

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, 2021

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 Ltd**

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

**Bermuda**

(Jurisdiction of incorporation or organization)

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(Address of principal executive offices)

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Copies to:

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

<b>Title of each class</b>	<b>Name of each exchange on which registered</b>
Common Shares	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, 2021: 102,272,614 common 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

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## 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 Ltd, Bermuda and its wholly owned subsidiaries, Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc), 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, 2021 and 2020, 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 \$1.2848, which was the noon buying rate of the Federal Reserve Bank of New York on April 22, 2022. 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 STATEMENT 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 Foralumab, anti-IL6R monoclonal antibody (TZLS-501), Milciclib, 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 Foralumab, anti-IL6R monoclonal antibody (TZLS-501), Milciclib, 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, 2021 and 2020 and for the years ended December 31, 2021, 2020 and 2019 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, 2018 and 2017 and for the years ended December 31, 2018 and 2017 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, 2021, and 2020, the representative exchange rate was £1.00 = \$1.330836 and £1.00 = \$1.36516, 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,				
	2021	2020	2019	2018	2017
	(in thousands except share and per share data)				
Operating expenses:					
Research and development	\$ (13,208)	\$ (5,993)	\$ (3,714)	\$ (5,510)	\$ (6,015)
General and administrative	(13,311)	(11,203)	(6,207)	(4,357)	(4,478)
Realization bonus	(855)	(13,214)	-	-	-
Impairment of asset	-	(279)	-	-	-
Disposal of Intellectual Property	-	2,663	-	-	-
Total operating expenses	(27,374)	(28,026)	(9,921)	(9,867)	(10,493)
Loss from operations	(27,374)	(28,026)	(9,921)	(9,867)	(10,493)
Other income (expense), net	717	(312)	(91)	(12)	(12)
Tax provision	3,240	2,207	689	1,945	1,912
Net loss attributable to ordinary shareholders	(23,417)	(26,131)	(9,323)	(7,934)	(8,593)
Other comprehensive loss:					
Foreign currency translation adjustment	(4, 478)	3,474	(27)	(21)	61
Total comprehensive loss	(27,895)	(22,657)	(9,350)	(7,955)	(8,532)
Basic and diluted net loss per ordinary share	(0.24)	(0.16)	(0.07)	(0.06)	(0.09)

**Consolidated Balance Sheet Data:**

	As of December 31,				
	2021	2020	2019	2018	2017
	(in thousands except share and per share data)				
Cash and cash equivalents	\$ 42,186	\$ 65,824	\$ 200	\$ 5,304	\$ 64
Working capital	41, 133	62,196	(5,846)	513	(2,302)
Total assets	48,826	70,656	2,378	6,920	2,471
Total shareholders’ equity/(deficit)	41,280	62,386	(5,514)	519	(2,278)

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 execution of development due to financial instability of our CROs, CMOs and CDMOs
- 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**

***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 \$23.3 million, \$26.1 million and \$9.3 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated loss of \$84.6 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 Foralumab in Phase 2 trials in patients with Crohn's disease; nasally administered Foralumab in patients with progressive multiple sclerosis (pMS) and subcutaneously administered Foralumab in patients at risk for developing Type 1 Diabetes Mellitus (T1DM)
- initiate a Phase 2 trial for Milciclib in combination with gemcitabine in patients with KRAS-mutated (mut) non-small cell lung cancer (NSCLC) after failure of standard-of-care (SoC) therapy.
- accelerate development and cGMP manufacturing of anti-IL6R mAb for treatment Interpulmonary Fibrosis (IPF) patients and 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 Common shares, 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 cGMP manufacture Foralumab (TZLS-401) drug product, Milciclib (TZLS-201) and anti-Interleukin 6 Receptor monoclonal antibody (anti-IL6R mAb, TZLS-501) drug substance and drug product 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 are heavily reliant upon licenses and sublicenses from Nerviano, Lonza 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. Tiziana was granted a new patent by USPTO in June 2020 covering lyophilized formulation of Foralumab..

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 several 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 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, 2021, we had 8 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 if 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.

***A pandemic, epidemic or outbreak of an infectious disease, such as COVID-19, may materially and adversely affect our business and operations.***

The outbreak of COVID-19 originated in Wuhan, China, in December 2019 and has since spread to multiple countries, including the United States and several European countries. On March 11, 2020, the World Health Organization declared the outbreak a pandemic. The COVID-19 pandemic is affecting the United States and global economies and may affect our operations and those of third parties on which we rely, including by causing disruptions in the supply of our product candidates and the conduct of future clinical trials. Disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing preclinical studies and clinical trials, as applicable.

In addition, the COVID-19 pandemic may affect the operations of the FDA and other health authorities, which could result in delays of reviews and approvals, including with respect to our product candidates. Additionally, while the potential economic impact brought by, and the duration of the COVID-19 pandemic is difficult to assess or predict, the impact of the COVID-19 pandemic on the global financial markets may reduce our ability to access capital, which could negatively impact our short-term and long-term liquidity. The ultimate impact of the COVID-19 pandemic is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, financing or clinical trial activities or on healthcare systems or the global economy as a whole. However, these effects could have a material impact on our liquidity, capital resources, operations and business and those of the third parties on which we rely.

***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 Common shares 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 our common shares may be volatile and fluctuate substantially, which could result in substantial losses for holders of our common shares.*

The market prices of our common shares on the Nasdaq Global Market 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 our common shares may not be able to sell their common shares at or above the price at which they were purchased. The market price for the common shares may be influenced by many factors, including:

- the success of competitive products or technologies;
- results of clinical trials of Foralumab, anti-IL6R mAb (TZLS-501), Milciclib 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 Foralumab, anti-IL6R mAb (TZLS-501), Milciclib 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 our common shares on the Nasdaq Global Market; and
- the other factors described in this “Risk Factors” section.

### **Because we are a foreign corporation, you may not have the same rights as a shareholder in a U.S. corporation.**

We are a Bermuda exempted company. Our Memorandum of Association and Bye-laws and the Companies Act 1981 of Bermuda (the “Companies Act”) govern our affairs. While many provisions of the Companies Act resemble provisions of the corporation laws of a number of states in the United States, Bermuda law may not as clearly establish your rights and the fiduciary responsibilities of our directors as do statutes and judicial precedent in some U.S. jurisdictions. In addition, apart from three non-executive directors, our directors and officers are not resident in the United States and all or substantially all of our assets are located outside of the United States. As a result, investors may have more difficulty in protecting their interests and enforcing judgments in the face of actions by our management, directors or controlling shareholders than would shareholders of a corporation incorporated in a U.S. jurisdiction.

In addition, you should not assume that courts in the country in which we are incorporated or where our assets are located would enforce judgments of U.S. courts obtained in actions against us based upon the civil liability provisions of applicable U.S. federal and state securities laws or would enforce, in original actions, liabilities against us based on those laws.

Shareholders of Bermuda exempted companies such as the Company also have no general rights under Bermuda law to inspect corporate records and accounts other than rights to review the Company’s memorandum of association and bye-laws, financial statements, minutes of the shareholder meetings and the shareholder register. This could make it more difficult for you to obtain the information needed to establish any facts necessary for a shareholder motion or to solicit proxies from other shareholders in connection with a proxy contest.

As a result of all of the above, public shareholders might have more difficulty in protecting their interests in the face of actions taken by management, members of the board of directors or controlling shareholders than they would as public shareholders of a U.S. company.

***U.S. persons who own our securities may have more difficulty in protecting their interests than U.S. persons who are shareholders of a U.S. corporation.***

The Companies Act, which applies to the Company, differs in some material respects from laws generally applicable to U.S. corporations and their shareholders. These differences include, but are not limited to, the manner in which directors must disclose transactions in which they have an interest, the rights of shareholders to bring class action and derivative lawsuits, the scope of indemnification available to directors and officers and provisions relating to amalgamations, mergers and acquisitions and takeovers. Holders of our common shares may therefore have more difficulty protecting their interests than would shareholders of a corporation incorporated in a jurisdiction within the U.S.

