have agreed to pay a non-accountable expense allowance to the underwriters equal to 1.0% of the gross proceeds received in this offering.

We have agreed to reimburse the Representative for all reasonable out-of-pocket accountable fees and costs incurred by the Representative in connection with this offering up to a maximum of $124,500 in the aggregate, consisting of: (a) the cost associated with the use of Ipreo's book-building prospectus tracking and compliance software

for this offering up to a maximum of $29,500; (b) the Representative's actual accountable road show expenses for this offering up to $20,000; and (c) the fees and expenses of the underwriters' legal counsel up to $75,000.

We estimate the expenses of this offering payable by us, not including underwriting discounts and commissions, will be approximately $354,500.

Representatives' Warrants

Upon closing of this offering, we have agreed to issue to the Representative as compensation warrants to purchase a number of ADSs equal to 2% of the aggregate number of ADSs sold in this offering (excluding the over-allotment option), or the Representative's Warrants. The Representative's Warrants will be exercisable at a per share exercise price equal to 125% of the public offering price per ADS sold in this offering. The Representative's Warrants are exercisable at any time and from time to time, in whole or in part, during the four and one-half year period commencing 180 days following the effective date of the registration statement related to this offering. We have registered the ordinary shares comprising the ADSs issuable upon the exercise of the Representative's Warrants in the registration statement of which this prospectus is a part.

The Representative's Warrants have been deemed compensation by FINRA and are therefore subject to a 180-day lock-up pursuant to Rule 5110(g)(1) of FINRA. The Representative (or permitted assignees under Rule 5110(g)(1)) will not sell, transfer, assign, pledge, or hypothecate these warrants or the securities underlying these warrants, nor will they engage in any hedging, short sale, derivative, put, or call transaction that would result in the effective economic disposition of the warrants or the underlying securities for a period of 180 days from the effective date of the registration statement. In addition, the warrants provide for registration rights upon request, in certain cases. The single demand registration right provided will not be greater than five years from the effective date of this offering in compliance with FINRA Rule 5110(f)(2)(G)(iv). The piggyback registration right provided will not be greater than seven years from the effective date of this offering in compliance with FINRA Rule 5110(f)(2)(G)(v). We will bear all fees and expenses attendant to registering the securities, including only one demand registration right granted by us to the Representative, issuable on exercise of the warrants other than underwriting commissions incurred and payable by the holders. The exercise price and number of securities issuable upon exercise of the warrants may be adjusted in certain circumstances including in the event of a stock dividend or our recapitalization, reorganization, merger or consolidation. However, the warrant exercise price or the underlying securities will not be adjusted for issuances of ADSs at a price below the warrant exercise price.

Right of First Refusal

Until six months from the closing date of this offering, the Representative will have, subject to certain exceptions, an irrevocable right of first refusal to act as sole investment banker, sole book-runner and/or sole placement agent, at the Representative's discretion, for each and every future U.S. public and private equity and debt offering, including all equity linked financings, during such six month period for us, or any successor to or any subsidiary of us, on terms customary for the Representative. The Representative will have the sole right to determine whether or not any other broker-dealer shall have the right to participate in any such offering and the economic terms of any such participation.

Lock-Up Agreements

Each of our directors and officers have agreed for a period of 180 days after the date of this prospectus, and we and certain of our stockholders have agreed for a period of at least 90 days after the date of this prospectus, without the prior written consent of the Representative, not to directly or indirectly (subject to limited exceptions):

- issue (in the case of us), offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of our capital stock, including, but not limited to our ADSs and ordinary shares, or any securities convertible into or exercisable or exchangeable for shares of our capital stock; or
- file or cause the filing of any registration statement under the Securities Act with respect to any shares of our capital stock, including, but not limited to our ADSs and ordinary shares, or any securities convertible into or exercisable or exchangeable for shares of our capital stock; or

- in the case of us, complete any offering of our debt securities, other than entering into a line of credit with a traditional bank; or
- enter into any swap or other agreement, arrangement, hedge or transaction that transfers to another, in whole or in part, directly or indirectly, any of the economic consequences of ownership of our ADSs or ordinary shares or other capital stock or any securities convertible into or exercisable or exchangeable for our ADSs, ordinary shares or other capital stock, whether any transaction described in any of the foregoing bullet points is to be settled by delivery of our ADSs, ordinary shares or other capital stock, other securities, in cash or otherwise, or publicly announce an intention to do any of the foregoing.

Price Stabilization, Short Positions and Penalty Bids

In connection with this offering, the underwriters may purchase and sell ADSs in the open market. These transactions may include short sales in accordance with Regulation M under the Exchange Act, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of ADSs than they are required to purchase in this offering. “Covered” short sales are sales made in an amount not greater than the underwriters’ option to purchase additional ADSs in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional ADSs or purchasing ADSs in the open market. In determining the source of ADSs to close out the covered short position, the underwriters will consider, among other things, the price of ADSs available for purchase in the open market as compared to the price at which they may purchase additional ADSs pursuant to the option granted to them. “Naked” short sales are any sales in excess of such option. The underwriters must close out any naked short position by purchasing ADSs in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the ADSs in the open market after pricing that could adversely affect investors who purchase in this offering. Stabilizing transactions consist of various bids for, or purchases of, ADSs made by the underwriters in the open market prior to the completion of this offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased ADSs sold by, or for the account of, such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the ADSs, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the ADSs. As a result, the price of the ADSs may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they are required to be conducted in accordance with applicable laws and regulations, and they may be discontinued at any time. These transactions may be effected on the Nasdaq, the over-the-counter market or otherwise.

Passive Market Making

In connection with this offering, the underwriters and selling group members may engage in passive market making transactions in our ADSs on the Nasdaq Global Market in accordance with Rule 103 of Regulation M under the Exchange Act, during a period before the commencement of offers or sales of the ADSs and extending through the completion of the distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker’s bid, that bid must then be lowered when specified purchase limits are exceeded.

Indemnification

We have agreed to indemnify the underwriters against liabilities relating to this offering arising under the Securities Act and the Exchange Act, liabilities arising from breaches of some or all of the representations and warranties contained in the underwriting agreement, and to contribute to payments that the underwriters may be required to make for these liabilities.

Discretionary Accounts

The underwriters do not intend to confirm sales of the securities offered hereby to any accounts over which they have discretionary authority.

Nasdaq and AIM Listings

Our ADSs are listed on the Nasdaq Global Market under the symbol "TLSA." Our ordinary shares are listed on the AIM market of the London Stock Exchange under the symbol "TILS."

Electronic Distribution

A prospectus in electronic format will be made available on the websites maintained by one or more of the underwriters or one or more securities dealers. One or more of the underwriters may distribute prospectuses electronically. The underwriters may agree to allocate a number of ADSs for sale to their online brokerage account holders. ADSs to be sold pursuant to an Internet distribution will be allocated on the same basis as other allocations. In addition, ADSs may be sold by the underwriters to securities dealers who resell ADSs to online brokerage account holders.

Other Relationships

From time to time, certain of the underwriters and/or their affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees. In the course of their businesses, the underwriters and their affiliates may actively trade our securities or loans for their own account or for the accounts of customers, and, accordingly, the underwriters and their affiliates may at any time hold long or short positions in such securities or loans.

Selling Restrictions

No action has been taken in any jurisdiction (except in the United States) that would permit a public offering of our ADSs, or the possession, circulation or distribution of this prospectus supplement, the accompanying prospectus or any other material relating to us or our ADSs in any jurisdiction where action for that purpose is required. Accordingly, our ADSs may not be offered or sold, directly or indirectly, and none of this prospectus or any other offering material or advertisements in connection with our ADSs may be distributed or published, in or from any country or jurisdiction, except in compliance with any applicable rules and regulations of any such country or jurisdiction.

For the avoidance of doubt, such prospectus will not constitute a "prospectus" for the purposes of Regulation (EU) 2017/1129, or Prospectus Regulation, and will not have been reviewed by any competent authority in any member state of the European Economic Area, or EEA Member State.

European Economic Area

In relation to each EEA Member State, an offer to the public of any ADSs which are the subject of this offering contemplated by this document may not be made in that EEA Member State except that an offer to the public in that EEA Member State of any ADSs may be made at any time under the following exemptions under the Prospectus Regulation:

- to any legal entity which is a "qualified investor" as defined in the Prospectus Regulation;
- to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Regulation), as permitted under the Prospectus Regulation, subject to obtaining the prior consent of the underwriters or the underwriters nominated by us for any such offer; or
- in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of ADSs or ordinary shares shall require us or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

Each person located in an EEA Member State to whom any offer of ADSs is made or who receives any communication in respect of an offer of ADSs, or who initially acquires any ADSs will be deemed to have represented, warranted, acknowledged and agreed to and with the underwriter and us that (1) it is a "qualified investor" as defined in the Prospectus Regulation; and (2) in the case of any ADSs acquired by it as a financial intermediary as that term is used in the Prospectus Regulation, the ADSs acquired by it in the offer have not been acquired on behalf of, nor

have they been acquired with a view to their offer or resale to, persons in any EEA Member State other than qualified investors, as that term is defined in the Prospectus Regulation, or in circumstances in which the prior consent of the underwriters or the underwriters nominated by us has been given to the offer or resale; or where ADSs have been acquired by it on behalf of persons in any EEA Member State other than qualified investors, the offer of those ADSs to it is not treated under the Prospectus Regulation as having been made to such persons.

The company, the underwriter and their respective affiliates will rely upon the truth and accuracy of the foregoing representations, warranties, acknowledgments and agreements.

