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

FORM 20-F

REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934

OR

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from to

OR

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

Commission file number:

Tiziana Life Sciences plc

(Exact name of Registrant as specified in its charter and translation of Registrant's name into English)

England and Wales
(Jurisdiction of incorporation or organization)

3rd Floor, 11-12 St James's Square
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Securities registered or to be registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
American Depositary Shares, each representing 10 ordinary shares, having a nominal value of £0.03 each Ordinary share, nominal value of £0.03 each*	NASDAQ Global Market

(*) Not for trading, but only in connection with the listing of the American Depositary Shares

Securities registered or to be registered pursuant to Section 12(g) of the Act: **None**

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act: **None**

Number of outstanding shares of each of the issuer's classes of capital or common stock as of December 31, 2018: 136,463,818 ordinary shares.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

☐ Yes ☒ No

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934.

☒ Yes ☐ No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

☐ Yes ☐ No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

☐ Yes ☐ No

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

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

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by checkmark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards† provided pursuant to Section 13(a) of the Exchange Act. ☐

† 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.

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

U.S. GAAP ☐ International Financial Reporting Standards as issued by the International Accounting Standards Board ☒ Other ☐

If "Other" has been checked in response to the previous question, indicate by check mark which financial statement item the registrant has elected to follow:

☐ Item 17 ☐ Item 18

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

☐ Yes ☐ No

TABLE OF CONTENTS

	PART I	
Item 1	Identity of Directors, Senior Management and Advisers	1
Item 2	Offer Statistics and Expected Timetable	1
Item 3	Key Information	1
Item 4	Information on the Company	37
Item 4A	Unresolved Staff Comments	61
Item 5	Operating and Financial Review and Prospects	61
Item 6	Directors, Senior Management and Employees	71
Item 7	Major Shareholders and Related Party Transactions	79
Item 8	Financial Information	80
Item 9	The Offer and Listing	80
Item 10	Additional Information	81
Item 11	Quantitative and Qualitative Disclosures About Market Risk	89
Item 12	Description of Securities Other than Equity Securities	90
	PART II	
Item 13	Defaults, Dividend Arrearages and Delinquencies	92
Item 14	Material Modifications to the Rights of Security Holders and Use of Proceeds	92
Item 15	Controls and Procedures	92
Item 16A	Audit Committee Financial Expert	92
Item 16B	Code of Ethics	92
Item 16C	Principal Accountant Fees and Services	92
Item 16D	Exemptions From the Listing Standards for Audit Committees	92
Item 16E	Purchases of Equity Securities by the Issuer and Affiliated Purchasers	92
Item 16F	Change in Registrant’s Certifying Accountant	92
Item 16G	Corporate Governance	93
Item 16H	Mine Safety Disclosure	93
	PART III	
Item 17	Financial Statements	94
Item 18	Financial Statements	94
Item 19	Exhibits	94

INTRODUCTION

In this Annual Report on the Form 20-F references to “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 annual report 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 annual report, 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 annual report, 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 annual report 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 United States dollars. 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 $1.3278, which was the noon buying rate of the Federal Reserve Bank of New York on March 15, 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.

CAUTIONARY STATEMEMT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report contains forward-looking statements that involve substantial risks and uncertainties. All statements contained in this Annual Report, other than statements of historical fact, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue” and “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The forward-looking statements and opinions contained in this registration statement are based upon information available to us as of the date of this registration statement 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 potentially available relevant information. Forward-looking statements include 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 foreign countries.

You should refer to the section titled “Risk Factors” for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this registration statement will prove to be accurate.

Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this Annual Report and the documents that we have filed as exhibits to this Annual Report 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.

PART I

ITEM 1: IDENTITY OF DIRECTORS, SENIOR MANAGEMENT AND ADVISERS

Not Applicable

ITEM 2: OFFER STATISTICS AND EXPECTED TIMETABLE

Not applicable.

ITEM 3: KEY INFORMATION

A. Selected Financial Data

The following table summarizes our consolidated financial data as of the dates and for the periods indicated. The consolidated financial statement data as of December 31, 2018 and 2017 and for the years ended December 31, 2018, 2017 and 2016 have been derived from our consolidated financial statements, as presented at the end of this Annual Report, which have been prepared in accordance with IFRS, as issued by the IASB, and audited in accordance with the standards of the Public Company Accounting Oversight Board (United States). The consolidated financial statement data as of December 31, 2016, 2015 and 2014 and for the years ended December 31, 2015 and 2014 have been derived from our consolidated financial statements, which are not presented herein, which have also been prepared in accordance with IFRS as issued by the IASB.

Our functional currency is the pound Sterling. However, for financial reporting purposes, our financial statements, which are prepared using the functional currency, have been translated into U.S. dollars. Our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates for the period presented and shareholders' equity is translated based on historical exchange rates. Translation adjustments are not included in determining net income (loss) but are included in foreign exchange translation adjustment to other comprehensive loss, a component of shareholders' equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in general and administrative expense in the statement of operations and comprehensive loss.

As of December 31, 2018, and 2017, the representative exchange rate was £1.00 = $1.2737 and £1.00 = $1.3515, respectively.

Our historical results are not necessarily indicative of the results that may be expected in the future. The following selected consolidated financial data should be read in conjunction with our audited consolidated financial statements included at the end of this Annual Report and the related notes and Item 5, "Operating and Financial Review and Prospects" below.

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

We define working capital as current assets less current liabilities.

B. Capitalization and Indebtedness

Not applicable.

C. Reasons for the Offer and Use of Proceeds

Not applicable.

D. Risk Factors

Our business has significant risks. You should consider carefully the risks described below, together with the other information contained in this Annual Report, including our financial statements and the related notes. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. This Annual Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in these forward-looking statements, as a result of certain factors including the risks described below and elsewhere in this Annual Report and our other SEC filings. See "Cautionary Statement Regarding Forward-Looking Statements" above.

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.

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, $8.7 million and $9.8 million for the years ended December 31, 2018, 2017 and 2016, 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 standard of care 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 April 12, 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

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. We cannot predict the effect such delisting of our ordinary shares on AIM would have on the market price of the ADSs on the Nasdaq Global Market.

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.

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 IPO, 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 annual report, our executive officers, directors and 10% or more stockholders, together with their respective affiliates, owned approximately 43% 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 are considered to be a “concert party” for the purposes of the Takeover Code, or the Cerrone Concert Party. The Cerrone Concert Party holds shares carrying voting rights equal to approximately 46.7%. 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.

ADSs 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 (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as 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 Income 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 Income Tax Considerations-Material U.S. Federal Income 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.

ITEM 4: INFORMATION ON THE COMPANY

A. History and Development of the Company

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 Napoleone Ferrara, M.D., Arun Sanyal, M.D., Howard Weiner, M.D. and Kevan Herold, M.D., 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.

The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers, such as we, that file electronically, with the SEC at www.sec.gov. 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 annual report.

Our agent for service of process in the United States is Tiziana Therapeutics, Inc, 420 Lexington Avenue, Suite 2525, New York, NY 10170.