Generally, the duties of directors and officers of a Bermuda company are owed to the company and not, in the absence of special circumstances, to the shareholders as individuals. Shareholders of Bermuda companies typically do not have rights to take action against directors or officers of the company and may only do so in limited circumstances. Class actions and derivative actions are typically not available to shareholders under Bermuda law. The Bermuda courts, however, would ordinarily be expected to permit a shareholder to commence an action in the name of a company to remedy a wrong to the company where the act complained of is alleged to be beyond the corporate power of the company or illegal, or would result in the violation of the company's memorandum of association or bye-laws.

#### ***Certain Other Bermuda Law Considerations.***

All Bermuda "exempted companies" are exempt from certain Bermuda laws restricting the percentage of share capital that may be held by non-Bermudians. However, exempted companies may not participate in certain business transactions, including (1) the acquisition or holding of land in Bermuda except that required for their business and held by way of lease or tenancy for a term not exceeding 50 years or, with the consent of the Minister of Economic Development (the "Minister") granted in his discretion by way of lease or tenancy for a term not exceeding 21 years in order to provide accommodation or recreational facilities for officers and employees of the Company, (2) the taking of mortgages on land in Bermuda to secure an amount in excess of \$50,000 without the consent of the Minister, (3) the acquisition of any bonds or debentures secured by any land in Bermuda, other than certain types of Bermuda government securities or securities issued by Bermuda public authorities or (4) the carrying on of business of any kind in Bermuda, except in furtherance of business carried on outside Bermuda or under license granted by the Minister.

All Bermuda companies must comply with the provisions of the Companies Act regulating the payment of dividends and making distributions from contributed surplus. A company may not declare or pay a dividend, or make a distribution out of contributed surplus, if there are reasonable grounds for believing that: (a) the company is, or would after the payment be, unable to pay its liabilities as they become due; or (b) the realizable value of the company's assets would thereby be less than its liabilities.

***Bermuda Exchange Control Regulation.*** The permission of the Bermuda Monetary Authority is required, under the provisions of the Exchange Control Act 1972 of Bermuda and related regulations, for all issuances and transfers of shares (which includes our common shares) of Bermuda companies to or from a non-resident of Bermuda for exchange control purposes, other than in cases where the Bermuda Monetary Authority has granted a general permission. The Bermuda Monetary Authority, in its notice to the public dated June 1, 2005, has granted a general permission for the issue and subsequent transfer of any securities of a Bermuda company from and/or to a non-resident of Bermuda for exchange control purposes for so long as any "Equity Securities" of the company (which include our common shares) are listed on an "Appointed Stock Exchange" (which include Nasdaq). In granting the general permission the Bermuda Monetary Authority accepts no responsibility for our financial soundness or the correctness of any of the statements made or opinions expressed in this annual report.

Although the Company is incorporated in Bermuda, as an exempted company, the Company is classified as a non-resident of Bermuda for exchange control purposes by the Bermuda Monetary Authority. Other than transferring Bermuda Dollars out of Bermuda, there are no restrictions on the Company's ability to transfer funds into and out of Bermuda or to pay dividends in currency other than Bermuda Dollars to nonresidents of Bermuda who are holders of our common shares.

***If we engage in future acquisitions or strategic partnerships, this may increase our capital requirements, dilute our 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 common shareholders 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 our home country 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. In order to maintain our current status as an FPI, either (a) a majority of our Common shares 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 common shares 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 common shares less attractive because we may rely on these exemptions. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and the price of our common shares may be more volatile in the event that we decide to make an offering of our common shares.

***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.

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 42.03% 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.

***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, as amended, or the 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, 2021 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 common shares 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 may also be 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 common shares 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. tax 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, 2021, we had cumulative carryforward tax losses of \$41.8 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. On August 20, 2021 we announced that we had formally commenced a strategic plan to change our corporate structure by establishing Tiziana Life Sciences Ltd, a Bermuda-incorporated company, to become the ultimate parent company of the Tiziana Group. The reorganisation was performed under a scheme of arrangement under Part 26 of the UK Companies Act 2006 and became effective on October 20, 2021, at which point all shareholders became shareholders in the new Bermuda company.

Our registered office is located at Clarendon House, 2 Church Street, Hamilton HM 11, Bermuda 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](http://www.sec.gov). Our website address is [www.tizianalifesciences.com](http://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, 5 Penn Plaza, 19<sup>th</sup> Floor, Suite 1954, New York, NY 10001.

## B. Business Overview

### Overview

We are a biotechnology company that is focused on the discovery and development of novel molecules to treat high unmet medical needs in oncology and immunology. Our mission is to design and deliver next generation therapeutics for oncology and immune diseases of high unmet medical need by combining deep understanding of disease biology with clinical development expertise. 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.

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 neurodegenerative diseases such as progressive Multiple Sclerosis (pMS), Crohn's disease and delayed onset of Type I Diabetes Mellitus (T1DM). As the only fully human engineered human anti-CD3 mAb in clinical development, Foralumab has significant potential advantages such as a shorter treatment duration and reduced immunogenicity. 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 IRRs. With completion of the intravenous dosing for Phase 2a trial in Crohn's Disease, Foralumab's ability to modulate T-cell response enables potential extension into a wide range of other autoimmune and inflammatory diseases, such as Graft versus Host Disease (GvHD), ulcerative colitis (UC), multiple sclerosis (MS), type-1 diabetes (T1D), inflammatory bowel disease (IBD), psoriasis (PSA) and rheumatoid arthritis (RA).

Foralumab is being developed as both an immunosuppressive and immunomodulatory agent, with therapeutic benefits of rendering T-cells unable to orchestrate an immune response and induction of immune tolerance via maintenance of regulatory T-cells. There is further potential for Foralumab to be combined with the Company's TZLS-501, a fully human anti-IL-6R mAb in development to target autoimmune and inflammatory diseases.

In November 2016, Tiziana announced new data for oral efficacy in humanized mouse models with Foralumab, a major milestone and a potential breakthrough for the treatment of NASH and autoimmune disease. This unique oral technology stimulates the natural gut immune system and potentially provides a therapeutic effect in inflammatory and autoimmune diseases with greatly reduced toxicity. Positive therapeutic effects with Foralumab were consistently demonstrated in animal studies conducted by Prof. Kevan Herold (Yale University) and Prof. Howard Weiner (Harvard University).

On 16 April, 2018, the Group entered into an exclusive license agreement with The Brigham and Women's Hospital, Inc. relating to a novel formulation of Foralumab dosed in a medical device for nasal administration. An investigational new drug application (IND) for the first-in-human evaluation of the nasal administration of Foralumab in healthy volunteers for progressive multiple sclerosis indication was filed in the second quarter of 2018. Subsequent to IND approval, a single-site, double-blind, placebo-controlled, dose-ranging Phase 1 trial with nasally administered Foralumab at 10, 50 and 250 µg per day, consecutively for 5 days to evaluate biomarkers of immunomodulation of clinical responses was initiated in November 2018. The trial conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA, in healthy volunteers. 18 subjects received Foralumab treatment and 9 patients received placebo. The study was completed in September 2019. Phase 1 clinical data demonstrated that nasally administered Foralumab, was well-tolerated and no drug-related safety issues were reported at any of the doses. No drug-related changes were observed in vital signs among subjects at predose, during treatment and at discharge. Nasally administered Foralumab at the 50 µg dose suppressed cytotoxic CD8+ as well as perforin-secreting CD8+ cells, which have been implicated in neurodegeneration in multiple sclerosis (MS). Treatment at 50 µg stimulated production of anti-inflammatory cytokine IL-10 and suppressed production of pro-inflammatory cytokine IFN-γ. Taken together, the treatment showed significant positive effects on the biomarkers for activation of mucosal immunity, which are capable of inducing site-targeted immunomodulation to elicit anti-inflammatory effects. Systemic levels of Foralumab were below the lower quantitation limit of 8 ng/mL suggesting that nasally administered Foralumab appears to exert its effects via nasal epithelium utilizing local and lymphatic immune systems directly. These data support other clinical and pre-clinical studies showing that this route of administration is capable of inducing site-targeted immunomodulation and anti-inflammatory effects. Furthermore, these pharmacodynamic data point to a clinical dose range that Tiziana intends to test in further clinical development among MS patients.