This document has been prepared on the basis that any offer of ADSs in any EEA Member State will be made pursuant to an exemption under the Prospectus Regulation from the requirement to publish a prospectus for offers of securities. Accordingly any person making or intending to make an offer in that EEA Member State of ADSs which are the subject of this offering may only do so in circumstances in which no obligation arises for us or the underwriter to publish a prospectus pursuant to Article 23 of the Prospectus Regulation in relation to such offer. Neither we nor the underwriter have authorized or will authorize the making of any offer of ADSs in circumstances in which an obligation arises for the company or the underwriter to publish a prospectus for such offering.

For the purposes of this provision, the expression an "offer to the public" in relation to any offer of ADSs in any EEA Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any ADSs to be offered so as to enable an investor to decide to purchase or subscribe for the ADSs and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

Information to Distributors

Solely for the purposes of the product governance requirements contained within: (a) EU Directive 2014/65/EU on markets in financial instruments, as amended, or MiFID II; (b) Articles 9 and 10 of Commission Delegated Directive (EU) 2017/593 supplementing MiFID II; and (c) local implementing measures, (together, the "MiFID II Product Governance Requirements"), and disclaiming all and any liability, whether arising in tort, contract or otherwise, which any "manufacturer" (for the purposes of the MiFID II Product Governance Requirements) may otherwise have with respect thereto, the ADSs have been subject to a product approval process, which has determined that such securities are: (i) compatible with an end target market of retail investors and investors who meet the criteria of professional clients and eligible counterparties, each as defined in MiFID II; and (ii) eligible for distribution through all distribution channels as are permitted by MiFID II, or the Target Market Assessment. Notwithstanding the Target Market Assessment, distributors should note that: the price of the ADSs may decline and investors could lose all or part of their investment; the ADSs offer no guaranteed income and no capital protection; and an investment in the ADSs is compatible only with investors who do not need a guaranteed income or capital protection, who (either alone or in conjunction with an appropriate financial or other adviser) are capable of evaluating the merits and risks of such an investment and who have sufficient resources to be able to bear any losses that may result therefrom. The Target Market Assessment is without prejudice to the requirements of any contractual, legal or regulatory selling restrictions in relation to this offering.

For the avoidance of doubt, the Target Market Assessment does not constitute: (a) an assessment of suitability or appropriateness for the purposes of MiFID II; or (b) a recommendation to any investor or group of investors to invest in, or purchase, or take any other action whatsoever with respect to the ADSs.

Each distributor is responsible for undertaking its own target market assessment in respect of the ADSs and determining appropriate distribution channels.

United Kingdom

Each of the underwriters has represented and agreed that:

- it has not made or will not make an offer of the ADSs to the public in the United Kingdom within the meaning of section 102B of FSMA, except to legal entities which are authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities or otherwise in circumstances which do not require the publication by us of a prospectus pursuant to the Prospectus Rules of the U.K. Financial Conduct Authority;

- it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation;
- or inducement to engage in investment activity (within the meaning of section 21 of FSMA) to persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Regulation that also are (i) investment professionals falling within Article 19(5) of the FSMA (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the Order and other persons to whom it may lawfully be communicated (each such person being referred to as a "relevant person"); and
- it has complied with and will comply with all applicable provisions of FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

In the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at, relevant persons. This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents. Any investment or investment activity to which this prospectus relates is available only to relevant persons and will be engaged in only with relevant persons.

Canada

This offering of our ADSs in Canada is being made on a private placement basis in reliance on exemptions from the prospectus requirements under the securities laws of each applicable Canadian province and territory where our ADSs may be offered and sold, and therein may only be made with investors that are purchasing, or deemed to be purchasing, as principal and that qualify as both an "accredited investor" as such term is defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario) and as a "permitted client" as such term is defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations.* Any offer and sale of our ADSs in any province or territory of Canada may only be made through a dealer that is properly registered under the securities legislation of the applicable province or territory wherein our ADSs is offered and/or sold or, alternatively, where such registration is not required.

Any resale of our ADSs by an investor resident in Canada must be made in accordance with applicable Canadian securities laws, which require resales to be made in accordance with an exemption from, or in a transaction not subject to, prospectus requirements under applicable Canadian securities laws. These resale restrictions may under certain circumstances apply to resales of the ADSs outside of Canada.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* ("NI 33-105"), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Upon receipt of this prospectus, each Québec investor hereby confirms that it has expressly requested that all documents evidencing or relating in any way to the sale of the securities described herein (including for greater certainty any purchase confirmation or any notice) be drawn up in the English language only. *Par la réception de ce document, chaque investisseur québecois confirme par les présentes qu'il a expressément exigé que tous les documents faisant foi ou se rapportant de quelque manière que ce soit à la vente des valeurs mobilières décrites aux présentes (incluant, pour plus de certitude, toute confirmation d'achat ou tout avis) soient rédigés en anglais seulement*.

EXPENSES OF THIS OFFERING

We estimate that our expenses in connection with this offering, other than underwriting discounts and commissions, will be as follows:

	Amount
SEC registration fee	$ 427
FINRA filing fee	950
Printing and engraving expenses	25,000
Legal fees and expenses	225,000
Transfer agent and registrar fees and expenses	10,000
Accounting fees and expenses	20,000
Miscellaneous costs	73,123
Total	$ 354,500

All amounts in the table are estimates except the SEC registration fee and the FINRA filing fee. We will pay all of the expenses of this offering.

LEGAL MATTERS

The validity of our ordinary shares registered hereby and certain other matters of English law will be passed upon for us by Cooley (UK) LLP and certain matters of U.S. federal law will be passed upon for us by Sheppard, Mullin, Richter & Hampton LLP, New York, New York. Certain legal matters respect will be passed upon for the underwriters by Gracin & Marlow, LLP.

EXPERTS

The consolidated financial statements of Tiziana Pharma Limited as of December 31, 2017 and 2018, and for each of the years then ended, have been included herein and in the registration statement in reliance on the report of Mazars LLP, an independent registered public accounting firm, appearing elsewhere herein, and upon the authority of said firm as experts in accounting and auditing. The registered business address of Mazars LLP is Tower Bridge House, St Katharine's Way, London E1W 1DD.

SERVICE OF PROCESS AND ENFORCEMENT OF LIABILITIES

We are incorporated and currently existing under the laws of England and Wales. In addition, certain of our directors and officers reside outside the United States, and most of the assets of our non-U.S. subsidiaries are located outside the United States. As a result, it may be difficult for investors to effect service of process on us or those persons in the United States or to enforce in the United States judgments obtained in United States courts against us or those persons based on the civil liability or other provisions of the United States securities laws or other laws. In addition, uncertainty exists as to whether the courts of England and Wales would:

- Recognize or enforce judgments of United States courts obtained against us or our directors or officers predicated upon the civil liabilities provisions of the securities laws of the United States or any state in the United States; or
- entertain original actions brought in England and Wales against us or our directors or officers predicated upon the securities laws of the United States or any state in the United States.

We have been advised by Cooley (UK) LLP that there is currently no treaty between (i) the United States and (ii) England and Wales providing for reciprocal recognition and enforcement of judgments of United States courts in civil and commercial matters (although the United States and the United Kingdom are both parties to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards) and that a final judgment for the payment of money rendered by any general or state court in the United States based on civil liability, whether predicated solely upon the United States securities laws, would not be automatically enforceable in England and Wales. We have also been advised by Cooley (UK) LLP that any final and conclusive monetary judgment for a definite sum obtained against us in United States courts would be treated by the courts of England and Wales 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:

- the relevant U.S. court had jurisdiction over the original proceedings according to English conflicts of laws principles at the time when proceedings were initiated;
- England and Wales courts had jurisdiction over the matter on enforcement and we either submitted to such jurisdiction or were resident or carrying on business within such jurisdiction and were duly served with process;
- the U.S. judgment was final and conclusive on the merits in the sense of being final and unalterable in the court that pronounced it and being for a definite sum of money;
- the judgment given by the courts was not in respect of penalties, taxes, fines or similar fiscal or revenue obligations (or otherwise based on a U.S. law that an English court considers to relate to a penal, revenue or other public law);
- the judgment was not procured by fraud;
- recognition or enforcement of the judgment in England and Wales would not be contrary to public policy or the Human Rights Act 1998;
- the proceedings pursuant to which judgment was obtained were not contrary to natural justice;
- the U.S. judgment was not arrived at by doubling, trebling or otherwise multiplying a sum assessed as compensation for the loss or damages sustained and not being otherwise in breach of Section 5 of the U.K. Protection of Trading Interests Act 1980, or is a judgment based on measures designated by the Secretary of State under Section 1 of that Act;
- there is not a prior decision of an English court or the court of another jurisdiction on the issues in question between the same parties; and
- the English enforcement proceedings were commenced within the limitation period.

Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the United States 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.

Subject to the foregoing, investors may be able to enforce in England and Wales judgments in civil and commercial matters that have been obtained from U.S. federal or state courts. Nevertheless, we cannot assure you that those judgments will be recognized or enforceable in England and Wales.

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. In addition, it may not be possible to obtain an English judgment or to enforce that judgment if the judgment debtor is or becomes subject to any insolvency or similar proceedings, or if the judgment debtor has any set-off or counterclaim against the judgment creditor. Also note that, in any enforcement proceedings, the judgment debtor may raise any counterclaim that could have been brought if the action had been originally brought in England unless the subject of the counterclaim was in issue and denied in the U.S. proceedings.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We have filed with the SEC a registration statement (including amendments and exhibits to the registration statement) on Form F-1 under the Securities Act. This prospectus, which is part of the registration statement, does not contain all of the information in the registration statement and its exhibits. For further information with respect to us and the ADSs offered by this prospectus, we refer you to the registration statement and the exhibits and schedules to the registration statement. Statements contained in this prospectus as to the contents of any contract or any other document referred to are not necessarily complete, and in each instance, we refer you to the copy of the contract or other document filed as an exhibit to the registration statement. Each of these statements is qualified in all respects by the filed exhibits.