B. Business Overview

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 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. MAbs represent a single pure antibody produced by single clones and are an important class of human therapeutics for treating cancers and autoimmune diseases. Antibodies produced in animals for use in humans, 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 have a drug discovery pipeline of small molecule new chemical entities, or NCEs, and biologics. 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 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 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 believe that oral or intranasal administration of Foralumab has the potential to reduce inflammation while minimizing the toxicity and related side effects. 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 safe and well-tolerated and produced immunologic effects consistent with potential clinical benefit while demonstrating mild to moderate infusion related reactions, or IRR. We plan to initially investigate Foralumab for safety and its immunomodulatory activity in healthy volunteers in two Phase 1 trials. In one of the Phase 1 trials, subjects will be dosed Foralumab in a newly developed oral formulation (enteric capsule) with an intention to treat patients with NASH and/or Crohn’s disease and in the other Phase 1 trial, Foralumab will be dosed via intranasal administration using a hand-held nasal device with an intention to treat patients with MS. An IND for the first-in-human, intranasal evaluation of Foralumab in healthy volunteers was filed on June 1, 2018 and accepted by the FDA on August 20, 2018. Dosing was initiated in November 2018 for this dose-ranging, Phase 1 trial to evaluate safety and biomarkers of immunomodulation of clinical responses . Topline results from this study are expected in the third quarter of 2019. In addition, we have submitted an IND on March 18, 2019, to the FDA and expect to initiate a Phase 1 trial of the enteric capsule formulation of Foralumab in healthy volunteers in the second quarter of 2019 and a Phase 2 trial by the end of the second quarter 2020, in patients with NASH and/or Crohn’s disease. On April 16, 2018 we entered into an exclusive license agreement with The Brigham and Women’s Hospital, Inc., or BWH, relating to a novel formulation of Foralumab in a medical device for intranasal administration.

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 completed and ongoing 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 and expect top-line results in July 2019. We expect to initiate a Phase 2b trial for Milciclib in combination with Sorafenib (also known under its brand name Nexavar®, used to treat some types of kidney, liver and thyroid cancers) in patients with HCC in 2019.

In addition, we are developing a fully human mAb targeting the IL-6R (TZLS-501). 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, Dr. Fayez Hamzeh, 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 quarter of 2019 and a Phase 2 trial in the second quarter 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 third quarter 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 Sorafenib.

- Continue to leverage relationships with key opinion leaders to promote clinical trial success and enhance future commercialization.

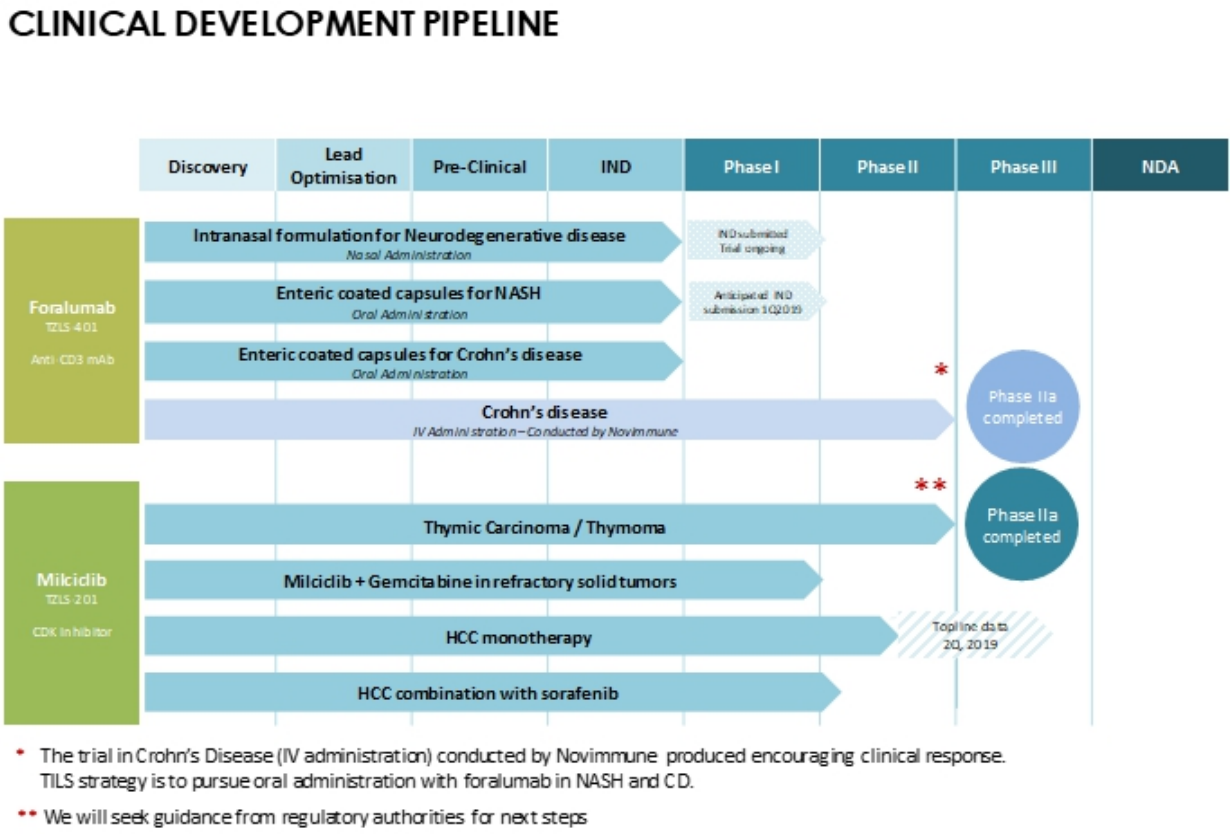
- Continue preclinical studies and non-clinical development of our product candidate, TZLS-501, a fully human mAb targeting the IL-6R (a biological mAb which may control the proteins involved in cell signaling relevant to many inflammatory diseases and cancers), for treatment of inflammatory and oncology 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 such as NASH and is based on the landmark discovery by Prof. Howard Weiner of Harvard University, one of our Scientific Advisory Committee members. We plan to initially investigate Foralumab for safety and its immunomodulatory activity in healthy volunteers in two Phase 1 trials. In one of the Phase 1 trials, for which an IND was submitted to the FDA on March 18, 2019, subjects will be dosed with Foralumab using a newly developed oral formulation (enteric capsule) with an intention to treat patients with NASH and/or Crohn's disease and in the other Phase 1 trial, which is ongoing, healthy volunteers are being dosed via intranasal administration using a hand-held nasal device with an intention to treat patients with MS. An IND for the first-in-human intranasal evaluation of Foralumab in healthy volunteers was filed on June 1, 2018 and accepted by the FDA on August 20, 2018. Dosing of subjects intranasally for the dose-ranging Phase 1 trial to evaluate biomarkers of immunomodulation of clinical responses was initiated in November 2018. Topline results from this study are expected in the third quarter of 2019.

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 45 under "—Milciclib—Hepatocellular Cancer." NASH is predicted to become the leading cause of liver transplantation in the US by 2020. 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). Although the exact etiology remains unknown, the occurrence of Crohn's disease is strongly associated with mutations of a receptor for microbial pathogens (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.

At least 25% 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) 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.