An enteric-coated capsule formulation using a proprietary and novel technology has been developed for oral administration of Foralumab. cGMP manufacturing of clinical trial materials for a Phase 1 study has been completed and an IND was submitted in March 2019.

On September 9, 2019, the FDA granted approval to initiate the Phase 1 clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. The study was completed in December 2019 at Brigham and Women's Hospital (Boston, MA USA). A total of 12 subjects were enrolled; 9 received the single dose of foralumab and 3 received placebo. The median age (range) for the oral foralumab subjects was 23 (21 – 55) years, and for the placebo subjects it was 34 (27 – 51). Of the foralumab subjects, 6 were male and 3 were female. All 3 of the placebo subjects were female. No subjects discontinued the study. Formulated Foralumab powder encapsulated in enteric-coated capsule was well-tolerated at all doses tested and there were no drug-related safety issues observed even at the highest dose of 5 mg in this trial. Based on successful Phase 1 data, we intend to conduct a Phase 1b multiple ascending dose study using Crohn's Disease patients starting in Q2 2022.

A collaborative clinical trial was initiated on November 2, 2020 in Brazil investigating nasally administered Foralumab, either alone or in combination with orally administered dexamethasone ("Dexa") in COVID-19 patients. The clinical study was completed in collaboration with scientific teams at the Harvard Medical School (Boston, USA), and INTRIALS, a full-service Latin American CRO based in São Paulo, Brazil. The objectives of the trial were to assess safety of the treatment and to evaluate if progression of the diseases is delayed with nasally administered 100mcg/day Foralumab (50mcg/nostril). This study enrolled 39 patients randomized in three cohorts: cohort 1, control with no treatment (n=16); cohort 2; nasally administered Foralumab plus 3 days of priming with orally administered 6 mg Dexamethasone (n=11) and cohort 3; nasally administered Foralumab (n=12). The Foralumab treatment regimen was once a day dosing for 10 consecutive days. The trial was completed in January 2021. There were no significant differences between cohort 2 and 3. All treatments were well-tolerated. There were no grade 3 or 4 severe adverse events ("SAEs") in any of the cohorts. The CT scans of the lungs showed the improvement was approximately double that shown in patients treated with Foralumab as compared to those in the control group. The results of the study were published in the peer-reviewed journal, *Frontiers in Immunology* entitled "Nasal Administration of Anti-CD3 Monoclonal Antibody (Foralumab) Reduces Lung Inflammation and Blood Inflammatory Biomarkers in Mild to Moderate COVID-19 Patients: A Pilot Study" in August 2021.

On September 2, 2021 the Company and Precision BioSciences Inc announced an exclusive license agreement to explore Foralumab as an agent to induce tolerance of allogeneic CAR T cells to potentially improve the clinical outcome of CAR T cell therapy. Precision's approach to manufacturing produces CAR T cells that are virtually CD3-negative. Foralumab will be used as a lymphodepletion or tolerizing agent, either alone or in combination with other co-stimulatory molecules, to improve the long-term survival of CAR T cells in cancer treatment.

On May 25, 2021 the Company announced that the first expanded access (EA) patient with secondary progressive multiple sclerosis (SPMS) was dosed with nasally administered Foralumab at the Brigham and Women's Hospital (BWH), Harvard Medical School, Boston, MA. Nasal Foralumab 50 mcg (25 mcg/nostril) was administered in 3-week cycles, with 3 times/week dosing for the first 2 weeks followed by 1 week of rest period. This first-ever clinical study in SPMS patients, under an Individual Patient Expanded Access IND, was to continue for six months to evaluate routine safety, tolerability, and neurological behaviors. The study also examined microglial activation, by positron emission tomography (PET), immunological and neurodegenerative markers to assess clinical responses following the dosing regimen

On March 10, 2022, the Company reported positive clinical data in the first EA SPMS patient following completion of six months of treatment with intranasally administered foralumab, at the Brigham and Women's Hospital (BWH), Harvard University, Boston, MA. In addition to being well-tolerated, both biological and clinical improvements were seen in this patient using Tiziana's novel immunotherapy technology, which, importantly overcame the challenge of delivering this antibody across the blood-brain barrier to affect immunomodulation in the brain using nasal administration.

Foralumab was given to an EA SPMS patient intranasally into each nostril on a regimen of M-W-F for two weeks followed by one week off therapy for a period of six months. This regimen was well-tolerated with associated beneficial clinical and biomarker changes. Importantly, the PET imaging data indicated inhibition of microglial cell activation observed at 3 months following treatment initiation and was sustained at 6 months after treatment start (see Table 1). The reduction in microglial activation was seen in all parts of brain.

**Table 1. Percent Reduction\* in Activated Microglial Cells (AMCs) PET Signal After Starting Intranasal Foralumab as Compared to Baseline, in Whole Brain and Selected Brain Regions**

	<b>WHOLE BRAIN</b>	<b>CEREBRAL CORTEX</b>	<b>THALAMUS</b>	<b>WHITE MATTER</b>	<b>CEREBELLUM</b>
<b>3 MONTHS</b>	-23%	-23%	-20%	-25%	-22%
<b>6 MONTHS</b>	-38%	-38%	-50%	-36%	-38%

\* Percent reduction is based on changes from baseline in SUVR-1, a surrogate index for PET binding potential. SUVR=Standardized Uptake Value Ratio, calculated with reference to a pseudo reference region in cerebral white matter that showed minimal change in PET SUV, across time points.

Consistent with clinical and PET observations, intranasally administered foralumab also downregulated serum levels of pro-inflammatory cytokines, including interferon-gamma (IFN-g), interleukin (IL-18), IL-1 $\beta$  and IL-6, which are associated with multiple sclerosis pathogenesis and progression. Clinical evaluation showed improvement in Timed 25-Foot Walk Test (T25FW), 9-Hole Peg Test (9HPT) and Symbol Digit Modality Test (SDMT). Other published PET studies have shown an increase in activated microglial cells (AMCs) in patients with secondary progressive MS (SPMS), and the increase in AMCs associated with higher scores on the Expanded Disability Status Scale (EDSS), a widely-used scale to measure disability<sup>1,2</sup>. Several FDA-approved drugs, such as TYSABRI<sup>®</sup>, MAYZENT<sup>®</sup> and ZEPOSIA<sup>®</sup> have been shown to suppress microglial activation and exert neuroprotective effects in the central nervous system (CNS) in animal studies but longitudinal assessment of drug effects on microglial activation in exclusive cohorts of SPMS patients are lacking.

Prior to treatment, this patient had continued to experience worsening disease progression despite several MS therapies, including B cell depletion. The patient’s gait and limb strength had been deteriorating over the prior two years. The patient then started on intranasal foralumab, which stabilized his disease course. Tiziana also received FDA authorization to continue treating this patient for an additional 6 months to determine if 12 months of consistent treatment maintains clinical stabilization and provides sustained clinical benefits.

On January 20, 2022, FDA approved enrollment of a second EA SPMS patient for treatment with intranasal foralumab.

These data were presented in a virtual Key Opinion Leader (KOL) event hosted by Tiziana on March 14<sup>th</sup>, 2022, entitled “Foralumab Clinical Update in Multiple Sclerosis; A Landmark Study with Intranasal Immunotherapy” featuring four Key Opinion Leaders and a live Q&A session. The company plans to continue treatment of EA SPMS patients at Brigham and Women’s Hospital and elsewhere and continue evaluation of foralumab treatment.