You may review a copy of the registration statement, including exhibits and any schedule filed therewith, and obtain copies of such materials at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet website (*www.sec.gov*) that contains reports, proxy and information statements and other information regarding issuers, like us, that file electronically with the SEC.

Upon completion of this offering, we will be subject to the information reporting requirements of the Exchange Act applicable to FPIs. Accordingly, we will be required to file reports and other information with the SEC, including annual reports on Form 20-F and reports on Form 6-K. Those reports may be inspected without charge at the locations described above. As an FPI, we will be exempt from the rules under the Exchange Act related to the furnishing and content of proxy statements, and our officers, directors and principal shareholders will be exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act. In addition, we will not be required under the Exchange Act to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. companies whose securities are registered under the Exchange Act.

We also maintain a website at *www.tizianalifesciences.com* contained in, or accessible through, our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS
TIZIANA LIFE SCIENCES PLC

The Board of Directors and Shareholders of Tiziana Life Sciences plc

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheet of Tiziana Life Sciences plc and its subsidiaries (the Group) as of December 31, 2018 and 2017, together with the related consolidated statements of operations and comprehensive loss, changes in shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Group as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 21, 2018, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

Material uncertainty related to going concern

We draw attention to note 2 in the financial statements concerning the applicability of the going concern basis of preparation. The Group is pre revenue and its business model requires significant ongoing expenditure on research and development. In the period to December 31, 2018 the Group incurred losses after taxation of $7,994,000. At December 31, 2018 the Group had net assets of $519,000 and cash and cash equivalents of $5,304,000. In note 2 the directors explain that to date they have successfully raised funds to finance clinical trials, but that further funding will be required within the foreseeable future to continue their development programmes and to meet liabilities as they fall due. As the directors are confident that the Group will raise the additional funding they have prepared the consolidated financial statements on the going concern basis. However, until the Group secures sufficient investment to fund their clinical trials, and ongoing working capital requirements these events or conditions indicate that a material uncertainty exists that may cast a significant doubt about the Group's ability to continue as a going concern.

Our opinion is not modified in respect of this matter.

Basis for Opinion

These consolidated financial statements are the responsibility of the company's management. Our responsibility is to express an opinion on these 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 Group in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB. 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.

We conducted our audits 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. Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Mazars LLP

London, England

April 3, 2019

Consolidated Balance Sheets
(In thousands)

	Year ended December 31,	
	2018	**2017**
	$	$
ASSETS		
Current assets:		
Cash and cash equivalents	5,304	64
Prepayments and other receivables	1,609	2,384
Total current assets	6,913	2,448
Property and Equipment, net	7	23
Total non-current assets	7	23
Total assets	6,920	2,471
LIABILITIES AND SHAREHOLDERS' EQUITY		
Liabilities:		
Current liabilities:		
Accounts payable and accrued expenses	6,401	4,749
Total current liabilities	6,401	4,749
Total liabilities	6,401	4,749
Shareholders' Equity:		
Called up share capital	8,592	8,141
Share premium	40,862	31,284
Share based payment reserve – Options	3,854	3,213
Share based payment reserve – warrants	743	579
Convertible loan note reserve	—	—
Merger relief reserve	—	—
Other reserve	(46,171)	(46,171)
Translation reserve	1,977	1,997
Capital reduction reserve	41,292	41,292
Retained earnings	(50,630)	(42,613)
Total shareholders' equity	519	(2,278)
Total liabilities and shareholders' equity	6,920	2,471

The accompanying notes are an integral part of these consolidated financial statements.

Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except loss per share)

	Year ended December 31,		
	2018	**2017**	**2016**
	$	$	$
Revenue			
Cost of revenue	—	—	—
Gross Profit	—	—	—
Operating expenses:			
Research and Development	(5,510)	(6,015)	(4,007)
Operating Expenses	(4,417)	(4,601)	(5,872)
Total operating expenses	(9,927)	(10,616)	(9,879)
Loss from operations	(9,927)	(10,616)	(9,879)
Other income/(expense):			
Finance Income/(expense)	(12)	(12)	(12)
Loss from operations before income taxes	(9,939)	(10,628)	(9,891)
Income tax provision	1,945	1,912	121
Loss for the year	(7,994)	(8,716)	(9,770)
Other Comprehensive loss:			
Currency translation	(20)	70	650
Comprehensive loss	(8,014)	(8,646)	(9,120)
			Restated
Basic and diluted loss per share attributable to common shareholders	$ (0.06)	$ (0.09)	$ (0.11)

Consolidated Statements of Shareholders' Equity

(In thousands)

	Share Capital	Share Premium	Share Based Payment Reserve (Options)	Share Based Payment Reserve (warrants)	Convertible Loan Note Reserve	Merger Reserve	Other Reserve	Retained Earnings	Capital Redemption Reserve	Translation Reserve	Capital Reduction Reserve	Total Equity
	$	$	$	$	$	$	$	$	$	$	$	$
Balance at 1 January 2016	**15,563**	**33,496**	**1,503**	**162**	**15,510**	**9,448**	**(46,171)**	**(19,091)**	**—**	**2,121**	**—**	**12,540**
Transactions with owners												
Issue of share capital	84	546	—	—	—	—	—	—	—	—	—	630
Share based payment (options)	—	—	1,144	—	—	—	—	—	—	—	—	1,144
Share based payment (warrants)	—	—	—	109	—	—	—	—	—	—	—	109
Convertible loan note – equity component	—	—	—	—	1,649	—	—	(851)	—	—	—	798
Cancellation of deferred shares	(8,744)	—	—	—	—	—	—	—	8,744	—	—	—
Capital Reduction	—	(25,099)	—	—	—	(9,448)	—	—	(8,744)	—	41,292	(1,999)
Prior Year Adjustment	—	—	—	—	—	—	—	(14)	—	—	—	(14)
Total transactions with owners	(8,660)	(24,553)	1,144	109	1,649	(9,448)	—	(865)	—	—	41,292	(669)
Comprehensive income												
Loss for the period	—	—	—	—	—	—	—	(9,770)	—	—	—	(9,770)
Translation	—	—	—	—	—	—	—	—	—	650	—	650
Total comprehensive income	—	—	—	—	—	—	—	(9,770)	—	650	—	(9,120)
Balance at 31 December 2016	**6,903**	**8,943**	**2,647**	**271**	**17,158**	**—**	**(46,171)**	**(29,726)**	**—**	**2,771**	**41,292**	**4,088**
Issue of share capital	84	1,464	—	—	—	—	—	—	—	—	—	1,548
Share based payment (options)	—	—	1,324	—	—	—	—	—	—	—	—	1,324
Share based payment (warrants)	—	—	—	308	—	—	—	—	—	—	—	308
Option forfeited in the year	—	—	(758)	—	—	—	—	—	—	—	—	(758)
Options cancelled in the year	—	—	—	—	—	—	—	(142)	—	—	—	(142)
Convertible loan note – equity component	—	—	—	—	419	—	—	(419)	—	—	—	—
Convertible loan note interest	—	—	—	—	3,610	—	—	(3,610)	—	—	—	—
Convertible Loan Note Conversion	1,154	20,877	—	—	(21,188)	—	—	—	—	(844)	—	—
Total transactions with owners	1,237	22,341	566	308	(17,158)	—	—	(4,171)	—	(844)	—	2,280
Comprehensive income												
Loss for the period	—	—	—	—	—	—	—	(8,716)	—	—	—	(8,716)
Translation	—	—	—	—	—	—	—	—	—	70	—	70
Total comprehensive income	—	—	—	—	—	—	—	(8,716)	—	70	—	(8,646)
Balance at 31 December 2017	**8,141**	**31,284**	**3,213**	**579**	**—**	**—**	**(46,171)**	**(42,613)**	**—**	**1,997**	**41,292**	**(2,278)**
Issue of share capital	**451**	**9,556**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**—**	**10,007**
Convertible loan note interest	1	22	—	—	—	—	—	(23)	—	—	—	**—**
Share based payment (options)	—	—	**641**	—	—	—	—	—	—	—	—	**641**
Share based payment (warrants)	—	—	—	**164**	—	—	—	—	—	—	—	**164**
Total transactions with owners	**452**	**9,578**	**641**	**164**	**—**	**—**	**—**	**(23)**	**—**	**—**	**—**	**10,812**

Consolidated Statements of Shareholders' Equity – (Continued)
(In thousands)

	Share Capital	Share Premium	Share Based Payment Reserve (Options)	Share Based Payment Reserve (warrants)	Convertible Loan Note Reserve	Merger Reserve	Other Reserve	Retained Earnings	Capital Redemption Reserve	Translation Reserve	Capital Reduction Reserve	Total Equity
	$	$	$	$	$	$	$	$	$	$	$	$
Comprehensive income	—	—	—	—	—	—	—	—	—	—	—	—
Loss for the period	—	—	—	—	—	—	—	**(7,994)**	—	—	—	**(7,994)**
Translation	—	—	—	—	—	—	—	—	—	**(20)**	—	**(20)**
Total comprehensive income	—	—	—	—	—	—	—	**(7,994)**	—	**(20)**	—	**(8,014)**
Balance at 31 December 2018	**8,592**	**40,862**	**3,854**	**743**	**—**	**—**	**(46,171)**	**(50,630)**	**—**	**1,977**	**41,292**	**519**

The capital reduction reserve includes reserves designated as realized profits available for distribution under section 830(2) of the Companies Act 2006 arising from the court approved capital reduction detailed in notes 16 and 21.