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.

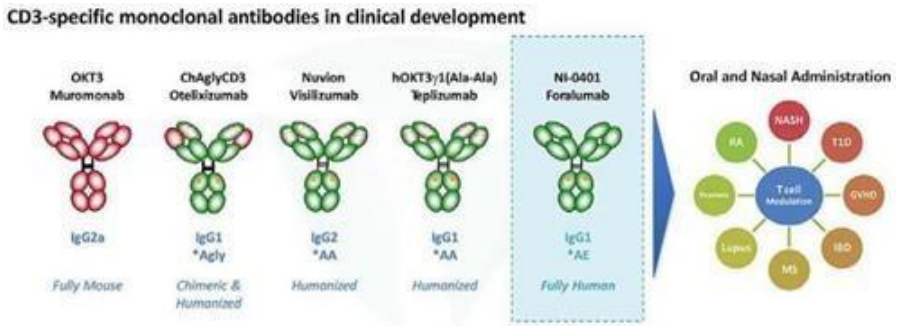
Autoimmune and Inflammatory Diseases

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, 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. 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. 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.

On April 16, 2018 we entered into an exclusive license agreement with BWH relating to a novel formulation of Foralumab in a medical device for intranasal administration. 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. 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 (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).

Ongoing Phase 1 Clinical Trial for Foralumab for the Treatment of Multiple Sclerosis

The ongoing 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 is being 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, if the resultant data indicates that the drug is well tolerated and free from significant adverse events, the next higher dose will be administered nasally for 5 consecutive days followed by 30 days of monitoring each time for tolerance and adverse events. If data from the Phase 1 trials indicate that the drug is well tolerated and free from adverse events, Phase 2a trials will be initiated at a later date for the treatment of MS. The primary endpoint of the Phase 1 study is safety and tolerability of Foralumab in humans dosed intranasally using a hand-held nasal spray device.

Intravenous Foralumab has been studied in a total of three Phase 1 and 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 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)

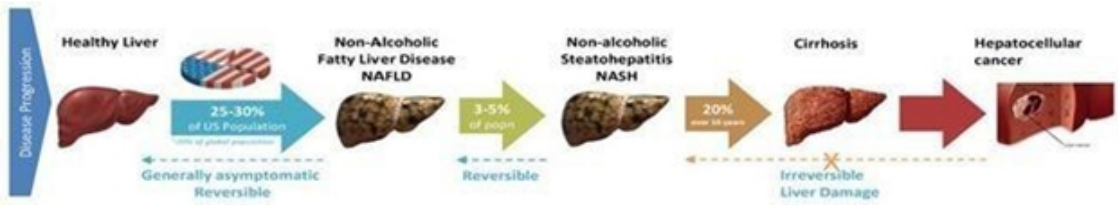
Milciclib is an orally bioavailable, small molecule broad spectrum inhibitor of CDKs (CDKs): 1, 2, 4, 5 and 7 and Src family kinases. CDKs are a family of highly conserved enzymes that are involved in regulating the cell cycle, which is a series of events that takes place in cells leading to division 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 completed and ongoing 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 initiated a Phase 2a trial (CDKO-125a-010) for Milciclib as a single therapy in patients with HCC in the second half of 2017 and expect to initiate a Phase 2b trial (TZLS (201)-125a-011) for Milciclib in combination with Sorafenib (the standard of care for treatment of HCC) in patients with HCC in 2019.

Hepatocellular Cancer

We are initially developing Milciclib for the treatment of HCC. HCC, or liver cancer, is the sixth most common worldwide and second most leading cause of death in the United States. 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.

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

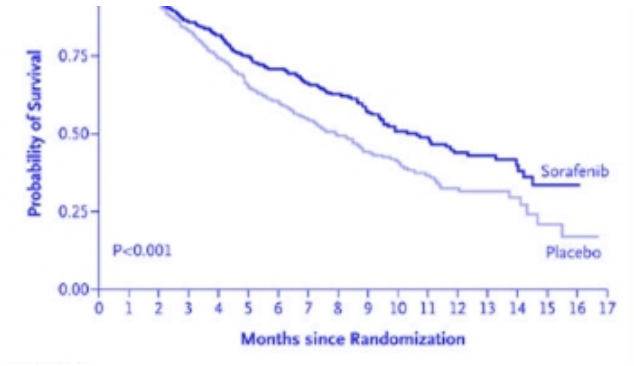
In July 2017, we initiated dosing in a single-arm, multicenter, Phase 2a clinical trial (CDK-125a-010) for Milciclib in adult patients with unresectable or metastatic HCC and good liver function. The trial is studying the tolerability and safety of Milciclib in these adult patients. As of 2019, we have enrolled and treated 30 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 tolerability 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. A second interim evaluation will be conducted when 20 evaluable patients have completed their 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 safety and tolerability profile of Milciclib in the first cohort, is acceptable and that there are no safety signals that preclude continuation of enrollment of the remaining cohorts as planned. The IDMC has also been informed of the patients who opted to continue Milciclib on “compassionate use basis.” Four patients have completed protocol mandated treatment (six cycles, six months). Three of these patients and their health care-provider/investigator opted to continue treatment with Milciclib (compassionate use) with approval of their local Ethics Committee. These three patients have completed treatment with milciclib for 9, 13, and 16 months, respectively. Based on this IDMC assessment, the study actively enrolled 20 more patients. 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. Topline results from this study are expected in July 2019.

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

In 2019, we intend to initiate a randomized, multicenter study to explore tolerability and antitumor activity, of Milciclib in combination with Sorafenib, administered as first-line systemic therapy in adult patients with recurrent, unresectable or metastatic HCC and good liver function.

Sorafenib (Nexavar®) is the standard of care 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.



Clinical Data

Milciclib has been studied in a total of eight completed and ongoing 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 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	*Pharmacokinetics:* Comparable plasma pharmacokinetic parameters between the two schedules were observed. 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) 34 patients (Phase 2)	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 54 mg/m2 (RP2D)	*Pharmacokinetics:* Results indicated that the pharmacokinetics of Milciclib was dose-independent in the dose range 18 – 72 mg/m2. 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. 18 of 30 treated patients (54.5%) had OS of 48 months. Upper and lower 95% confidence limits could not be calculated because the median survival probability was not reached.
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	Ongoing

Source: Milciclib Investigators Brochure version 14

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 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, it out intent 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 -80°C 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 March 25, 2019, 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/ Pending	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
	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 five 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 forth 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 (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.

C. Organizational Structure

The following table sets out details of the Company's 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

D. Property, Plant and Equipment

The below table contains information regarding existing or planned material tangible fixed assets owned or leased by Tiziana and its 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

ITEM 4A: UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 5: OPERATING AND FINANCIAL REVIEW AND PROSPECTS

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 at the end of this Annual Report. 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 Annual Report 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 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. MAbs represent a single pure antibody produced by single clones and are an important class of human therapeutics for treating cancers and autoimmune diseases. 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 also have a drug discovery pipeline of small molecule NCEs, and biologics. 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 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 are developing Foralumab, for which we in-licensed the intellectual property from Novimmune SA, or Novimmune, in December 2014, as a potential treatment for NASH, and Crohn's disease as well as neurodegenerative diseases such a MS. We believe that oral or nasal administration of Foralumab has the potential to reduce inflammation while minimizing the toxicity and related side effects. 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 and produced immunologic effects consistent with potential clinical benefit while demonstrating mild to moderate IRR.