We are evaluating subcutaneous administration of Foralumab to delay onset and progression of T1DM in at-risk individuals. T1DM is characterized as a chronic and progressive autoimmune disease leading to the destruction of insulin-producing  $\beta$ -cells of the pancreas. Teplizumab (Provention Bio), a humanized Fc-mutated anti-CD3 monoclonal antibody that alters the function of the T-lymphocytes that mediate the destruction of the insulin-producing  $\beta$ -cell is seeking FDA approval. The Company believes that Foralumab, a fully human anti-CD3 mAb, would have a better safety profile and clinical benefit than Teplizumab based on Foralumab’s fully human protein sequence and binding affinity for CD3e compared to Teplizumab. cGMP manufacturing of Foralumab solution for subcutaneous injection drug product was initiated in April 2022 and IND submission is anticipated in Q3 2022.

In addition, on August 18, 2020 the United States Patent and Trademark Office, or USPTO, granted us a patent on use and methods of treatment of Crohn’s disease with Foralumab, its proprietary fully human monoclonal antibody, and all other anti-CD3 mAbs. The CD3 (cluster of differentiation 3) is a protein complex on T-cells, which is important for the regulation of the immune system. The patent was published by the USPTO on September 1, 2020 as Patent No. 10,759,858. Recently, we also announced the issuance of the first-ever patent on oral administration of anti-CD3 mAbs for treatment of human diseases (Patent No. 10,688,186). We believe the grant of this additional composition-of-matter and use patent further strengthens our intellectual property, consisting of proprietary technologies on oral and nasal administration of Foralumab and other anti-CD3 mAbs for the treatment of human diseases.

On July 16, 2020, we announced that we had submitted a patent application on the potential use of Foralumab, a fully human anti-CD3 mAbs, to improve success of chimeric antigen receptor T-cell, or CAR-T, therapy for cancer and other human diseases. The patent application conveys inventions related lymphodepletion to improving CAR-T expansion and/or survival using anti-CD-3 mAbs administered either alone or in combination with other co-stimulatory molecules, such as an anti-IL-6R mAb, an anti-CD28 mAb or specific inhibitors of signaling pathways of phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or mammalian target of rapamycin (mTOR).

On July 31, 2020, we announced that we had submitted a patent application for the potential use of nasally administered Foralumab, a fully human anti-CD3 mAb, for the treatment of COVID-19 either alone or in combination with other anti-viral drugs. Recent clinical studies implied that a combination of anti-inflammatory and anti-viral drugs may be more effective to treat patients at different stages of COVID-19 disease.

We are accelerating development of a fully human mAb targeting the IL-6R (TZLS-501) for which the intellectual property was licensed 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 acute inflammation resulting from infection with viral agents such as Coronaviruses and 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.)

The Company is advancing development of TZLS--501 for treatment of Idiopathic Pulmonary Fibrosis (IPF). Tocilizumab (Actemra®, Roche) a humanized interleukin-6 (IL-6) receptor mAb antagonist. was approved by the FDA as a subcutaneous injection for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), a debilitating condition with limited treatment options. Actemra® is the first biologic therapy approved by the FDA for the treatment of the disease. The Company believes that fully human TZLS-501 administered by inhalation directly to inflamed lung will have greater clinical benefit and an improved safety profile compared to parenterally administered Actemra based on higher binding affinity for IL6 receptor complex and focused delivery to the target inflamed pulmonary tissue. Also TZLS-501 reduces circulating levels of IL6 via the trans-signaling pathways.

On April 9, 2020 The Company announced that it had developed investigational new technology to treat COVID-19 infections, consisting of direct delivery of anti-IL-6 receptor (anti-IL-6R) monoclonal antibodies (mAbs) into the lungs using a handheld inhaler or nebulizer for treatment of patients infected with COVID-19 (SARS-CoV-2) coronavirus. On June 29, 2020 the Company announced that it was advancing GMP manufacturing of TZLS-501 with STC Biologics concurrently with the development of inhalation technology using a hand-held nebulizer with Sciarra Laboratories and safety toxicology studies in Cynomolgus monkeys with ITR Canada Laboratories. GMP batches were initiated in January 2021 and completed in March 2021. Safety inhalation toxicology studies were initiated in November 2020 and completed in March 2021. Technological assessment of nebulizers for inhalation treatment of patients was initiated in September 2020 and completed in February 2021. Going forward, the Company has refocused TZLS-501 development for treatment of IPF given the plethora of available COVID treatment options. Additional cGMP manufacturing activity is scheduled in April 2022 to support an IND in Q3 2022.

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 pan KRAS mutations in NSCLC patients.

To date, Milciclib has been studied in a total of eight completed Phase 1 and 2 clinical trials in 316 patients. In these trials, Milciclib was observed to be well-tolerated and showed initial signals of anti-tumor action. Prior to in-licensing, Milciclib was granted orphan designation by the European Commission and by the U.S. Food and Drug Administration ("FDA") for the treatment of malignant thymoma and an aggressive form of thymic carcinoma in patients previously treated with chemotherapy. In two Phase 2a trials, CDKO-125a-006 and CDKO125a-007, Milciclib showed signs of slowing disease progression and acceptable safety.

In the first half of 2017, the Group initiated a Phase 2a trial (CDKO-125a-010) of Milciclib to explore safety, tolerability and antitumor activity of milciclib as a single therapy in Sorafenib-resistant patients with unresectable or metastatic HCC and good liver function.. Typically, this population of patients have an advanced form of the disease with poor prognosis and an average overall survival expectancy of 3-5 months. The compound was administered as home-based treatment at the dose of 100 mg/day for 4 consecutive days a week in a 4-week cycle (4 days on/3 days off x q4 wks) for a total of 24 weeks.

The Phase 2a trial was completed in June 2019 with clinical safety result reported in July 2019 and efficacy results reported in September 2019.

The clinical activity assessment in evaluable patients was based on the independent radiological review using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

- 14 out of 28 (50%) evaluable patients completed 6-month duration of the trial.
- Both median TTP and PFS were 5.9 months (95% Confidence Interval (“CI”) 1.5-6.7 months) out of the 6-months duration of the trial.
- 16 of 28 (57.1%) evaluable patients showed ‘Stable Disease’
- One patient (3.6%) showed unconfirmed ‘Partial Response’ (PR).
- 17 of 28 (60.7%) evaluable patients showed ‘Clinical Benefit Rate’ defined as CBR=CR+PR+SD (with CR representing Complete Remission).

Since overexpression of CDKs and dysregulation in pRB pathway (regulates transcription factors critical for cell cycle progression) are prominently associated with tumor cell resistance to certain chemotherapeutic drugs, inhibition of multiple CDKs is an appealing approach to improve clinical responses in cancer patient’s refractory to existing treatment options. A Phase 1 dose-escalation study of Milciclib in combination with gemcitabine in patients with refractory solid tumors exhibited clinical activity in patients including those refractory to gemcitabine. Milciclib shows inhibitory effects against multiple cell lines with mutationally active G12D (non-small cell lung carcinoma), G13D (colorectal cancer), G12V(pancreatic cancer), and G12C (pancreatic cancer). The Company also intends to evaluate milciclib in combination with gemcitabine for treatment of pan KRAS mutations in NSCLC patients. cGMP manufacturing of milciclib capsules was completed in January 2022 and IND filing is anticipated in Q2 2022.

## Our Competitive Strengths

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

- **Advanced, novel pipeline.** We have an advanced pipeline of novel and proprietary drug candidates, including antibodies and small molecules, to address high unmet medical needs in the inflammation, autoimmune and oncology markets with significant commercial potential.
- **Proprietary technology.** Our proprietary technology enables the development of alternative routes of administration of antibodies, including oral delivery. We believe that oral and nasal routes of delivery will alleviate the significant time and cost burden associated with other routes of administration, including intravenous delivery.
- **Broad and engaged network of experts.** Our strong relationships with key opinion leaders contribute to our clinical development efforts and position us well to support our products, if approved. Dr. Napoleone Ferrara, Dr. Arun Sanyal, Dr. Kevan Herold, and Dr. Howard Weiner are among the thought leaders on our scientific advisory committee.
- **Specialized expertise and focus on oncology and inflammation.** Our management team, including Dr. Kunwar Shailubhai, Jules Jacob, 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 Crohn's disease using a novel and proprietary oral formulation by initiating a Phase 1b trial in the second quarter of 2022. 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 progressive MS, was initiated in November 2018. The study was completed in September 2019.
- Accelerate development and cGMP manufacturing of our product candidate, TZLS-501, a fully human mAb targeting the IL-6 receptor (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 especially IPF. Complete additional cGMP manufacturing and IND-enabling GLP safety toxicology studies in Cynomolgus monkeys as required and evaluate/qualify hand-held nebulizers for pulmonary administration of TZLS-501 for IPF treatment.
- Continue to advance the clinical development and obtain regulatory approval for our lead oncology product candidate, Milciclib, as a combination therapy for the treatment of refractory solid tumors (being cancers which are non-responsive or become resistant to treatment), especially NSCLC by filing an IND in Q2 2022.