Consolidated Statements of Cash Flows
(In thousands)

	Year ended December 31,		
	2018	**2017**	**2016**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Loss from operations before income taxes	$ (9,939)	$ (10,628)	$ (9,891)
Adjustments to reconcile net loss to net cash used in operating activities:			
Convertible loan interest accrued	12	12	12
Convertible loan interest paid as equity	21	—	—
Shares issued in lieu of fees	55	—	—
Share based payment – options	672	539	1,257
Cancellation of options	—	(135)	—
Share based payment – warrants	171	294	121
Net (increase)/decrease in operating assets/other receivables	(180)	54	121
Net increase/(decrease) in operating liabilities /other liabilities	2,123	2,304	1,174
Depreciation	16	13	11
Loss on foreign exchange	(296)	45	214
Lease adjustment	3	(31)	55
Cash inflow from taxation	2,791	—	—
Net cash used in operating activities	(4,551)	(7,533)	(6,926)
CASH FLOWS FROM INVESTING ACTIVITIES			
PPE	—	(1)	(48)
Acquisition of other investments	—		(294)
Net cash used in investing activities	—	(1)	(342)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from issuance of ordinary shares	9,917	1,542	614
Proceeds from issuance of convertible loan notes	—	—	961
Proceeds from issuance of warrants	1,509	—	—
Fundraising cost	(1,385)	—	—
Net cash provided by financing activities	10,041	1,542	1,575
Net increase/(decrease) in cash and cash equivalents	5,490	(5,992)	(5,693)
Cash and cash equivalent, beginning of period	64	5,802	13,128
Exchange difference	(249)	254	(1,633)
Cash and cash equivalent, end of period	5,304	64	5,802

1. GENERAL INFORMATION

Tiziana Life Sciences PLC is a public limited company incorporated in the United Kingdom under the Companies Act and quoted on AIM, a market of the London Stock Exchange (AIM: TILS). The principal activities of the company and its subsidiaries (the Group) are that of a clinical stage biotechnology company focused on targeted drugs to treat diseases in oncology and immunology.

These financial statements are presented in thousands of dollars ($'000) which is the presentational currency of the company. The functional currency is Pounds sterling (£) indicative of the primary economic environment in which the company operates.

The ultimate parent of the group is Planwise Group Limited, incorporated in the British Virgin Islands. Gabriele Cerrone is the ultimate beneficial owner of the entire issued share capital of Planwise Group Limited.

2. ACCOUNTING POLICIES

The principal accounting policies applied in the preparation of these consolidated financial statements are set out below. These policies have been applied consistently to all the years presented unless otherwise stated.

Basis of preparation

The consolidated financial statements of the Group have been prepared in accordance with International Financial Reporting Standards (IFRS) as issued by the International Accounting Standards Board, IFRIC interpretations and the Companies Act 2006 as applicable to companies reporting under IFRS. These accounts have been prepared under the historical cost convention.

Going Concern

The Group incurred losses during the year and has net liabilities at the year end.

The Group is in the early stages of developing its business focusing on the discovery and development of novel molecules that treat human disease in oncology and immunology. The directors expect the company to incur further losses and to require significant capital expenditure in continuing to develop clinical stage development therapeutic candidates in both oncology and immunology. The Group has successfully funded clinical trials to date and is in the process of securing additional investment for purposes of continuing to fund their clinical trials moving forward.

The directors have prepared cash flow projections that include the costs associated with the continued clinical trials and additional investment to fund that operation. On the basis of those projections, the directors conclude that the company will be able to meet its liabilities as they fall due for the foreseeable future, and therefore that it is appropriate to prepare the financial statements under the going concern basis of preparation.

However, until and unless the company secures sufficient investment to fund their clinical trials, there is a material uncertainty about the company's ability to continue as a going concern, and therefore about the applicability of the going concern basis of preparation. The financial statements do not include the adjustments that would be required if the going concern basis of preparation was considered inappropriate.

Basis of consolidation

Subsidiary undertakings are all entities over which the Group exercises control. The Group has control when it can demonstrate all of the following: (a) power over the investee; (b) exposure, or rights, to variable returns from its involvement with the investee; and (c) the ability to use its power over the investee to affect the amount of the investor's return.

The existence and effect of both current voting rights and potential voting rights that are currently exercisable or convertible are considered when assessing whether control of an entity is exercised. Subsidiaries are consolidated from the date at which the Group obtains control and are de-consolidated from the date at which control ceases.

2. ACCOUNTING POLICIES (cont.)

Business combination

The consolidated position of the Group is as a result of the reverse acquisition of Alexander David Investments plc by Tiziana Pharma Ltd and the subsequent listing of the Company as Tiziana Life Sciences Plc on 24 April 2014. Tiziana Pharma Limited was incorporated on 4 November 2013 and prepared its first set of financial statements to 31 December 2014. Therefore, the parent and subsidiary had the same reporting date but Tiziana Pharma Limited had a long period of account. No adjustment was made in the consolidated financial statements for the difference in length of reporting period because the only transaction in Tiziana Pharma Limited at 31 December 2013 was the issue of ordinary share capital of £1.

Segment reporting

Operating segments are reported in a manner consistent with the internal reporting provided to the Board. The Board allocates resources to and assess the performance of the segments. The Board considers there to be only one operating segment being the research and development of biotechnological and pharmaceutical products.

Taxation

The tax expense for a period represents the total of current taxation and deferred taxation. The charges in respect of current taxation are based on the estimated taxable profit for the relevant year. Taxable profit for the year is based on the profit as shown in the income statement, as adjusted for items of income or expenditure which are not deductible or chargeable for tax purposes. The current tax liability for the year is calculated using tax rates which have either been enacted or substantively enacted at the relevant balance sheet date.

Foreign currency translation

Items included in the financial statements of each of the Group's entities are measured using the currency of the primary economic environment in which the entity operates (the functional currency). The consolidated financial statements are presented in US dollars, which is the Group's presentation currency.

Foreign currency transactions are translated into the functional currency using exchange rates prevailing at the dates of the transactions. Foreign exchange gains and losses resulting from the settlement of foreign currency transactions and from the translation at year-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recognized in the income statement.

The financial statements of overseas subsidiary undertakings are translated into US dollars on the following basis:

- Assets and liabilities at the rate of exchange ruling at the year-end date.
- Profit and loss account items at the average rate of exchange for the year.

Exchange differences arising from the translation of the net investment in foreign entities, borrowings and other currency instruments designated as hedges of such investments, are taken to equity (and recognized in the statement of comprehensive income) on consolidation.

License fees

Payments related to the acquisition of rights to a product or technology are capitalized as intangible assets if it is probable that future economic benefits from the asset will flow to the entity and the cost of the asset can be reliably measured.

2. ACCOUNTING POLICIES (cont.)

Payments made which provide the right to perform research are carefully evaluated to determine whether such payments are to fund research or acquire an asset. Where fees related to research and development projects are recognized as an expense in the income statement, due to the uncertainty in the length of time that the Group will hold them the expense is recognized fully at the point of recognition.

Research and development

All on-going research and development expenditure is currently expensed in the period in which it is incurred. Due to the regulatory environment inherent in the development of the Group's products, the criteria for development costs to be recognized as an asset, as set out in IAS 38 'Intangible Assets', are not met until a product has been granted regulatory approval and it is probable that future economic benefit will flow to the Group. The Group currently has no qualifying expenditure.

Financial instruments

Financial assets

The Group classifies a financial instrument, or its component parts, as a financial liability, a financial asset or an equity instrument in accordance with the substance of the contractual arrangement and the definitions of a financial liability, a financial asset and an equity instrument.

The Group evaluates the terms of the financial instrument to determine whether it contains an asset, a liability or an equity component. Such components shall be classified separately as financial assets, financial liabilities or equity instruments.

A financial instrument is any contract that gives rise to a financial asset of one entity and a financial liability or equity instrument of another entity.

(a) Financial assets, initial recognition and measurement and subsequent measurement

All financial assets not recorded at fair value through profit or loss, such as receivables and deposits, are recognized initially at fair value plus transaction costs. Financial assets carried at fair value through profit or loss are initially recognized at fair value, and transaction costs are expensed in the income statement. The measurement of financial assets depends on their classification. Financial assets such as receivables and deposits are subsequently measured at amortized cost using the effective interest method, less loss allowance. The Group does not hold any financial assets at fair value through profit or loss or fair value through other comprehensive income.

(b) Financial liabilities, initial recognition and measurement and subsequent measurement

Financial liabilities are classified as measured at amortized cost or FVTPL.

A financial liability is classified as at FVTPL if it is a derivative. Financial liabilities at FVTPL are measured at fair value and net gains and losses, including any interest expense, are recognized in profit or loss. Other financial liabilities are subsequently measured at amortized cost using the effective interest method. Interest expense and foreign exchange gains and losses are recognized in profit or loss. Any gain or loss on derecognition is also recognized in profit or loss.

The Group's financial liabilities include trade and other payables.

Share capital

Ordinary shares of the company are classified as equity.

2. ACCOUNTING POLICIES (cont.)

Property, IT and equipment

(i) Recognition and measurement

Items of property, IT and equipment are measured at cost less accumulated depreciation and accumulated impairment losses. Costs include expenditures that are directly attributable to the acquisition of the asset. Purchased software that is integral to the functionality of the related equipment is capitalized as part of that equipment.

When parts of an item of property, IT and equipment have different useful lives, they are accounted for as separate items (major components) of property, IT and equipment.

Gains and losses on disposal of an item of property, IT and equipment are determined by comparing the proceeds from disposal with the carrying amount of property, IT and equipment, and are recognized in profit or loss. When revalued assets are sold, the amounts included in the revaluation reserve are transferred to retained earnings.

(ii) Depreciation

Depreciation is calculated on the depreciable amount, which is the cost of an asset, or other amount substituted for cost, less its residual value.