We plan to initially investigate Foralumab for safety and its immunomodulatory activity in healthy volunteers in two Phase 1 trials. In one of the Phase 1 trials, subjects will be dosed Foralumab in a newly developed oral formulation (enteric capsule) with an intention to treat patients with NASH and/or Crohn's disease and in the other Phase 1 trial, Foralumab will be dosed via intranasal administration using a hand held nasal device with an intention to treat patients with MS. 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. We expect to commence enrollment for the dose ranging Phase 1 trial to evaluate biomarkers of immunomodulation of clinical responses in healthy human volunteers in late November 2018. In addition, the IND for the oral administration of Foralumab was submitted to the FDA on March 18, 2019. We expect to initiate a Phase 1 trial in the second quarter of 2019 and a Phase 2 trial for oral Foralumab by the end of the second quarter of 2020, in patients with NASH and/or Crohn's disease. On April 16, 2018 we entered into an exclusive license agreement with BWH relating to a novel formulation of Foralumab in a medical device for nasal administration.

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 Standard of Care. To date, Milciclib has been studied in a total of seven completed and ongoing Phase 1 and Phase 2 clinical trials in a total of 296 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 fourth quarter of 2017 and expect to initiate a Phase 2b trial for Milciclib in combination with Sorafenib (a multikinase inhibitor drug, also known under its brand name Nexavar®, used to treat some types of kidney, liver and thyroid cancers) in patients with HCC in the first quarter of 2019.

Cumulative Patient Exposure in Completed and Ongoing 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/-0061/-0071 Phase 2	Milciclib	Malignant Pleural Mesothelioma (-005) Thymic carcinoma and malignant thymoma (-0061 and -0071)	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 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. Following successful completion of this study we plan to launch additional clinical trials to study the potential of the oral administration of Foralumab in NASH, NAFLD and Crohn's Disease.

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	2016	2015
Direct research and development expense by program:	(in thousands)			
Foralumab	$ 2,261	$ 1,202	$ 715	$ 530
Milciclib	2,581	2,625	1,542	6,630
BCL-3	-	347	714	293
TZLS-0501	-	-	-	-
StemPrintER	166	1,201	529	951
Total direct research and development expense	$ 5,008	$ 5,375	$ 3,500	$ 8,404
Indirect research and development expense	502	640	507	665
Total research and development expense	$ 5,510	$ 6,015	$ 4,007	$ 9,609

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.

A. 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)	-
Tax credit	1,945	1,912	33
Net Loss	$ (7,994)	$ (8,716)	$ 722
Other comprehensive loss:			
Foreign currency translation adjustment	(20)	70	(90)
Total Comprehensive (Loss)/Profit	$ (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 $1m 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 $0.2m.

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.

Comparison of Years Ended December 31, 2017 and 2016

	Year Ended December 31,		
	2017	**2016**	**Change**
Operating Expenses:		(in thousands)	
Research and development	$ (6,015)	$ (4,007)	$ (2,008)
General and administrative	$ (4,601)	$ (5,872)	$ 1,271
Total Operating expenses	$ (10,616)	$ (9,879)	$ (737)
Other Income/ (Expense)	(12)	(12)	-
Tax credit	1,912	121	1,791
Net Loss	$ (8,716)	$ (9,770)	$ 1,054
Other comprehensive loss:			
Foreign currency translation adjustment	70	650	(580)
Total Comprehensive (Loss)/Profit	$ (8,646)	$ (9,120)	$ 474

Research and Development Expenses

Research and development activities were $6 million for the year ended December 31, 2017 compared to $4 million for the year ended December 31, 2016. The increase of $2 million was primarily due to the continuation of Phase 2 clinical trials for Milciclib and Foralumab, and engaging a CRO for StemPrintER. The research and development costs increased due to the introduction of a per patient cost.

General and Administrative Expenses

General and administrative expenses were $4.6 million and $5.8 million for the years ended December 31, 2017 and 2016, respectively. Within general and administrative expenses, there were decreases in legal and professional fees of $0.5 million driven by a reduction in ad hoc activity, travel of $0.4 million, and exchange rate charges of $0.2 million. As the company finalized its restructuring the general and administrative costs decreased.

Income Tax Credit

Income tax credits of $1.9 million and $0.1 million are recognized for the years ended December 31, 2017 and 2016, 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 a provision made in the year ended December 31, 2017.

B. 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	2016
Net cash used in operating activities	$ (4,551)	$ (7,533)	$ (6,926)
Net cash used in investing activities	-	(1)	(342)
Net cash provided by financing activities	10,041	1,542	1,575
Effect of exchange rate changes on cash and cash equivalents	(249)	254	(1,633)
Net decrease in cash and cash equivalents	$ 5,241	$ (5,738)	$ (7,326)

Net Cash Used in Operating Activities

Our use of cash in each of the years ended December 31, 2018, 2017 and 2016, 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.

Our use of cash in each of the years ended December 31, 2017 and 2016 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 $7.5 million during the year ended December 31, 2017 increased by $0.6 million compared to the year ended December 31, 2016. The increase in net cash used in operating activities was primarily due to an increase of $0.6 million in operating expenses.

Net Cash Used in Investing Activities

During the year ended December 31, 2016, 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.

During the years ended December 31, 2017 and 2016, net cash provided by financing activities was $1.5 million and $1.6 million, respectively, consisting of net cash proceeds from our sale and issuance of ordinary shares and warrants.

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, will enable us to fund our operating expenses and capital expenditure requirements for the foreseeable future. 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 £100,000 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 £300,000 at an interest rate of 20% per annum to be repaid no later than 24 months after the date of the agreement.

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.

The loans were converted into ordinary shares in November 2018.

C. Research and Development Expenses, Patents and Licenses, etc.

See “Item 4.B.—Intellectual Property,” “Item 4.B.—Research and Development,” and “Item 5. Operating and Financial Review and Prospects.”

D. Trend Information

See “Item 5. Operating and Financial Review and Prospects—Trend Information.”

E. Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

F. Tabular Disclosure of Contractual Obligations

The following table summarizes our contractual commitments and obligations as of December 31, 2018 and 2017.

As at December 31, 2018	Payments Due by Period				
(in thousands)	**Total**	**Less than 1 Year**	**Between 1 and 5 Years**	**~~Between 3 and 5 Years~~**	**More than 5 Years**
Borrowings	-	-	-	-	-
Operating lease obligations	$ 1,114	$ 423	$ 691	-	-
Total	$ 1,114	$ 423	$ 691	-	-

As at December 31, 2017	Payments Due by Period				
(in thousands)	**Total**	**Less than 1 Year**	**Between 1 and 5 Years**	**~~Between 3 and 5 Years~~**	**More than 5 Years**
Borrowings	-	-	-	-	-
Operating lease obligations	$ 853	$ 278	$ 575	-	-
Total	$ 853	$ 278	$ 575	-	-

Please refer to “Item 4.B. Business Overview” and “Item 10.C. Material Contracts” for further details.