Continue development of platform drug delivery technologies that provide competitive advantage over existing approved products, e.g. inhalation delivery, nasal delivery and enteric delivery of mAbs.

Continue relationship with Precision Biosciences to improve CAR-T therapy using foralumab immunomodulation to enhance survival of CAR-T cells

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

### DEVELOPMENT PIPELINE

	Subject	PC	IND	Phase 1/IAP	Phase 2	Phase 3
<b>FORALUMAB</b> <i>Fully human anti-CD3 mAb</i>	Intranasal	Progressive Multiple Sclerosis (expanded program)			Ongoing IAP, 6 months data showed positive clinical response	
	Oral	Crohn's Disease			2Q 2022 Phase 1b	
	Subcutaneous	Type 1 Diabetes			2Q-2022 IND Submission	
<b>ANTI IL-6 RECEPTOR</b> <i>Fully human mAb</i>	Inhalation	Pulmonary Fibrosis			3Q-2022 IND Submission	
<b>MILCICLIB</b> <i>Pan-CDK inhibitor</i>	Oral	Milciclib + Gemcitabine in NSCLC Kras+ mutants			2Q-2022 IND Submission	



## 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 (CD3 $\epsilon$ ) 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 inflammatory bowel disease such as Crohn's disease, MS, type-1 diabetes, or T1D, 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.

On April 16, 2018, the Group entered into an exclusive license agreement with The Brigham and Women's Hospital, Inc. relating to a novel formulation of Foralumab dosed in a medical device for nasal administration. An investigational new drug application (IND) for the first-in-human evaluation of the nasal administration of Foralumab in healthy volunteers for progressive multiple sclerosis indication was filed in the second quarter of 2018. Subsequent to IND approval, a single-site, double-blind, placebo-controlled, dose-ranging Phase 1 trial with nasally administered Foralumab at 10, 50 and 250  $\mu$ g per day, consecutively for 5 days to evaluate biomarkers of immunomodulation of clinical responses was initiated in November 2018. The trial conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA, in healthy volunteers. 18 subjects received Foralumab treatment and 9 patients received placebo. The study was completed in September 2019. Phase 1 clinical data demonstrated that nasally administered Foralumab, was well-tolerated and no drug-related safety issues were reported at any of the doses. No drug-related changes were observed in vital signs among subjects at predose, during treatment and at discharge. The mean blood pressure (BP) during the 5 days of treatment were; Cohort A (10  $\mu$ g/d):124/73, Cohort B (50  $\mu$ g/d): 119/67 and Cohort C (250  $\mu$ g/d):113/65 compared to placebo:118/67). Heart rates, respiratory rates and oral temperatures were unchanged among the 3 cohorts compared to the placebo. Nasally administered Foralumab at the 50  $\mu$ g dose suppressed cytotoxic CD8+ as well as perforin secreting CD8+ cells, which have been implicated in neurodegeneration in multiple sclerosis (MS). Treatment at 50 mg stimulated production of anti-inflammatory cytokine IL-10 and suppressed production of pro-inflammatory cytokine IFN- $\gamma$ . Taken together, the treatment showed significant positive effects on the biomarkers for activation of mucosal immunity, which are capable of inducing site-targeted immunomodulation to elicit anti-inflammatory effects. Based on the results we intend to conduct a Phase 2 trial in secondary progressive MS (SPMS) patients starting in Q4 2021.

An enteric-coated capsule formulation using a proprietary and novel technology has been developed for oral administration of Foralumab. cGMP manufacturing of clinical trial materials for a Phase 1 study has been completed and an IND has been submitted in March 2019.

On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. The study was completed in December 2019 at Brigham and Women's Hospital (Boston, MA USA). A total of 12 subjects were enrolled; 9 received the single dose of foralumab and 3 received placebo. The median age (range) for the oral foralumab subjects was 23 (21 – 55) years, and for the placebo subjects it was 34 (27 – 51). Of the foralumab subjects, 6 were male and 3 were female. All 3 of the placebo subjects were female. No subjects discontinued the study. Formulated Foralumab powder encapsulated in enteric-coated capsule was well-tolerated at all doses tested and there were no drug-related safety issues observed even at the highest dose of 5 mg in this trial. Based on successful Phase 1 data, we intend to conduct a Phase 1b study using Crohn's Disease patients starting in the second quarter of 2021.

A collaborative clinical study was initiated on November 2, 2020, investigating nasally administered Foralumab either alone or in combination with orally administered dexamethasone in COVID-19 patients in Brazil. In view of the importance and urgency, scientific teams at the Harvard Medical School, Santa Casa de Misericórdia de Santos Hospital (Jabaquara, Santos, Brazil) and at our company closely collaborated to facilitate initiation of this study in expedited time frames. The clinical trial was coordinated by the team at INTRIALS, a leading, full-service Latin America Clinical Research Organization, (CRO) based in Sao Paulo City, Brazil. The trial was completed in January 2021. This trial, the first-ever trial on nasal administration of Foralumab for treatment of COVID-19, is of enormous significance because the underlying scientific approach is to modulate immune system, which is dysregulated and crippled to protect against the virus. The results of the trial were All treatments were well-tolerated. There were no grade 3 or 4 severe adverse events ("SAEs") in any of the cohorts. The CT scans of the lungs showed the improvement was approximately double that shown in patients treated with Foralumab as compared to those in the control group. The results of the study were published in the peer-reviewed journal, *Frontiers in Immunology* entitled "Nasal Administration of Anti-CD3 Monoclonal Antibody (Foralumab) Reduces Lung Inflammation and Blood Inflammatory Biomarkers in Mild to Moderate COVID-19 Patients: A Pilot Study" in August 2021. The study served as "proof of concept" that nasal administration of foralumab could be used to treat systemic inflammatory response related to COVID infection and could be used for treatment of other systemic inflammatory diseases. The Company has refocused development of Foralumab for treatment of Crohn's disease (oral treatment) and progressive MS (nasal treatment) utilizing site specific delivery technologies to limit systemic exposure of foralumab which achieving local delivery to inflamed tissue.

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.

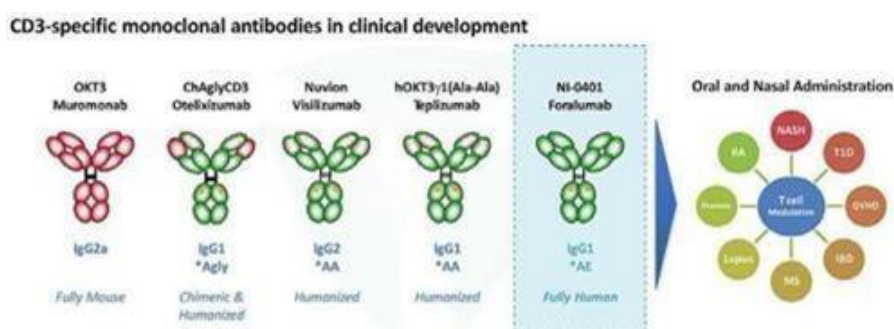
### Autoimmune and Inflammatory Diseases

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 binding, 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 Syndrome (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-lipopopolysaccharide 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 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.

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An enteric-coated capsule formulation using a proprietary and novel technology has been developed for oral administration of Foralumab. cGMP manufacturing of clinical trial materials for a Phase 1 study has been completed and an IND was submitted in March 2019.