Depreciation is recognized in profit or loss on a straight-line basis over the estimated useful life of each part of an item of property, IT and equipment. Leased assets are depreciated over the shorter of the lease term and their useful lives unless it is reasonably certain that the company will obtain ownership by the end of the lease term.

The estimated useful lives for the current period and the comparative period are as follows.

IT and equipment	**3 years**
Fixtures and fittings	**5 years**

Depreciation methods, useful lives and residual values are reviewed at each reporting date. Depreciation is allocated to the operating expenses line of the income statement.

Impairment

Impairment of financial assets measured at amortised cost

At each reporting date the Group recognises a loss allowance for expected credit losses on financial assets measured at amortised cost.

In establishing the appropriate amount of loss allowance to be recognised, the Group applies either the general approach or the simplified approach, depending on the nature of the underlying group of financial assets.

General approach

The general approach is applied to the impairment assessment of refundable lease deposits and other refundable lease contributions, restricted cash and cash and cash equivalents.

Under the general approach the Group recognises a loss allowance for a financial asset at an amount equal to the 12-month expected credit losses, unless the credit risk on the financial asset has increased significantly since initial recognition, in which case a loss allowance is recognised at an amount equal to the lifetime expected credit losses.

Simplified approach

The simplified approach is applied to the impairment assessment of trade receivables.

2. ACCOUNTING POLICIES (cont.)

Under the simplified approach the Group always recognises a loss allowance for a financial asset at an amount equal to the lifetime expected credit losses.

Non-financial assets are tested for impairment whenever events or changes in circumstances indicate that the carrying amount may not be recoverable.

Non-financial assets are impaired when its carrying amount exceed its recoverable amount. The recoverable amount is measured as the higher of fair value less cost of disposal and value in use. The value in use is calculated as being net projected cash flows based on financial forecasts discounted back to present value.

Operating leases

Payments made under operating leases are recognized in profit and loss on a straight-line basis over the term of the lease. Lease incentives received are recognized as an integral part of the total lease expense, over the term of the lease.

Share based payments

The calculation of the fair value of equity-settled share based awards and the resulting charge to the statement of comprehensive income requires assumptions to be made regarding future events and market conditions. These assumptions include the future volatility of the company's share price. These assumptions are then applied to a recognized valuation model in order to calculate the fair value of the awards.

Where employees, directors or advisers are rewarded using share based payments, the fair value of the employees', directors' or advisers' services are determined by reference to the fair value of the share options / warrants awarded. Their value is appraised at the date of grant and excludes the impact of any nonmarket vesting conditions (for example, profitability and sales growth targets). Warrants issued in association with the issue of Convertible Loan Notes are also considered as share based payments and a share based payment charge is calculated for these too.

In accordance with IFRS 2, a charge is made to the Statement of Comprehensive Income for all share-based payments including share options based upon the fair value of the instrument used. A corresponding credit is made to a Share Based Payment Reserve, in the case of options/warrants awarded to employees, directors, advisers, and other consultants.

If vesting periods or other vesting conditions apply, the expense is allocated over the vesting period, based on the best available estimate of the number of share options / warrants expected to vest. Non market vesting conditions are included in assumptions about the number of options / warrants that are expected to become exercisable.

Estimates are subsequently revised, if there is any indication that the number of share options / warrants expected to vest differs from previous estimates. No adjustment is made to the expense or share issue cost recognized in prior periods if fewer share options ultimately are exercised than originally estimated. Exercise of share options / warrants, the proceeds received are allocated to share capital with any excess being recorded as share premium.

Where share options are cancelled, this is treated as an acceleration of the vesting period of the options. The amount that otherwise would have been recognized for services received over the remainder of the vesting period is recognized immediately within the Statement of Comprehensive Income.

All goods and services received in exchange for the grant of any share based payment are measured at their fair value.

2. ACCOUNTING POLICIES (cont.)

Convertible loan notes

Under IAS 32 the liability and equity components of convertible loan notes must be presented separately on the Statement of Financial Position. The Group has examined the terms of each issue of convertible loan notes and determined their accounting treatment accordingly. Convertible loan notes are treated differently depending upon a number of factors.

Where there is no option to repay as cash and the interest rate is fixed

The Group considers these to be Convertible Equity Instruments and records the principal of the loan note as an equity in a Convertible loan note reserve. The accrued interest on the principal amount, for which there is no obligation to settle in cash, is also recorded in the Convertible loan note reserve. Upon redemption of the instrument and the issue of share capital, the amount is reclassified from the convertible loan note reserve to share capital and share premium.

Where there is no option to repay as cash and the interest rate is variable

The Group considers these to be Convertible Debt Instruments and records the principal of the loan note as a debt liability in the liabilities section of the balance sheet. The accrued interest on the principal amount is recorded in the income statement and as an increase in the debt liability. Upon redemption of the instrument and the issue of share capital, the amount is reclassified from the debt liability to share capital and share premium.

3. CRITICAL ACCOUNTING ESTIMATES AND JUDGEMENTS

The preparation of financial information in accordance with generally accepted accounting practice, in the case of the Group being International Financial Reporting Standards as adopted by the European Union, requires the directors to make estimates and judgements that affect the reported amount of assets, liabilities, income and expenditure and the disclosures made in the financial statements. Such estimates and judgements must be continually evaluated based on historical experience and other factors, including expectations of future events.

When entering into agreements with third parties which provide the rights to conduct research into specific biological processes the group account for these agreements as an expense if the agreements are ‘milestone’ in nature and relate to the Group’s own research and development costs. Such agreements involve periodic payments and are evaluated as representing payments made to fund research.

The only other critical accounting estimates and judgements in the preparation of the financial statements were fair value estimates used in the calculation of share based payments and warrants which have been detailed above in note 2, accounting policies, and note 16, share based payments, to the accounts.

The Group has also made a judgement on the impact of Brexit during the preparation of the financial statements and considered it to not be significant.

4. OPERATING LOSS

The Group and Company’s operating loss are stated after charging the following:

	Year Ended December 31,		
	2018 $’000	**2017 $’000**	**2016 $’000**
License fee	**1,041**	**662**	**561**
Depreciation	**16**	**13**	**11**
Foreign exchange (gain)/losses	**(296)**	**45**	**215**
	761	**720**	**788**

5. SEGMENTAL REPORTING

During the year under review Management identified the Group's only operating segment as the research and development of biotechnological and pharmaceutical products. This one segment is monitored and strategic decisions are made based upon it and other non-financial data collated from industry intelligence. The form of financial reporting reported to the Board is consistent with those presented in the annual financial statements.

6. EMPLOYEES

	Year ended December 31,		
	2018	2017 $'000	2016 $'000
Group			
Staff costs comprised:			
Directors' salaries	201	211	214
Wages and salaries	1,669	1,107	786
Social security costs	596	491	38
Share based payment charge	671	539	1,015
	3,138	2,348	2,053
The average monthly number of employees, including directors, employed by the group during the year was:			
Research and Development	6	6	2
Corporate and administration	5	5	4
	11	11	6

7. REMUNERATION OF KEY MANAGEMENT PERSONNEL

	Year ended December 31,					
	2018		2017		2016	
$'000	Directors fees	Salary	Directors fees	Salary	Directors fees	Salary
W Simon	51		49		52	—
G. Cerrone	124		86		108	—
R. Dalla-Favera	26		26		27	—
K. Shailubhai[1]	—	300	10	286	27	—
	201	**300**	**171**	**286**	**214**	**—**

(1) Kunwar Shailubhai became an employee of the company on May 24, 2017, at which point he ceased to be a non-executive director.

The following share options were granted to directors in the following periods:

	Year ended December 31,		
	2018 Number of options	2017 Number of options	2016 Number of options
G. Cerrone	550,000	—	3,259,403
K. Shailubhai	6,500,000	400,000	—
L. Zanbeletti	550,000		
	7,600,000	**400,000**	**3,259,403**

7. REMUNERATION OF KEY MANAGEMENT PERSONNEL (cont.)

The key management personnel of the Group are considered to be represented by the directors and officers of the company.

No director has yet benefitted from any increase in the value of share capital since issuance of the options.

No director exercised share options in the year.

For the year ended December 31, 2017, the company made $17k (2017: $6k; 2016: $0k) of payments to defined contribution pension schemes on behalf of directors or employees.

8. FINANCE COSTS

	Year ended December 31,		
	2018 $'000	2017 $'000	2016 $'000
Group			
Finance charge accrued on convertible loan notes (recognized as debt)	12	12	12
	12	12	12

9. TAXATION

	Year Ended December 31,		
	2018 $'000	2017 $'000	2016 $'000
Group			
Current year tax (credit)	(1,067)	(489)	—
Adjustments due to prior periods	(879)	(1,423)	(121)
Total tax (credit) for the period	(1,945)	(1,912)	(121)
The tax charge for the year is different from the standard rate of corporation tax in the United Kingdom of 21.49%. The difference can be reconciled as follows:			
Loss before taxation	(9,939)	(10,628)	(9,770)
Loss charged at standard rate of corporation tax 19 % (2017: 19.25%; 2016: 20%)	(1,888)	(2,046)	(1,953)
Other timing differences	1,104	2,889	1,656
Expenses not deductible for taxation	176	31	297
Adjustments due to prior periods	(879)	(1,423)	(121)
Research and development claim	(459)	(1,366)	—
Other timing differences		3	—
	(1,945)	(1,912)	(121)

The Research and Development claim has been calculated in accordance with the R&D tax relief available to small and medium sized entities, whereby the entity is able to claim a cash tax credit (if loss making), worth up to 14.5% of the surrenderable losses.