G. Safe Harbor

This Annual Report on Form 20-F contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act and as defined in the Private Securities Litigation Reform Act of 1995. See the section titled “Cautionary Statement Regarding Forward-Looking Statements”.

ITEM 6: DIRECTORS, SENIOR MANAGEMENT AND EMPLOYEES

A. Directors and Senior Management

The following table sets forth information regarding our directors as of the date of this annual report.

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 the date of this annual report:

Name	Position
Tiziano Lazzaretti	Chief Financial Officer
Fayez Hamzeh, MD, PhD	Senior Vice President, Clinical Development
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 2111. 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 2112 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 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 and Rasna Therapeutics, Inc., respectively, 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. 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.

Fayez Hamzeh, MD, Ph.D. – ***Senior Vice President, Clinical Development***

Dr. Fayez Hamzeh has served as Sr. Vice President for Clinical Development since February 2018. Before joining us, Dr. Hamzeh served as Head of Clinical Trials Planning and Implementation Strategy of Immunology and Infectious Diseases at Roche Innovation Center, New York from 2015 to 2017. During this period Dr. Hamzeh focus was Phase 1 and Phase 2 clinical trials in immunology, hepatology and infectious diseases. Dr. Hamzeh served as a Group Medical Director and Head of Infectious Disease, Transplantation and Hepatology at Genentech Inc, South San Francisco from 2009 through 2011 and 2013 through 2015 where he was responsible for glioblastoma and avastin pan tumor indications. Dr. Hamzeh served as Sr. Medical Director of Hepatology, Transplantation and Infectious Diseases at Roche Pharmaceutical, Nutley NJ from 2003 through 2009. During this period, Dr. Hamzeh was responsible for clinical trials in virology focusing on anti-HIV, anti-influenza, anti-cytomegalovirus, anti-HCV and anti-HBV drugs. Prior to joining the industry in 2003, Dr. Hamzeh served as an Assistant Professor of Medicine and Pharmacology and Molecular Therapeutics at Johns Hopkins School of Medicine, Baltimore MD. During his academic and industry career, Dr. Hamzeh served on many National Institute of Health scientific steering committees including, AIDS Clinical Trials Group, AIDS Malignancy Consortium, Hepatitis-C (HALT-C) Scientific Steering Committee. Dr. Hamzeh received his MD degree in 1981 from the University of Jordan Medical School and his PhD from Johns Hopkins School of Medicine in 1990.

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 and Rasna Therapeutics, Inc., respectively, 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, Non-Clinical Studies*

Dr. Palejwala has served as Director, Non-Clinical Studies of the company since January 2017 and has 18 years of experience in drug discovery and development. Dr. Palejwala also currently serves as director of discovery and preclinical research at Rasna Therapeutics, Inc. 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.

B. 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 ($)	Options awarded ($)	Total ($)
Kunwar Shailubhai	Executive Director	300,000	1,275,754	1,561,579
Tiziano Lazzaretti	Chief Financial Officer	141,343	-	141,343

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 of 1986, as amended). 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	25/06/2014	25/06/2024
		2,000,000	0.35	25/06/2014	25/06/2024
		3,259,403	1.50	09/06/2016	09/06/2026
		550,000	0.8175	30/04/2018	30/04/2028
Willy Simon	-				
Kunwar Shailubhai	-	300,000	0.50	25/06/2014	25/06/2024
		400,000	1.595	30/08/2017	30/08/2027
		2,500,000	0.8175	30/04/2018	30/04/2028
		4,000,000	0.8175	30/04/2018	30/04/2028
Leopoldo Zambeletti	-	550,000	0.8175	30/04/2018	30/04/2028
Tiziano Lazzaretti	-	200,000	1.26	23/03/2016	23/03/2026
		100,000	1.86	05/11/2016	05/11/2026
Fayez Hamzeh	-	600,000	0.8175	30/04/2018	30/04/2028
Jules Jacob	-	50,000	1.595	30/08/2017	30/08/2027
Evangeline Priya-Eddy	-	50,000	1.595	30/08/2017	30/08/2027
Vaseem Palejwala	-	40,000	1.595	30/08/2017	30/08/2027

C. 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. Our board of directors has determined that, of our four directors, none have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of two of the directors, Mr. Dalla-Favera and Mr. Simon, and that each of these directors is "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	2014	2020
Kunwar Shailubhai	2015	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

Prior to effectiveness of this registration statement, we plan to adopt a Code of Business Conduct and Ethics applicable to our employees, executive officers and directors.

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. This agreement entitles Dr. Shailubhai to receive an initial annual base salary of $300,000 per year. Dr. Shailubhai is eligible to receive an annual bonus of up to 35% of his base salary, such bonus amount to be determined in the company's sole discretion. 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 his 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, among other things, his execution of our standard separation agreement and a general release of claims in our favor.

The agreement provides that Dr. Shailubhai's employment with us is at-will. If required by the company, the 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 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.

D. 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.

E. Share Ownership

See "Item 7. Major Shareholders and Related Party Transactions."

ITEM 7: MAJOR SHAREHOLDERS AND RELATED PARTY TRANSACTIONS

A. Major Shareholders

The following table sets forth information relating to the beneficial ownership of our ordinary shares as of April 2, 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 April 2, 2019 through the exercise of any option, warrant or other right. 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]	67,387,745	42.5
Executive Officers and Directors:		
Gabriele Cerrone[1]	67,387,745	42.5
Riccardo Dalla-Favera[2]	420,000	*
Willy Simon	-	-
Leopoldo Zambeletti	-	-
Kunwar Shailubhai[3]	330,000	*
Tiziano Lazzaretti[4]	168,666	*
All directors and executive officers as a group (6 persons)[5]	68,306,411	43.0

* 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 April 2, 2019.
(2) Consists of 420,000 stock options which are currently exercisable or exercisable within 60 days of April 2, 2019.
(3) Includes of 325,000 stock options which are currently exercisable or exercisable within 60 days of April 2, 2019.
(4) Includes of 166,666 stock options which are currently exercisable or exercisable within 60 days of April 2, 2019.
(5) Includes 4,078,333 stock options which are currently exercisable or exercisable within 60 days of April 2, 2019.

B. 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.

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, the date on which our registration statement on Form F-1 was declared effective. 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.

C. Interests of Experts and Counsel

Not applicable.

ITEM 8: FINANCIAL INFORMATION

A. Consolidated Statements and Other Financial Information

See “Item 18. Financial Statements”.

Legal Proceedings

Save as disclosed in this paragraph, there are no governmental, legal or arbitration proceedings (including any such proceedings which are pending or threatened of which the Company is aware), which may have, or have had during the 12 months prior to the date of this registration statement, a significant effect on the Company’s and/or our financial position or profitability. In addition to the proceedings set out in this section, the Company is involved in other legal proceedings and claims in the ordinary course of business.

B. Significant Changes

See Note 25 of our consolidated financial statements at the end of this Annual Report for a description of the significant changes since December 31, 2018.