On September 9, 2019, the FDA granted approval to initiate the Phase I clinical trials to evaluate the safety and pharmacokinetics of oral Foralumab at 1.25, 2.5 and 5.0 mg/day as a single ascending dose study. The study was completed in December 2019 at Brigham and Women's Hospital (Boston, MA USA). Formulated Foralumab powder encapsulated in enteric-coated capsule was well-tolerated at all doses tested and there were no drug-related safety issues observed even at the highest dose of 5 mg in this trial. Based on successful Phase 1a data, we intend to conduct a Phase 1b study using Crohn's Disease patients starting in the second quarter of 2022.

#### *Clinical Development Plan*

##### ***Phase 1a Clinical Trial for Oral Foralumab in Healthy Volunteers***

This Phase 1a trial, conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, was a single-site, double-blind, placebo-controlled, single ascending dose ("SAD") study in healthy subjects in which Foralumab was orally administered at 1.25, 2.5 and 5.0 mg per dose as enteric-coated capsules. The primary endpoint of the Phase 1 study is safety and tolerability of Foralumab in humans. Each cohort comprised of 4 subjects, of whom 3 received Foralumab treatment and 1 received a placebo capsule. All subjects completed the trial without any safety concerns at any of the doses.

A Phase 1b multiple ascending dose trial is expected to be initiated in the second quarter of 2022 followed by a Phase 2 trial with the intent to treat patients with Crohn's disease.

##### ***Proposed Phase 1b Clinical Trial for Oral Foralumab Treatment of Crohn's Disease***

This is an double-blind, multiple ascending dose (MAD) study of orally administered foralumab in male and female subjects with mild-to-moderate active CD. Two different doses of foralumab enteric coated capsules (2.5 mg, and 5 mg), administered once daily for 5 consecutive days) will be studied for safety and tolerability. Subjects will be hospitalized in clinic for 5 days. Sixteen subjects are planned and the study will consist of 2 different dose groups with 8 subjects per dose group (6 active-treated, 2 placebo treated), i.e., each dose group will be treated with one of two different ascending doses of foralumab enteric coated capsules (, 2.5 mg, or 5 mg) once daily. Subjects in Cohort 1 will receive an initial dose of 2.5 mg. The SMC review will be performed after all the 8 randomized subjects are dosed with the initial 2.5 mg dose. The dose can be escalated to 5 mg daily in Cohort 2 subjects, only if there are no safety findings in the SMC review of the results of the 2.5 mg dose

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. Secondary endpoints , systemic foralumab circulation examined by PK; change from baseline in inflammatory responses by analysis of fecal calprotectin and incidence of detectable anti-drug antibody (ADA). Exploratory endpoints will include: change from baseline in T-cell subsets in blood and detection of foralumab in stool samples

##### ***Phase 1 Clinical Trial of Nasally-Administered Foralumab for Treatment of Secondary Progressive Multiple Sclerosis***

This Phase 1 trial, conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA, was a single-site, double-blind, placebo-controlled, dose-ranging study with nasally administered Foralumab at 10, 50 and 250 µg per day, consecutively for 5 days in healthy volunteers for the treatment of progressive multiple sclerosis (pMS). 18 subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. Prominent results included:

- Treatment was well-tolerated and no drug-related safety issues were reported at any of the doses.
- No drug-related changes were observed in vital signs among subjects at predose, during treatment and at discharge. The mean blood pressure (BP) during the 5 days of treatment were; Cohort A (10 µg/d):124/73, Cohort B (50 µg/d): 119/67 and Cohort C (250 µg/d):113/65 compared to placebo:118/67). Heart rates, respiratory rates and oral temperatures were unchanged among the 3 cohorts compared to the placebo.

- Nasally administered Foralumab at the 50 µg dose suppressed cytotoxic CD8+ as well as perforin secreting CD8+ cells, which have been implicated in neurodegeneration in multiple sclerosis (MS).
- Treatment at 50 mg stimulated production of anti-inflammatory cytokine IL-10 and suppressed production of pro-inflammatory cytokine IFN-γ.
- Taken together, these results suggest stimulation of Tregs that are needed to provide clinical benefits

On May 25, 2021 the Company announced that the first expanded access (EA) patient with secondary progressive multiple sclerosis (SPMS) was dosed with nasally administered Foralumab at the Brigham and Women’s Hospital (BWH), Harvard Medical School, Boston, MA. Nasal Foralumab 50 mcg (25 mcg/nostril) was administered in 3-week cycles, with 3 times/week dosing for the first 2 weeks followed by 1 week of rest period. This first-ever clinical study in SPMS patients, under an Individual Patient Expanded Access IND, was to continue for six months to evaluate routine safety, tolerability, and neurological behaviors. The study also examined microglial activation, by positron emission tomography (PET), immunological and neurodegenerative markers to assess clinical responses following the dosing regimen

On March 10, 2022, the Company reported positive clinical data in the first SPMS EA patient following completion of six months of treatment with intranasally administered foralumab, at the Brigham and Women’s Hospital (BWH), Harvard University, Boston, MA. In addition to being well-tolerated, both biological and clinical improvements were seen in this patient using Tiziana’s novel immunotherapy technology, which, importantly overcame the challenge of delivering this antibody across the blood-brain barrier to affect immunomodulation in the brain using nasal administration.

Foralumab was given to an SPMS patient intranasally into each nostril on a regimen of M-W-F for two weeks followed by one week off therapy for a period of six months. This regimen was well-tolerated with associated beneficial clinical and biomarker changes. Importantly, the PET imaging data indicated inhibition of microglial cell activation observed at 3 months following treatment initiation and was sustained at 6 months after treatment start (see Table 1). The reduction in microglial activation was seen in all parts of brain.

**Table 1. Percent Reduction\* in Activated Microglial Cells (AMCs) PET Signal After Starting Intranasal Foralumab as Compared to Baseline, in Whole Brain and Selected Brain Regions**

	<b>WHOLE BRAIN</b>	<b>CEREBRAL CORTEX</b>	<b>THALAMUS</b>	<b>WHITE MATTER</b>	<b>CEREBELLUM</b>
<b>3 MONTHS</b>	-23%	-23%	-20%	-25%	-22%
<b>6 MONTHS</b>	-38%	-38%	-50%	-36%	-38%

\* Percent reduction is based on changes from baseline in SUVR-1, a surrogate index for PET binding potential. SUVR=Standardized Uptake Value Ratio, calculated with reference to a pseudo reference region in cerebral white matter that showed minimal change in PET SUV, across time points.

Consistent with clinical and PET observations, intranasally administered foralumab also downregulated serum levels of pro-inflammatory cytokines, including interferon-gamma (IFN-g), interleukin (IL-18), IL-1 $\beta$  and IL-6, which are associated with multiple sclerosis pathogenesis and progression. Clinical evaluation showed improvement in Timed 25-Foot Walk Test (T25FW), 9-Hole Peg Test (9HPT) and Symbol Digit Modality Test (SDMT). Other published PET studies have shown an increase in activated microglial cells (AMCs) in patients with secondary progressive MS (SPMS), and the increase in AMCs associated with higher scores on the Expanded Disability Status Scale (EDSS), a widely-used scale to measure disability<sup>1,2</sup>. Several FDA-approved drugs, such as TYSABRI<sup>®</sup>, MAYZENT<sup>®</sup> and ZEPOSIA<sup>®</sup> have been shown to suppress microglial activation and exert neuroprotective effects in the central nervous system (CNS) in animal studies but longitudinal assessment of drug effects on microglial activation in exclusive cohorts of SPMS patients are lacking.

Prior to treatment, this patient had continued to experience worsening disease progression despite several MS therapies, including B cell depletion. The patient's gait and limb strength had been deteriorating over the prior two years. The patient then started on intranasal foralumab, which stabilized his disease course. Tiziana also received FDA authorization to continue treating this patient for an additional 6 months to determine if 12 months of consistent treatment maintains clinical stabilization and provides sustained clinical benefits.