The adjustments due to prior periods relates to R&D tax relief claims or the years ended December 31, 2017, 2016 and 2015. In prior periods there was not enough certainty to recognize an asset for these claims. Under UK tax legislation, a 2 year window is available under which R&D tax relief can be claimed.

9. TAXATION (cont.)

No deferred tax asset has been recognized in respect of trading losses carried forward because of uncertainty as to when these losses will be recoverable.

The amount of tax losses for which no deferred tax assets has been recognized for the year ended December 31, 2018 is $3,928 (2017; $4,738; 2016: $3,535).

10. LOSS PER SHARE

Basic loss per share is calculated by dividing the profit attributable to equity holders of the company by the weighted average number of ordinary shares in issue during the year.

	Year ended December 31,		
	2018	**2017**	**2016**
(Loss) attributable to equity holders of the company ($000)	(7,994)	(9,135)	(10,622)
Weighted average number of ordinary shares in issue	127,553,866	106,403,903	93,592,195
Basic loss per share (cents per share)	(6.27)	(8.59)	(11.35)

As the Group is reporting a loss from continuing operations for the year then, in accordance with IAS 33, the share options are not considered dilutive because the exercise of the share options would have an anti-dilutive effect. The basic and diluted earnings per share as presented on the face of the income statement are therefore identical. All earnings per share figures presented above arise from continuing and total operations and therefore no earnings per share for discontinued operations are presented.

The earnings have been amended to include the interest accrued on Convertible Loan Notes.

11. PROPERTY, IT AND EQUIPMENT

Details of the Groups property, IT and equipment are as follows:

$000	**Furniture and fixtures**	**IT equipment**	**Total**
Cost			
At 1 January 2017	15	30	45
Additions	—	1	1
Disposals	—	—	—
At 31 December 2017	15	31	46
Depreciation			
At 1 January 2017	1	9	10
Charge in year	2	11	13
At 31 December 2017	3	20	23
Net Book Value as at 31 December 2017	12	11	23

11. PROPERTY, IT AND EQUIPMENT (cont.)

$000	Furniture and fixtures	IT equipment	Total
Cost			
At 1 January 2018	15	31	46
Additions	—	—	—
Disposals	—	—	—
At 31 December 2018	15	31	46
Depreciation			
At 1 January 2018	3	20	23
Charge in year	6	10	16
At 31 December 2018	9	30	39
Net Book Value as at 31 December 2018	6	1	7

12. OTHER RECEIVABLES

	Year ended December 31,	
$000	2018	2017
Group		
Other receivables	246	110
Taxation receivable	1,019	1,944
Related party receivable	25	—
Prepayments	42	38
Other current assets	276	292
	1,609	2,384

There are no differences between the carrying amount and fair value of any of the trade and other receivables above.

13. OTHER ASSETS

In June 2016, the Board approved the purchase of the Data repository of DNA from SharDNA (an Italian entity in liquidation) for EUR 258,000, approximately $268,000.

Management recognizes that the transaction is not the purchase of a business but the purchase of key assets owned by SharDNA. These assets are to be owned by Tiziana Life Sciences PLC and will be loaned to its subsidiary Longevia SRL for no extra cost.

No research and development work has been carried out to this date, but Management anticipates that this will commence within the next 12 months.

As there is current legal action pending against the liquidators as to the validity to the sale of the assets, the company is unable to utilize these assets until the legal action is resolved. For this reason, the investment has been recognized as a current asset until such a time that the company is able to use this asset. In the event the company is unable to use the asset as a result of the legal action denoted above, the company will receive their money back.

14. INVESTMENTS IN SUBSIDIARIES

The company's interest in subsidiary undertakings is as follows:

Name	Principal activity	Registered Address	Percentage shareholding	Country of incorporation
Tiziana Pharma Limited	Clinical stage biotechnology company	3rd Floor, 11-12 St James's Square, London, SW1Y 4LB	100%	England & Wales
Tiziana Therapeutics, Inc.	Clinical stage biotechnology company	420 Lexington Avenue Suite 2525 New York, NY 10170	100%	USA
Longevia Genomics SRL	Biotech Discovery Company	Via Constantinpoli 42 09100-Cagliari (CA)	100%	Italy

Tiziana Therapeutics, Inc. was incorporated on 28 October 2015. This entity was set up to house the company's US operations.

Longevia Genomics SRL was incorporated on 4 July 2016. This entity was established to enable the company to carry out R&D activities in Sardinia.

15. SHARE CAPITAL

Company and Group

	2018	2017	2018	2017	2018	2017
	Ordinary Shares		Deferred Shares		£000	
In issue at 1 January	125,054,805	94,393,401	—	—	3,752	2,832
Issued for cash	7,742,167	1,301,250	—	—	232	66
Conversion of Convertible Loan notes	—	700,000	—	—	—	854
Conversion of warrants	1,454,644	—	—	—	45	—
Conversion of Loan	2,137,625				65	
In lieu of commission	74,577	—	—	—	—	—
In issue at 31 December	136,463,818	125,054,805	—	—	4,094	3,752

Ordinary Shares

Ordinary shares have a par value of £0.03. They entitle the holder to participate in dividends, and to share in the proceeds of winding up the company in proportion to the number of and amounts paid on the shares held. On a show of hands every holder of ordinary shares present at a meeting in person or by proxy, is entitled to one vote, and upon a poll each share is entitled to one vote. The company does not have a limited amount of authorized capital.

Issuance of ordinary shares

In March 2017, a notification was received from warrant holders to exercise warrants over 1,789,524 ordinary shares in the company.

In August 2017, the Board passed a resolution to convert all outstanding Convertible Loan Notes effective from 26 July 2017. It also resolved that the Convertible loan note holders be offered an additional bonus coupon of three years of interest at the relevant applicable rate of return for agreeing to the immediate conversion of the Convertible loan note's into ordinary shares. The company has issued 28,455,214 new ordinary shares in respect of this conversion. All of the new shares are subject to a restriction on disposal for a period of 12 months.

15. SHARE CAPITAL (cont.)

In November 2017, 283,333 new ordinary shares were issued by way of a further placing of ordinary shares to raise finance.

An additional 133,333 new ordinary shares were issued in December 17 by way of a further placing of ordinary shares to raise finance.

Share issues since 1 January 2018

In January 2018, 166,667 new ordinary shares were issued by way of a placing of ordinary shares to raise finance.

In March 2018, 600,000 new ordinary shares were issued by way of a further placing of ordinary shares to raise finance.

An additional 1,031,250 new ordinary shares were issued in April 2018 by way of a further placing of ordinary shares to raise finance. In addition, 51,563 new ordinary shares were issued to intermediaries in lieu of commissions on the funds raised.

Also in April 2018, 23,014 new ordinary shares were issued in relation to a shortfall in capitalized interest due to a former holder of the Company's Class C Convertible Loan Notes which was discovered during the annual audit process.

In October 2018, 1,515,150 new ordinary shares were issued by way of a further placing of ordinary shares to raise finance.

In November 2018, 4,429,100 new ordinary shares were issued as part of the initial public offering of American Depositary Shares on the Nasdaq Global Market. In addition to the IPO, 2,137,625 new ordinary shares were issued to extinguish £1.3 million in debt.

In November 2018, notification was also received from warrant holders to exercise warrants over 1,400,644 ordinary shares.

In conjunction with the IPO, the Company resolved to allow the holders of its warrants to exercise at reduced exercise prices in the period ending on 30 November 2018. Notification was also received from warrant holders to exercise warrants over 54,000 ordinary shares in connection with this offer.

16. SHARE BASED PAYMENTS

Group and Company Options

The company operates share-based payment arrangements to remunerate directors and key employees in the form of a share option scheme. The exercise price of the option is normally equal to the market price of an ordinary share in the company at the date of grant.

	2018		2017		2016	
	Weighted Average exercise price (cents)	Options ('000)	Weighted Average exercise price (cents)	Options ('000)	Weighted Average exercise price (cents)	Options ('000)
Outstanding at 1 January	125	10,717	90	12,449	35	7,985
Granted	104	9,500	216	668	190	4,464
Forfeited	(219)	(1,600)	(20)	(2,400)	—	—
Outstanding at 31 December	107	18,617	125	10,717	90	12,449
Exercisable at 31 December	50	5,236	57	5,011	41	4,152

16. SHARE BASED PAYMENTS (cont.)

No options were exercised during the years ended 31st December 2018, 2017 and 2016.

The total outstanding fair value of the share option instruments is deemed to be approximately $6,591 as at December 31, 2018 (2017: $6,217k; 2016: $2,305k).

The Directors have used the Black-Scholes option pricing model to estimate the fair value of most of the options applying the assumptions below.

Historical volatility relies in part on the historical volatility of a group of peer companies that management believes is generally comparable to the company.

The company has not paid any dividends on common stock since its inception and does not anticipate paying dividends on its common stock in the foreseeable future.

The company has estimated a forfeiture rate of zero.

	10 March 2017	30 August 2017	30 April 2018
Grant date share price	£1.725	£1.595	£0.8175
Exercise share price	£1.725	£1.595	£0.8175
Vesting periods	Yr1, Yr 2, Yr 3, Yr4	Yr 1, Yr 2, Yr 3, Yr4	Yr1, Yr 2, Yr 3, Yr4
Risk free rate	0.38% to 1.09%	0.69% to 1.09%	0.69% to 1.03%
Expected volatility	80% to 167%	58% to 60%	58% to 60%
Option life	10 years	10 years	10 years

For the options issued with a market condition attached, the Directors have used the Monte Carlo simulation to estimate the fair value of these options, the company uses the following methods to determine its underlying assumptions:

- expected volatilities are based on the historical volatilities of the market
- the expected term of the awards is 15 years based on managements' assessment of when the market condition is likely to be achieved
- a range of fair values per share were produced and management have determined the most appropriate value based on their knowledge of the market and vesting conditions being fulfilled.