ITEM 9: THE LISTING

A. Listing Details

The principal trading market for our ordinary shares is AIM, of the London Stock Exchange, where our ordinary shares have been listed since 2014. The following table sets forth, for the periods indicated, the reported high and low closing prices on the London Stock Exchange for our ordinary shares in pounds Sterling. See “Exchange Rate Information” on page 4 for the exchange rates applicable to the periods set forth below.

Our ordinary shares have been trading on AIM under the symbol “TILS” since April 24, 2014.

The following table presents, for the periods indicated, the reported high and low sale prices, including intra-day sales, of our ordinary shares on AIM in Pounds Sterling and U.S. dollars. For the convenience of the reader, we have translated Pounds Sterling amounts in the table below into U.S. dollars at the noon buying rate of the Federal Reserve Bank of New York on March 15, 2019, which was £1.00 to $1.3278.

	Price Per Ordinary Share £		Price Per Ordinary Share $	
	High	**Low**	**High**	**Low**
Year Ended December 31, 2019				
First Quarter (through March 22, 2019)	0.64	0.43	0.85	0.57
Year Ended December 31, 2018				
First Quarter	1.49	0.82	1.98	1.09
Second Quarter	0.88	0.37	1.17	0.49
Third Quarter	1.45	0.37	1.93	0.49
Fourth Quarter	1.47	0.63	1.95	0.84
Year Ended December 31, 2017				
First Quarter	2.10	1.66	2.79	2.20
Second Quarter	2.40	1.65	3.19	2.19
Third Quarter	1.75	1.42	2.32	1.89
Fourth Quarter	1.80	1.39	2.39	1.85
Year Ended December 31, 2016				
First Quarter	2.15	1.22	2.85	1.62
Second Quarter	1.61	1.23	2.14	1.63
Third Quarter	2.02	1.35	2.68	1.79
Fourth Quarter	2.16	1.75	2.87	2.32

On March 25, 2019, the last reported sale price of our ordinary shares on AIM was £0.435 per ordinary share ($0.578 per ordinary share based on the exchange rate set forth above).

Our American Depositary Shares, or ADSs, have been trading on the Nasdaq Global Market under the symbol "TLSA" since November 20, 2018. The following table sets forth, for the periods indicated, the reported high and low closing sale prices of our ADSs on the Nasdaq Global Market in U.S. dollars.

	Price Per ADS $	
	High	**Low**
Monthly:		
November 2018	10.59	7.85
December 2018	8.85	6.70
January 2019	7.10	5.56
February 2019	6.75	5.7
March 2019 (through March 23, 2019)	5.81	5

On March 25, 2019, the last reported sale price of our ADS's on the Nasdaq Global Market was 5.81 per ADS.

B. Plan of Distribution

Not applicable.

C. Markets

Our ordinary shares are listed on AIM under the symbol "TILS" and our ADSs are listed on the Nasdaq Global Market under the symbol "TLSA."

D. Selling Shareholders

Not applicable.

E. Dilution

Not applicable.

F. Expenses of the Issue

Not applicable.

ITEM 10: ADDITIONAL INFORMATION

A. Share Capital

Not applicable.

B. Memorandum and Articles of Association

We incorporate by reference into this Annual Report the description of our amended articles of association contained in our Registration Statement on Form F-1 originally filed with the SEC on July 26, 2018, as amended.

C. Material Contracts

Except as otherwise disclosed in this Annual Report (including the exhibits hereto), we are not currently, and have not been in the last two years, party to any material contract, other than contracts entered into in the ordinary course of business.

D. Exchange Controls

There are no governmental laws, decrees, regulations or other legislation in the United Kingdom that may affect the import or export of capital, including the availability of cash and cash equivalents for use by us, or that may affect the remittance of dividends, interest, or other payments by us to non-resident holders of our ordinary shares or ADSs, other than withholding tax requirements. There is no limitation imposed by English law or our articles of association on the right of non-residents to hold or vote shares.

E. Taxation

Material U.S. Federal Income Tax Considerations for U.S. Holders

U.S. Federal Income Tax Considerations for U.S. Holders

The following discussion describes the 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 2017 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. 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 & 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 from 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%).

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%) 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.

F. Dividends and Paying Agents

Not applicable.

G. Statements by Experts

Not applicable

H. Documents on Display

We are subject to the informational requirements of the Exchange Act. Accordingly, we are required to file reports and other information with the SEC, including annual reports on Form 20-F and reports on Form 6-K. You may inspect and copy reports and other information filed with the SEC at the public reference facilities of the SEC located at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of the documents at prescribed rates by writing to the Public Reference Section of the SEC at 100 F Street, N.E., Washington, DC 20549. Please call the SEC at 1-800-SEC-0330 for further information on the public reference room. The SEC also maintains a website at http://www.sec.gov from which certain filings may be accessed.

We also make available on our website, free of charge, our Annual Report and the text of our reports on Form 6-K, including any amendments to these reports, as well as certain other SEC filings, as soon as reasonably practicable after they are electronically filed with or furnished to the SEC. Our website address is “www.tizianalifesciences.com.” The information contained on our website is not incorporated by reference in this Annual Report.

I. Subsidiary Information

For information on our subsidiaries, see “Item 4C. Organizational Structure.”

ITEM 11: QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business, which are principally limited to interest rate fluctuations and foreign currency exchange rate fluctuations. We maintain significant amounts of cash and cash equivalents that are in excess of federally insured limits in various currencies, placed with one or more financial institutions for varying periods according to expected liquidity requirements.

Interest Rate Risk

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

Foreign Currency Exchange Risk

We maintain our consolidated financial statements in the functional currency pounds Sterling. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income (loss) for the respective periods.

For financial reporting purposes, our consolidated financial statements are prepared using the functional currency, and translated into the U.S. dollar. Assets and liabilities are translated at the exchange rates at the balance sheet dates and revenue and expenses are translated at the average exchange rates and shareholders' equity is translated based on historical exchange rates. Translation adjustments are not included in determining net income (loss) but are included in foreign exchange adjustment to accumulate other comprehensive loss, a component of shareholders' equity.

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future. Instruments that may be used to hedge future risks may include foreign currency forward and swap contracts. These instruments may be used to selectively manage risks, but there can be no assurance that we will be fully protected against material foreign currency fluctuations.

ITEM 12: DESCRIPTION OF SECURITIES OTHER THAN EQUITY SECURITIES

A. Debt Securities

Not applicable.

B. Warrants and Rights

Not applicable.

C. Other Securities

Not applicable.

D. American Depositary Shares

Fees and Expenses

JPMorgan Chase Bank, N.A., or JPMorgan, as depositary, registers and delivers the American Depositary Shares, also referred to as ADSs. Each ADS represents an ownership interest in a designated number of ordinary shares that are on deposit with the custodian, as agent of the depositary, under the deposit agreement among ourselves, the depositary and the ADS holders. Each ADS will also represent any securities, cash or other property deposited with the depositary but which they have not distributed directly to the ADS holders. The depositary's office is located at 4 New York Plaza, Floor 12, New York, NY, 10004. A copy of the deposit agreement is incorporated by reference as an exhibit to this Annual Report on Form 20-F.

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. ("JPMorgan") 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.

J.P. Morgan, and/or its agent may act as principal for such conversion of foreign currency. For further details see https://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.