On January 20, 2022, FDA allowed enrollment of a second EA SPMS patient for treatment with intranasal foralumab.

These data were presented in a virtual Key Opinion Leader (KOL) event hosted by Tiziana on March 14<sup>th</sup>, 2022, entitled "Foralumab Clinical Update in Multiple Sclerosis; A Landmark Study with Intranasal Immunotherapy" featuring four Key Opinion Leaders and a live Q&A session.

The company plans to continue treatment of EA SPMS patients at Brigham and Women's Hospital and elsewhere and continue evaluation of foralumab treatment.

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 normalization 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 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/m<sup>2</sup>) 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 IFN $\gamma$  *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  $\mu$ g 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. A Phase 2a trial (CDKO-125a-010) for Milciclib as a single therapy in patients with HCC was completed in June 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 safety and efficacy outcomes from the Phase 2a trial were presented at the ASCO 2020 Scientific Meeting.

## 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 was the overall tolerability profile, evaluated based on laboratory findings and adverse events emerging during the trial. The occurrence of adverse events and laboratory tests was performed weekly during treatment. All the enrolled patients who received at least one drug administration were evaluated for safety. 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. As an exploratory endpoint, the expression of micro-RNAs and their possible association with Milciclib treatment was investigated. ... As an exploratory endpoint, the expression of micro-RNAs and their possible association with Milciclib treatment was investigated. The trial successfully met the primary endpoint that oral treatment with Milciclib was well tolerated with manageable toxicities and no recorded drug related deaths. The secondary endpoints for clinical activity assessment were based on the independent radiological review using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) Positive demonstrated clinical activity included:

1. 50% (14 out of 28) evaluable patients completed 6-month duration of the trial.
2. 64% (9 out of 14) patients requested and were approved by their respective ethical committees to continue the treatment.
3. Both median time to progression (TTP) and progression free survival (PFS) were 5.9 months (95% Confidence Interval (“CI”) 1.5-6.7 months) out of the 6-months duration of the trial.
4. Approximately 57% of evaluable patients showed ‘Stable Disease’ (SD; met at least once in an 8-week interval) and 3.6% patients showed ‘Partial Response’ (PR).
5. Approximately 61% of patients showed ‘Clinical Benefit Rate’ defined as CBR=CR+PR+SD (with CR representing Complete Remission).
6. Five patients on compassionate use continued the treatment for a total of 9, 9, 11, 13 and 16 months, respectively. Two patients continuing the treatment have reached 16 months.

Four patients 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.

Tiziana plans to conduct a Phase 2 study combination therapy of milciclib and gemcitabine in Non-Small Cell Lung Cancer (NSCLC) patients with a broad-spectrum of KRAS mutations (except G12C mutation) after failure of at least one line of standard-of-care (SoC) therapy. NSCLC is the most common type of lung cancer, occurring in approximately 80% of patients. Due to the asymptomatic nature of early disease, many patients are diagnosed with later stages of disease, and typically have short overall survival. In the United States, at initial diagnosis of NSCLC, approximately 55% of patients have distant metastases with a 5-year survival rate of 7%, despite the recent development of novel anticancer therapies and regimens. The results of clinical trials with sotorasib (Lumakras™) demonstrated that selective targeting of a single KRAS mutation is a promising therapeutic strategy. Although there is a clear benefit to target KRAS directly, KRAS represents a challenging molecular target due to the lack of suitable drug pockets where a small molecule can bind. An alternative approach is to target downstream signaling pathways. The rationale for evaluation of milciclib in combination with gemcitabine is suggested by preclinical studies conducted on a non-small cell lung xenograft model that demonstrated the efficacy of milciclib in terms of antitumor activity, both as a single agent and in combination with gemcitabine, at well tolerated doses. Given that gemcitabine is used for treatment of both pancreatic cancer (for which gemcitabine is the standard therapy) and NSCLC (for which gemcitabine is used in combination with cisplatin), an evaluation of the feasibility of the combination of milciclib and gemcitabine is considered appropriate in view of future uses in these diseases. In addition, the 2 compounds showed non-overlapping toxicities when administered as single agents, providing an additional rationale for their evaluation in combined treatment in the clinical setting.

Furthermore, in the Phase 1 CDKO-125a-004 study, 16 patients were treated with milciclib at 3 dose levels administered once daily for 7 days, followed by 7 days off treatment in a 4-week cycle and with a fixed dose of gemcitabine administered intravenously on Days 1, 8, and 15 in a 4-week cycle. Overall, the combination was well tolerated and showed clinical benefit with 1 PR and 10 patients with SD. The PR was documented in a patient with NSCLC whose disease was refractory to gemcitabine.

## Clinical Data

Milciclib has been studied in a total of eight completed 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.

<b>Trial</b>	<b>Patient Population</b>	<b>Treatment Schedule / Dosing</b>	<b>Key Findings</b>
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	<i>Pharmacokinetics:</i>  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).  <i>Clinical observations:</i>  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.

<b>Trial</b>	<b>Patient Population</b>	<b>Treatment Schedule / Dosing</b>	<b>Key Findings</b>
CDKO-125a-002	<p>Recurrent malignant glioma 28 patients (Phase 1)</p> <p>34 patients (Phase 2)</p>	<p>Escalating oral doses of 18, 36, 54 and 72 mg/m<sup>2</sup> once a day for 14 consecutive days followed by 7 days of rest in a 3-week cycle</p> <p>54 mg/m<sup>2</sup> (RP2D)</p>	<p><i>Pharmacokinetics:</i></p> <p>Results indicated that the pharmacokinetics of Milciclib was dose-independent in the dose range 18 – 72 mg/m<sup>2</sup>.</p> <p>Systemic exposure values of Milciclib maleate accumulated by a factor of 3</p> <p><i>Clinical observations:</i></p> <p>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).</p> <p>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 (<math>\geq</math> 6 months) was observed in one patient whose SD lasted for 24.9 months.</p> <p><i>Safety:</i></p> <p>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 (<math>\geq</math>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 (<math>\geq</math>90 vs. &lt;90), age (&lt;40 vs. <math>\geq</math>40) and interval between initial diagnosis and current recurrence (<math>\geq</math>52 weeks vs. &lt;52 weeks) indicated a better survival outcome for patients whose interval between initial diagnosis and current recurrence was (<math>\geq</math>52 weeks). Given the non-comparative nature of the study, it cannot be said whether the treatment played any role in this result.</p> <p>The influence of other factors cannot be excluded but was not apparent in the current sample.</p>

<b>Trial</b>	<b>Patient Population</b>	<b>Treatment Schedule / Dosing</b>	<b>Key Findings</b>
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/m <sup>2</sup>  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/m <sup>2</sup>	<i>Pharmacokinetics:</i>  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 C <sub>max</sub> (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 C <sub>max</sub> and AUC accumulated by a factor of 2-4, independent of the dose-level.  <i>Clinical observations:</i>  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/m <sup>2</sup> /day. One disease stabilization maintained for 12 cycles (10.5 months) at 48 mg/m <sup>2</sup> /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/m <sup>2</sup> 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/m <sup>2</sup> /day) on Days 1, 8, 15 over 30 minutes every 4 weeks	<i>Pharmacokinetics:</i>  Pharmacokinetic parameters (C <sub>max</sub> , 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.  <i>Clinical observations:</i>  One PR in 14 evaluable patients (7.1%) and one SD in 10 patients (71.4%).  Disease stabilizations lasting ≥ 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/m <sup>2</sup> /day plus 1000 mg/m <sup>2</sup> /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

<b>Trial</b>	<b>Patient Population</b>	<b>Treatment Schedule / Dosing</b>	<b>Key Findings</b>
CDKO-125a-005	Malignant pleural mesothelioma  38 patients	150 mg/day orally administered for 7 consecutive days every 14 days in 2-week cycles	<i>Pharmacokinetics:</i>  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.  <i>Clinical observations:</i>  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	<i>Clinical Observations:</i>  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	<i>Clinical Observations:</i>  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.