Warrants

The Directors have estimated the fair value of the warrants in services provided using the Black-Scholes valuation model. The total fair value of the warrant instruments is deemed to be approximately $340,501 as at 31 December 2017. For each set of warrants, the charge has been expensed over the vesting period. A share based payment charge for the year to December 31, 2017 of $120,441 (2016: $156,424) has been expensed in the statement of comprehensive income.

The directors estimate the total fair value of warrant instruments at 30 June 2018 is $1,397,662 (unaudited), and the share based payments charge taken to the statement of comprehensive income for the six month period to June 30, 2018 is $89,431 (unaudited).

17. CONVERTIBLE LOAN NOTES

Group and Company

Planwise Convertible Loan Notes 2016

From the date of the reverse acquisition a convertible loan note of $247k was in existence as detailed in the Admission Document dated 31 March 2014. Proceeds of the subscriptions for the notes are to be used exclusively to finance the company's on-going working capital requirements. The terms of the loan note are that the loan notes, plus accrued interest at a rate of 4 per cent above Bank of England base rate per annum, will convert into ordinary shares in the company at a price of £0.10 per share at the election of Planwise any time after the second anniversary of the readmission to AIM on 24 April 2014. The company considers this to be a Convertible Debt Instrument as detailed in the policy described at note 2.

Accounting for the convertible debt instrument

The net proceeds received from the issue of the Planwise Convertible Loan Note has been recorded as a debt liability in the balance sheet and the accrued interest charged to the income statement and the debt liability. The liability for the convertible debt instrument is;

Planwise Convertible Loan Note

	Year ended December 31,		
	2018	2017	2016
	$000	$000	$000
Convertible loan notes issued	290	278	247
Accrued interest	11	12	31
	302	290	278

18. RESERVES

The share based payment reserve for warrants represent the value of equity shares which could be issued in future accounting periods if the warrants in issue are exercised.

The share based payment reserve for options represents the value of equity shares which could be issued in future accounting periods if the share based payment options in issue are exercised.

The other reserve was created as a result of the reverse acquisition of Alexander David Investments plc in the year and the accounting treatment required, which is described in Note 2. The reserve is required due to the fact that the reverse acquisition accounting requires the legal parent's equity structure to be shown.

Retained earnings represent the cumulative profits/(losses) of the entity which have not been distributed to shareholders.

The capital reduction reserve is credited with $41.3m of reserves arising from the court approved capital reduction detailed below. These reserves are designated as realized profits available for distribution under section 830 (2) of the Companies Act 2006.

On September 14, 2016, the High court granted the company permission to cancel its share premium account and its capital redemption reserve. The order had previously been ratified at the AGM held on June 30, 2016.

The company also decided to cancel its merger relief reserve as part of the capital reduction exercise.

19. FINANCIAL INSTRUMENTS

The main risks arising from the Group's financial instruments are liquidity risk, foreign currency risk and credit risk. The directors regularly review and agree policies for managing each of these risks which are summarized below.

Market risk

Market risk encompasses three types of risk, being foreign currency exchange risk, price risk and fair value interest rate risk. The Group policies for managing fair value interest rate risk are considered along with those for managing cash flow interest rate risk and are set out in the subsection entitled "interest rate risk" below. The directors do not consider the Group's exposure to price risk to be significant. The Group's risk management is coordinated by the directors, and focuses on actively securing the Group's short to medium term cash flows by minimizing the exposure to financial markets. The Group does not engage in the trading of financial assets for speculative purposes nor does it write options.

Credit risk

Credit risk is managed on a group basis. Credit risk arises principally from cash and cash equivalents and deposits with banks and financial institutions as well as credit exposure to customers including committed transactions and outstanding receivables. The group reviews its banking arrangements carefully to minimize such risks and currently has no customers and therefore this risk is viewed as minimal. Management monitor loans between members of the group as part of their internal reporting and assess outstanding receivables for ability to be repaid.

Liquidity risk

The group's policy is to regularly monitor current and expected liquidity requirements to ensure that it maintains sufficient reserves of cash to meet its liquidity requirements in the short and long term. The Group ordinarily finances its activities through cash generated from operating activities and private and public offerings of equity and debt securities.

The table below summarizes the maturity profile of the Group's financial liabilities based on contractual undiscounted payments.

	2018		
$000	**Less than 3 months**	**3 to 12 months**	**Total**
Trade and other payables	2,631	1,010	3,641
Convertible loan notes (debt)	3	307	310
Related party payables	140	—	—
Total	2,774	1,317	4,091

Foreign currency risks

The group operates internationally although the majority of its operations are based in the United Kingdom and the majority of assets and liabilities denominated in British Pounds. It therefore is exposed to foreign exchange risk arising from exposure to various currencies primarily the Euro and US Dollar.

Due to the majority of assets being denominated in British Pounds the group has no formal policies for managing foreign currency risks.

Interest rate risk

The Group has limited exposure to interest-rate risk arising from its bank deposits. These deposit accounts are held at variable interest rates based on Allied Irish Bank base rate.

19. FINANCIAL INSTRUMENTS (cont.)

The directors do not consider the impact of possible interest rate changes based on current market conditions to be material to the net result for the year or the equity position at the year-end for the years ended 31 December 2018, 2017 or 2016.

20. CAPITAL RISK MANAGEMENT

For the purpose of the Group's capital management, capital includes called up share capital, share premium, share based payment reserve for options, convertible loan note reserve, share based payment reserve for warrants, capital reduction reserve and all other equity reserves attributable to the equity holders of the parent as reflected in the statement of financial position.

The Group adjusts its capital structure in light of changes in economic conditions and expected business demands on capital. In order to maintain or adjust its capital structure, the Group considers whether or not to pay dividends and adjusts the amount of any dividend payments to shareholders. The Group may also return capital to shareholders or issue additional shares.

21. TRADE AND OTHER PAYABLES

	Year ended December 31,		
Group	**2018**	**2017**	**2016**
	$000	**$000**	**$000**
Trade payables	3,641	3,738	1,496
Accruals	2,310	683	369
Convertible loan note liability	310	316	278
Related party payable	140	12	—
	6,401	4,749	2,143

22. RELATED PARTY TRANSACTIONS

Tiziana Pharma Limited is a wholly owned subsidiary of Tiziana Life Sciences plc. During the year, Tiziana Life Sciences Plc transferred $3,922k (2017: $5,146k; 2016:$3,604k) 2017: £2,566k) in total to Tiziana Pharma Limited.

Tiziana Therapeutics Inc. is a wholly owned subsidiary of Tiziana Life Sciences plc. During the year, Tiziana Life Sciences Plc transferred $1,534k (2017: $1,182k; 2016: $1,182k) to Tiziana Therapeutics Inc.

Longevia Genomics SRL. is a wholly owned subsidiary of Tiziana Life Sciences plc. During the year, Tiziana Life Sciences Plc transferred $23k (2017: $0) to Longevia Genomics SRL.

Rasna Therapeutics Inc is a related party as Kunwar Shailubhai, director of our Company, is also a director of Rasna. In addition, Tiziano Lazzaretti, CFO of Tiziana, is also CFO of Rasna. Rasna is also party to a Shared Services agreement with Tiziana whereby the Company is charged for shared services such as the payroll and rent. As of December 31, 2018, $130k was owed to Tiziana Life Sciences PLC.

OKYO Pharma Ltd is a related party as Kunwar Shailubhai, director of our Company, is also a director of OKYO. In addition, Tiziano Lazzaretti, CFO of Tiziana, is also CFO of OKYO. OKYO is also party to a Shared Services agreement with Tiziana whereby the Company is charged for shared services such as the payroll and rent. As of December 31, 2018, $9k was owed to Tiziana Life Sciences PLC.

Gensignia Life Sciences Inc is a related party as Kunwar Shailubhai, director of our Company, is also a director of Gensignia. In addition, Tiziano Lazzaretti, CFO of Tiziana, is also CFO of Gensignia. As of December 31, 2018, $55k was owed to Tiziana Life Sciences PLC.

23. OPERATING LEASES

The Group leases number of office premises under operating lease. The future minimum rentals payable under non-cancellable operating leases are as follows:

	Year ended December 31,		
	2018	2017	2016
	$000	$000	$000
Less than one year	423	278	266
Between one and five years	691	575	612
	1,113	853	878

Lease expenses during year ended December 30, 2018 amounted to $153k (2017: $142k; 2016: $146k).

24. POST BALANCE SHEET EVENTS — POST 31 DECEMBER 2018

On February 7, 2019, the company announced that Riccardo Dalla-Favera MD had resigned from his role as Non-Executive Director of the company.

On March 20, 2019, the Company announced that it had submitted an Investigational New Drug application (“IND”) to the U.S. Food and Drug Administration (FDA) to initiate a Phase 1 clinical trial of enteric-coated capsules of Foralumab in healthy volunteers. This single-site clinical study is expected to enroll 36 subjects and it will be conducted at the Brigham and Women’s Hospital (BWH), Harvard Medical School

25. FINANCIAL COMMITMENTS

The Group’s main financial commitments relate to the contractual payments in respect of its licensing agreements. Due to the uncertain nature of scientific research and development and the length of time required to reach commercialization of the products of this research and development, preclinical, clinical and commercial milestone obligations are not detailed until there is a reasonable certainty that the obligation will become payable. Contractual commitments are detailed where amounts are known and certain.

- Milciclib project research funding of approximately £1m has been committed to for 2019 and beyond. Diligence obligations are payable to BMS / Medarex should the project continue. Other payments relate to the achievement of clinical milestones or the payment of royalties.
- Foralumab project — Future payments relate to the achievement of clinical milestones or the payment of royalties.