PART II

ITEM 13: DEFAULTS, DIVIDEND ARREARAGES AN DELINQUENCIES

None.

ITEM 14: MATERIAL MODIFICATIONS TO THE RIGHTS OF SECURITY HOLDERS AND USE OF PROCEEDS

None.

ITEM 15: CONTROLS AND PROCEDURES

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Exchange Act), as of the end of the period covered by this Annual Report on Form 20-F. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

ITEM 16A: AUDIT COMMITTEE FINANCIAL EXPERT

The members of our audit committee are Mr Willy Simon and Mr. Leopoldo Zambeletti. Mr. Willy Simon is the chair of the audit committee. Each of our audit committee members satisfies the independence requirements of Rule 5605(a)(2) of the Nasdaq Stock Market Marketplace Rules and the independence requirements of Rule 10A-3(b)(1) under the Exchange Act. Our board of directors has determined that Mr. Willy Simon is an “audit committee financial expert” as defined in Item 16A of Form 20-F.

ITEM 16B: CODE OF 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. Information contained on, or that can be accessed through, our website is not incorporated by reference into this Annual Report, and you should not consider information on our website to be part of this Annual Report.

ITEM 16C: PRINCIPAL ACCOUNTANT FEES AND SERVICES

The following table sets forth, for each of the years indicated, the aggregate fees billed to us for services rendered by Mazars, our independent registered public accounting firm.

	Year Ending December 31,	
	2018	**2017**
	(in thousands)	
Audit fees	56	54
Other assurance services	57	24
Total	**113**	**78**

ITEM 16D: EXEMPTIONS FROM THE LISTING STANDARDS FOR AUDIT COMMITTEES

Not applicable.

ITEM 16E: PURCHASES OF EQUITY SECURITIES BY THE ISSUER AND AFFILIATED PURCHASERS

None.

ITEM 16F: CHANGE IN REGISTRANTS CERTIFYING ACCOUNTANT

None.

ITEM 16G: CORPORATE GOVERNANCE

The Sarbanes-Oxley Act of 2002, as well as related rules subsequently implemented by the SEC, requires foreign private issuers, including our company, to comply with various corporate governance practices. In addition, Nasdaq rules provide that foreign private issuers may follow home country practice in lieu of the Nasdaq corporate governance standards, subject to certain exceptions and except to the extent that such exemptions would be contrary to U.S. federal securities laws. The home country practices followed by our company in lieu of Nasdaq rules are described below:

- We do not follow Nasdaq's quorum requirements applicable to meetings of shareholders. Such quorum requirements are not required under U.K. law. In accordance with generally accepted business practice, our articles of association provide alternative quorum requirements that are generally applicable to meetings of shareholders.

- We do not follow Nasdaq's requirements that non-management directors meet on a regular basis without management present. Our board of directors may choose to meet in executive session at their discretion.

- We do not follow Nasdaq's requirements to seek shareholder approval for the implementation of certain equity compensation plans, the issuances of ordinary shares under such plans, or in connection with certain private placements of equity securities. In accordance with U.K. law, we are not required to seek shareholder approval to allot ordinary shares in connection with applicable employee equity compensation plans. We will follow U.K. law with respect to any requirement to obtain shareholder approval prior to any private placements of equity securities.

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 of 2002, the rules adopted by the SEC and Nasdaq's listing standards.

Because we are a foreign private issuer, our directors and senior management are not subject to short-swing profit and insider trading reporting obligations under Section 16 of the U.S. Securities Exchange Act of 1934, as amended, or Exchange Act. They are, however, subject to the obligations to report changes in share ownership under Section 13 of the Exchange Act and related SEC rules.

ITEM 16H: MINE SAFETY DISCLOSURE

Not applicable.

PART III

ITEM 17: FINANCIAL STATEMENTS

We have elected to furnish financial statements and related information specified in Item 18.

ITEM 18: FINANCIAL STATEMENTS

See the Financial Statements beginning on page F-1.

ITEM 19: EXHIBITS

Exhibit No.	Description
3.1	Memorandum and Articles of Association of Tiziana Life Sciences PLC.
2.1	Form of Deposit Agreement.
2.2	Form of American Depositary Receipt (included in Exhibit 4.1).
4.1	License Agreement relating to Milciclib between Nerviana Medical Services S.r.l. and Tiziana Life Sciences PLC, dated January 2015
4.2	License and Sublicence Agreement relating to CD3 (NI-0401) between Novimmune SA and Tiziana Life Sciences PLC, dated December 2014.
4.3	License and Sublicence Agreement relating to IL-6r (NI-1201) between Novimmune SA and Tiziana Life Sciences PLC, dated December 2016.
4.4	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.
4.5	Annual Lease for 55 Park Lane, Suite 14a, London W1K 1NA, United Kingdom, dated June 29, 2018.
4.6	Five-Year Lease for 420 Lexington Avenue, Suite 2525, New York, United States, dated August 2, 2016.
4.7*	Annual Lease for 3084 Old Easton Road, Doylestown, Pennsylvania, United States, as amended, dated October 1, 2018.
4.8	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.
4.9	Contract of Employment, dated May 2017, between the registrant and Dr. Kunwar Shailubhai.
4.10	Form of Deed of Indemnity for board members.
8.1	List of Subsidiaries.
12.1*	Certification by the Principal Executive Officer pursuant to Securities Exchange Act Rules 13a-14(a) and 15d-14(a) as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
12.2*	Certification by the Principal Financial Officer pursuant to Securities Exchange Act Rules 13a-14(a) and 15d-14(a) as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
13.1*	Certification by the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
13.2*	Certification by the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
15.1*	Consent of Mazars LLP.

* Filed Herewith

SIGNATURES

The Registrant hereby certifies that it meets all of the requirements for filing on Form 20-F and that it has duly caused and authorized the undersigned to sign this registration statement on its behalf.

TIZIANA LIFE SCIENCES plc

By: /s/ Kunwar Shailubhai
Kunwar Shailubhai
Chief Executive Officer

Date: April 4, 2019

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS
TIZIANA LIFE SCIENCES PLC

Report of Independent Registered Public Accounting Firm	F-2
Consolidated Balance Sheets	F-3
Consolidated Statements of Comprehensive Income	F-4
Consolidated Statements of Changes in Shareholders' Equity	F-5
Consolidated Statement of Cash Flows	F-6
Notes to Consolidated Financial Statements	F-7

Financial Statements and Notes to Financial Statements to be provided under separate cover

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

TIZIANA LIFE SCIENCES PLC

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.

TIZIANA LIFE SCIENCES PLC

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)

TIZIANA LIFE SCIENCES PLC

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**
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.

TIZIANA LIFE SCIENCES PLC

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

TIZIANA LIFE SCIENCES PLC

Notes to Consolidated Financial Statements

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.

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.

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.

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.

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.

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

$'000	Year ended December 31,					
	2018		2017		2016	
	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**

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.

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

$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

$000	Year ended December 31,	
	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.

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

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.

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

Group	Year ended December 31, 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.