474,683 American Depositary Shares

Representing 4,746,830 Ordinary Shares

PROSPECTUS

, 2019

ThinkEquity
a division of Fordham Financial Management, Inc.

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Unless otherwise indicated, all references to "Tiziana" or the "company," "we," "our," "us" or similar terms refer to Tiziana Life Sciences plc and its subsidiaries.

Item 6. Indemnification of Directors and Officers.

Subject to the U.K. Companies Act 2006, members of the registrant's board of directors and its officers (excluding auditors) have the benefit of the following indemnification provisions in the registrant's Articles:

Current and former members of the registrant's board of directors or officers shall be reimbursed for:

(iii) all costs, charges, losses, expenses and liabilities sustained or incurred in relation to his or her actual or purported execution of his or her duties in relation to the registrant, including any liability incurred in defending any criminal or civil proceedings; and

(iv) expenses incurred or to be incurred in defending any criminal or civil proceedings, in an investigation by a regulatory authority or against a proposed action to be taken by a regulatory authority, or in connection with any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company, or collectively the Statutes, arising in relation to the registrant or an associated company, by virtue of the actual or purposed execution of the duties of his or her office or the exercise of his or her powers.

In the case of current or former members of the registrant's board of directors, there shall be no entitlement to reimbursement as referred to above for (i) any liability incurred to the registrant or any associated company, (ii) the payment of a fine imposed in any criminal proceeding or a penalty imposed by a regulatory authority for non-compliance with any requirement of a regulatory nature, (iii) the defense of any criminal proceeding if the member of the registrant's board of directors is convicted, (iv) the defense of any civil proceeding brought by the registrant or an associated company in which judgment is given against the director, and (v) any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company in which the court refuses to grant relief to the director.

In addition, members of the registrant's board of directors and its officers who have received payment from the registrant under these indemnification provisions must repay the amount they received in accordance with the Statutes or in any other circumstances that the registrant may prescribe or where the registrant has reserved the right to require repayment.

The underwriting agreement the registrant will enter into in connection with this offering of ADSs being registered hereby provides that the underwriters will indemnify, under certain conditions, the registrant's board of directors and its officers against certain liabilities arising in connection with this offering.

Item 7. Recent Sales of Unregistered Securities.

The following list sets forth information regarding all unregistered securities sold by us since January 1, 2016 through the date of the prospectus that is a part of this registration statement:

On March 23, 2016, we issued options to purchase 200,000 ordinary shares.

On June 9, 2016, we issued options to purchase 3,264,403 ordinary shares.

On June 28, 2016, we issued 700,000 new ordinary shares upon conversion, with noteholder consent, $222,466 (£168,000) of convertible loan notes.

On November 11, 2016, we issued options to purchase 100,000 ordinary shares.

On August 16, 2017 we issued 27,645,013 new ordinary shares upon conversion, with noteholder consent, $16,733,146 (£12,969,219) of convertible loan notes.

On August 30, 2017, we issued options to purchase 548,000 ordinary shares.

From November 2017 to March 2018, we sold 1,183,333 new ordinary shares for cash to purchasers adding $1,954,312 (£1,475,000) to our share capital. In connection with these sales, we issued warrants to purchase an aggregate 763,001 ordinary shares.

On January 16, 2018 we issued 810,201 new ordinary shares to our former noteholders in respect of accrued interest (in respect of the convertible loan conversion on August 16, 2017).

On April 19, 2018 we issued 1,031,250 new ordinary shares adding $1,100,000 (£825,000) to our share capital and simultaneously issued 51,563 new ordinary shares, credited as fully paid to intermediaries in lieu of commissions on the fundraise. In connection with this sale, we issued warrants to purchase 51,563 ordinary shares.

On April 27, 2018 we issued 23,014 new ordinary shares to our former noteholders in respect of final accrued interest (in respect of the convertible loan conversion on August 16, 2017).

On April 30, 2018, we issued options to purchase 9,500,000 ordinary shares.

On October 26, 2018, we sold 1,515,150 new ordinary shares credited as fully paid at a price of $0.99 (75p) per share at a fixed exchange rate of GBP1:US$1.32 to raise deferred cash proceeds of $1,500,000. In connection with this sale, we issued warrants to purchase 335,000 ordinary shares.

None of the foregoing transactions involved any underwriters, underwriting discounts or commissions, or any public offering. Unless otherwise specified above, we believe these transactions were exempt from registration under the Securities Act in reliance upon Section 4(a)(2) of the Securities Act (and Regulation S promulgated thereunder), or Rule 701 promulgated under Section 3(b) of the Securities Act as transactions by an issuer not involving any public offering or pursuant to benefit plans and contracts relating to compensation as provided under Rule 701. The recipients of the securities in each of these transactions represented their intentions to acquire the securities for investment only and not with a view to or for sale in connection with any distribution thereof, and appropriate legends were placed upon the share certificates issued in these transactions. All recipients had adequate access, through their relationships with us, to information about us. The sales of these securities were made without any general solicitation or advertising.

Item 8. Exhibits and Financial Statement Schedules.

ITEM 19: EXHIBITS

Exhibit No.	Description
1.1*	Form of Underwriting Agreement.
3.1	Memorandum and Articles of Association of Tiziana Life Sciences plc (incorporated by reference to Exhibit 3.1 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
4.1	Form of Deposit Agreement (incorporated by reference to Exhibit 4.1 to Amendment No. 2 to Form F-1 filed on September 25, 2018).
4.2	Form of American Depositary Receipt (included in Exhibit 4.1).
4.3*	Form of Representative's Warrant.
5.1*	Opinion of Cooley (UK) LLP.
10.1	License Agreement relating to Milciclib between Nerviano Medical Services S.r.l. and Tiziana Life Sciences plc, dated January 2015 (incorporated by reference to Exhibit 10.1 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.2	License and Sublicense Agreement relating to CD3 (NI-0401) between Novimmune SA and Tiziana Life Sciences plc, dated December 2014(incorporated by reference to Exhibit 10.2 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.3	License and Sublicense Agreement relating to IL-6r (NI-1201) between Novimmune SA and Tiziana Life Sciences plc, dated December 2016 (incorporated by reference to Exhibit 10.3 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.4	License Agreement relating to a novel formulation of Foralumab in a medical device for nasal administration between The Brigham and Women's Hospital, Inc. and Tiziana Life Sciences plc, dated April 2018 (incorporated by reference to Exhibit 10.4 to Amendment No. 1 to Form F-1 filed on August 23, 2018).

Exhibit No.	Description
10.5	Annual Lease for 55 Park Lane, Suite 14a, London W1K 1NA, United Kingdom, dated June 29, 2018 (incorporated by reference to Exhibit 10.5 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.6	Five-Year Lease for 420 Lexington Avenue, Suite 2525, New York, United States, dated August 2, 2016 (incorporated by reference to Exhibit 10.6 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.7	Amendment to Lease Agreement for 3705 Old Easton Road, Doylestown, Pennsylvania, United States, dated October 1, 2018 (incorporated by reference to Exhibit 10.1 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
10.8	Tiziana Life Sciences plc Employee Share Option Plan, with Non-Employee Sub-Plan and US Sub-Plan, adopted by the Board on 23 March 2016 and approved by shareholders on June 30, 2016 (incorporated by reference to Exhibit 4.7 to Form 20-F filed on April 4, 2019).
10.9	Amended and Restated Service Agreement dated July 11, 2019, between the Registrant and Dr. Kunwar Shailubhai
10.10	Form of Deed of Indemnity for board members (incorporated by reference to Exhibit 10.10 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
21.1	List of subsidiaries (incorporated by reference to Exhibit 21.1 to Amendment No. 1 to Form F-1 filed on August 23, 2018).
23.1	Consent of Mazars LLP, independent registered public accounting firm, regarding the financial statements of Tiziana Life Sciences plc as of December 31, 2018 and 2017 and for each of the years then ended.
23.2*	Consent of Cooley (UK) LLP (included in Exhibit 5.1).
24.1*	Power of Attorney (included on signature page).

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* Previously Filed

Financial Statement Schedules.

All financial statement schedules are omitted because the information required to be set forth therein is not applicable or is shown in the consolidated financial statements or the notes thereto.

Item 9. Undertakings.

(a) The undersigned registrant hereby undertakes to provide to the underwriters at the closing specified in the underwriting agreement, certificates in such denominations and registered in such names as required by the underwriter to permit prompt delivery to each purchaser

(b) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the U.S. Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(c) The undersigned registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant has duly caused this Amendment No. 2 to the Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of London, United Kingdom, on the 20th day of September, 2019.

TIZIANA LIFE SCIENCES PLC

By: /s/ Kunwar Shailubhai
Kunwar Shailubhai
Chief Executive Officer and Director

Pursuant to the requirements of the Securities Act of 1933, as amended, this Amendment No. 1 to the Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Kunwar Shailubhai Kunwar Shailubhai	Chief Executive Officer and Director *(Principal Executive Officer)*	September 20, 2019
* Tiziano Lazzaretti	Chief Financial Officer *(Principal Financial Officer and Principal Accounting Officer)*	September 20, 2019
* Gabriele Cerrone	Executive Chairman	September 20, 2019
* Willy Simon	Director	September 20, 2019
* Leopoldo Zambeletti	Director	September 20, 2019

*By: /s/ Kunwar Shailubhai
Kunwar Shailubhai,
Attorney-In-Fact

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption “Experts” and to the use of our audit report dated April 3, 2019 on the financial statements as of December 31, 2018 and 2017, and for each of the years then ended, included by reference in the Registration Statement (Form F-1) and related Prospectus of Tiziana Life Sciences plc dated September 20, 2019.

/s/ Mazars LLP

London, United Kingdom

September 20, 2019