PENNSYLVANIA BIOTECHNOLOGY CENTER

Est. by the Hepatitis B Foundation

AMENDMENT TO LEASE AGREEMENT

THIS THIRD AMENDMENT TO LEASE AGREEMENT ("Third Amendment") is dated as of the 1 October 2018 between **BUCKS COUNTY BIOTECHNOLOGY CENTER, INC.**, a Pennsylvania nonprofit corporation ("Lessor") and **TIZIANA THERAPEUTICS INC** ("Lessee") (collectively, the "Parties").

WITNESSETH:

WHEREAS, by Lease Agreement (the "Lease") effective 1 February 2017, Lessor leased to Lessee approximately 427.50 square feet of office space being part 3705 Old Easton Road, Doylestown, Buckingham Township, Bucks County, Pennsylvania (the "Building"), which space (the "Leased Premises") is more particularly described in the Lease; and

WHEREAS, Lessor and Lessee previously amended the lease in accordance with the terms of the First Amendment, dated 6 December 2017

WHEREAS, Lessor and Lessee previously amended the lease in accordance with the terms of the Second Amendment, dated 1 August 2018

WHEREAS, Lessor and Lessee desire to modify the Lease in accordance with the terms of this Third Amendment.

NOW THEREFORE, in consideration of the mutual covenants and premises contained herein, as well as other good and valuable consideration, and intending to be legally bound hereby, the Parties hereto agree as follows;

1. Premises. Pursuant to Section 1 of the original Lease, Lessor and Lessee hereby agree that the Lessee will relinquish office 2220 as of 1 October 2018 and occupy office 2213.

2. Extension of Lease: Pursuant to Section 2 of the original Lease, Lessor and Lessee hereby agree to extend the Lease Term (which will currently expire on 31 January 2019) until 31 January 2020 ("extension period), provided that, at the time of commencement of the extension period, an Event of Default does not exist nor has any event occurred and is continuing which, with the passage of time or the giving of notice, will become an Event of Default.

3. Rent. Lessee shall continue to pay the Rent monthly at the adjusted amount provided for in Exhibit "D" attached.

4. Lease Otherwise in Full Force and Effect and Unmodified. Except as expressly provided herein, the Lease shall remain in full force and effect in accordance with its terms (as amended herein).

5. Capitalized Terms. Terms capitalized in this Third Amendment (unless otherwise defined herein) shall have the meanings set forth in the Lease.

6. Binding Effect. This Third Amendment will bind and inure to the benefit of the successors and assigns of the Parties hereto and will be governed in accordance with the laws of the Commonwealth of Pennsylvania.

7. Entire Agreement. This Third Amendment sets forth the entire agreement and understanding of the Parties with respect to the transactions contemplated hereby.

8. Counterparts. This Third Amendment may be executed in any number of counterparts, each of which shall be deemed an original, and all such counterparts shall constitute but one and the same agreement.

9. Facsimile Signatures Are Binding. It is agreed that a copy of this Third Amendment bearing a facsimile (faxed) version of a party's signature shall have the same force and effect as a copy bearing the party's original signature.

10. Recitals Constitute a Part of this Amendment. The recitals in this Amendment are a part of this Third Amendment and are incorporated herein.

IN WITNESS WHEREOF, and intending to be legally bound hereby, the authorized representatives of the Parties have signed this Third Amendment as of the date above provided.

LESSEE:	LESSOR:
TIZIANA THERAPEUTICS INC.	BUCKS COUNTY BIOTECHNOLOGY CENTER, INC.,
By:	By:
Name: TIZIANO LAZZARETTI	Name: LOUIS P KASSATT
Title: CFO	Title: EVP/COO
Date:	Date: 3-13-19

EXHIBIT "D"

LEASED PREMISES DESCRIPTION

Amended October 1, 2018

Lessee: Tiziana Therapeutics Inc

Point of Contact: Tiziano Lazzaretti Title: CFO

Phone: 207-495-2379 Email: tlazzaretti@tizianalifesciences.com

Orig.Lease Start Date: 2/1/17 End Date: 1/31/20

Type of Space: x Office ☐ Warehouse
☐ Lab ☐ Other

Location: x 3805 Old Easton Road, Doylestown, PA 18902
☐ 3765 Old Easton Road, Doylestown, PA 18902

Room Numbers: Offices 2213,2221,2222

	Leased Ft²	Rent Expense	CAM/Utilities
Office Space	407.90	12,693.50	2,569.77
Lab Space			
Warehouse			
Other			
Annual Charges		12,693.50	2,569.77
Monthly Charges		1,057.79	214.15

Security Deposit: $1,058.00 Total monthly charge $1,271.94

*CAM/Utilities are estimated for the current year. Lessee Approval: _____

Exhibit 12.1

CERTIFICATION

I, Kunwar Shailubhai, certify that:

1. I have reviewed this annual report on Form 20-F of Tiziana Life Sciences plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the company as of, and for, the periods presented in this report;

4. The company's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the company and have:

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

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

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

    d. Disclosed in this report any change in the company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the company's internal control over financial reporting; and

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

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

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

Date: April 4, 2019

/s/ Kunwar Shailubhai

Kunwar Shailubhai
Chief Executive Officer

Exhibit 12.2

CERTIFICATION

I, Tiziano Lazzaretti, certify that:

1. I have reviewed this annual report on Form 20-F of Tiziana Life Sciences plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the company as of, and for, the periods presented in this report;

4. The company's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the company and have:

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

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

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

    d. Disclosed in this report any change in the company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the company's internal control over financial reporting; and

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

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

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

Date: April 4, 2019

/s/ Tiziano Lazzaretti

Tiziano Lazzaretti
Chief Financial Officer

Exhibit 13.1

CERTIFICATION

The certification set forth below is being submitted in connection with Tiziana Life Sciences plc's Annual Report on Form 20-F for the fiscal year ended December 31, 2018 (the "Report") for the purpose of complying with Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code.

Kunwar Shailubhai, Chief Executive Officer of Tiziana Life Sciences plc, certifies that, to the best of his knowledge:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Tiziana Life Sciences plc

Date: April 4, 2019

/s/ Kunwar Shailubhai
Name: Kunwar Shailubhai
Chief Executive Officer

Exhibit 13.2

CERTIFICATION

The certification set forth below is being submitted in connection with Tiziana Life Sciences plc's Annual Report on Form 20-F for the fiscal year ended December 31, 2018 (the "Report") for the purpose of complying with Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code.

Dr. Tiziano Lazzaretti, Chief Financial Officer of Tiziana Life Sciences plc, certifies that, to the best of his knowledge:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Tiziana Life Sciences plc

Date: April 4, 2019

/s/ Tiziano Lazzaretti

Name: Tiziano Lazzaretti
Chief Financial Officer

Exhibit 15.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors of Tiziana Life Sciences plc:

We consent to the incorporation by reference of our report dated April 3, 2019 with respect to the consolidated balance sheets for the years ended December 31, 2018 and December 31,2017 and the related consolidated statements of operations and comprehensive loss, cash flows and shareholders' equity for each of the years in the three-year period ended December 31, 2018, and the related notes, for Tiziana Life Sciences plc, which report appears in the December 31, 2018 annual report on Form 20-F.

/s/ Mazars LLP.

Mazars LLP
London
April 3, 2019