<b>Trial</b>	<b>Patient Population</b>	<b>Treatment Schedule / Dosing</b>	<b>Key Findings</b>
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	<p>The trial successfully met the primary endpoint that oral treatment with Milciclib was well tolerated with manageable toxicities and no recorded drug related deaths.</p> <ul style="list-style-type: none"> <li>● The secondary endpoints for clinical activity assessment were based on the independent radiological review using the modified Response Evaluation Criteria in Solid Tumors (mRECIST)</li> <li>● Positive demonstrated clinical activity included: <ol style="list-style-type: none"> <li>1. 50% (14 out of 28) evaluable patients completed 6-month duration of the trial.</li> <li>2. 64% (9 out of 14) patients requested and were approved by their respective ethical committees to continue the treatment.</li> <li>3. Both median time to progression (TTP) and progression free survival (PFS) were 5.9 months (95% Confidence Interval (“CI”) 1.5-6.7 months) out of the 6-months duration of the trial.</li> <li>4. Approximately 57% of evaluable patients showed ‘Stable Disease’ (SD; met at least once in an 8-week interval) and 3.6% patients showed ‘Partial Response’ (PR).</li> <li>5. Approximately 61% of patients showed ‘Clinical Benefit Rate’ defined as CBR=CR+PR+SD (with CR representing Complete Remission).</li> <li>6. Five patients on compassionate use continued the treatment for a total of 9, 9, 11, 13 and 16 months, respectively. Two patients continuing the treatment have reached 16 months.</li> </ol> </li> </ul>

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.

### ***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.).

We intend to refocus development and cGMP manufacturing of TZLS-501. Originally TZLS-501 clinical development was intended for treatment of "cytokine storm"-induced lung damage in COVID-19 patients by aerosol delivery to lung, however, with the increasing number of effective therapies and vaccines now available for COVID patients the Company will use the same technology for treatment of IPF.

On April 9, 2020 The Company announced that it had developed investigational new technology to treat COVID-19 infections, consisting of direct delivery of anti-IL-6 receptor (anti-IL-6R) monoclonal antibodies (mAbs) into the lungs using a handheld inhaler or nebulizer for treatment of patients infected with COVID-19 (SARS-CoV-2) coronavirus. On June 29, 2020 the Company announced that it was advancing GMP manufacturing of TZLS-501 with STC Biologics concurrently with the development of inhalation technology using a hand-held nebulizer with Sciarra Laboratories and safety toxicology studies in Cynomolgus monkeys with ITR Canada Laboratories. GMP batches were initiated in January 2021 and completed in March 2021. Safety inhalation toxicology studies were initiated in November 2020 and completed in March 2021. Technological assessment of nebulizers for inhalation treatment of patients was initiated in September 2020 and completed in February 2021.

The development studies conducted to date will be used to support submission of an IPF IND in Q3 2022 and additional cGMP manufacturing of TZLS-501 drug substance at STC Biologics in April 2022 and drug product at Sciarra Labs in May 2022 will support a Phase 1a single ascending dose study.

### ***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 Crohn's disease, progressive MS and other autoimmune and inflammatory diseases.

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 18, 2022 our intellectual property portfolio was made up as follows:

Family	Subject	Priority	Status	Expires	Jurisdiction
Foralumab TZL S-401	Methods of use (autoimmune or inflammatory diseases and disorders)	2004	Issued	2025	Australia, Canada, China, Hong Kong, Israel, Japan, Mexico, Norway, Singapore, South Africa, Ukraine, Armenia, Austria, Azerbaijan, Belgium, Belarus, Switzerland, Germany, Denmark, Spain, France, United Kingdom, Ireland, Italy, Kyrgyzstan, Kazakhstan, Luxembourg, Moldova, Netherlands, Portugal, Russian Federation, Sweden, Tajikistan, and Turkmenistan
	Composition and methods of use	2004	Issued	2025	United States, Armenia, Australia, Austria, Azerbaijan, Belarus, Brazil, 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, United Kingdom, and Ukraine
	Methods of use (in combination with anti-IL-6/IL-6R antibodies)	2011	Pending	2032	United States
	Formulations and dosing regimen	2016	Issued/ Pending	2037	United States Pending: Australia, Canada, China, Europe, Hong Kong, Israel, Japan, United States
	Methods of use (CNS disorders)	2017	Pending	2038	Canada, Europe, Japan, United States
	Methods of use (gastrointestinal/autoimmune/inflammatory)	2018	Pending	2039	Australia, Canada, China, Europe, Hong Kong, Japan, United States
	Methods of use (CAR-T therapies)	2020	Pending	2041	PCT
	Methods of use (coronavirus)	2020	Pending	2041	PCT
	Method of administering foralumab by subcutaneous injection	2021	Pending	2042	United States (Provisional)
Miliciclib TZL S-201	Composition of matter, methods of use, process of manufacturing	2003	Issued/ Pending	2024	United States, Europe, Brazil, Eurasia, Africa, 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, Thailand, Trinidad & Tobago, Tunisia, Ukraine, Uzbekistan, Vietnam Pending: United States, Egypt, Venezuela
	Methods of use (multiple indications)	2008; 2009	Issued	2029; 2030	United States, Europe, China, Hong Kong, Japan
	Methods of use (combination therapies with cytotoxics)	2008; 2009	Issued/ Pending	2029; 2030	United States, Europe, China, Hong Kong, Japan Pending: Europe
	Compositions of related entities (salts and crystal forms), formulations and methods of treatment	2009	Issued	2030	United States, Europe, China, Hong Kong, Japan
	Methods of use (combination therapies with therapeutic antibodies)	2006	Issued	2027	United States, Europe, China, Japan
	Therapeutic combinations of Miliciclib for use in the treatment of cancer	2017	Issued/ Pending	2038	United States Pending: United States, Europe, Canada, Japan, Hong Kong
	Enteric-coated pharmaceutical formulations comprising miliciclib	2022	Pending	2043	United States (provisional)
	Method of treating KRAS mutated cancers by administering miliciclib and a chemotherapy	2021	Pending	2042	United States (provisional)

<b>Anti IL-6/IL-6R Antibody T ZL S-501</b>	Composition of matter and methods of use	2009	Issued	2029	United States, Austria, Australia, Belgium, Canada, China, Denmark, France, Germany, India, Ireland, Israel, Italy, Japan, Luxembourg, Mexico, Netherlands, Spain, Sweden, Switzerland and United Kingdom Pending: United States, Japan
	Compositions of IL-6/IL-6R antibodies and methods of use thereof (coronavirus includes combinations with dactinomycin)	2020	Pending	2041	PCT, United States
<b>Actinomycin D</b>	Use of Actinomycin D in the treatment of acute myeloid leukemia	2015	Issued/ Pending	2036	United States, Europe, Japan Pending: United States, Australia, Canada
	Actinomycin D compositions and use of the same in the treatment of myelodysplastic syndrome and acute myeloid leukemia	2016	Issued/ Pending	2037	United States Pending: United States, Europe, Australia, Canada, Japan

We have rights to a patent family that discloses the Milciclib compound, methods of using the compound, and processes for making the compound licensed from Nerviano Medical Sciences S.R.L. (which is further described below). This patent family includes six granted U.S. patents, one granted European patent, and one granted Eurasian patent. This patent family also includes granted patents in Africa (African Intellectual Property Organization, African Regional Intellectual Property Organization), Algeria, Argentina, Australia, Brazil, 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, Thailand, Trinidad & Tobago, 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 licensed from Nerviano Medical Sciences S.R.L. 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 licensed from Nerviano Medical Sciences S.R.L. 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 granted U.S. patent and pending applications in the U.S., Europe, Canada, Japan, and Hong Kong. The patent and patent applications in this family, if issued as patents, will expire in November 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 also have rights to a U.S. provisional application which covers enteric-coated pharmaceutical formulations comprising Milciclib. The patent applications in this family, if issued as patents, will expire in March 2043, 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 U.S. provisional application that discloses method of treating KRAS mutated cancers by administering micliclib and a chemotherapy. Any patents issued in this family will expire in August 2042, excluding any patent term adjustment and patent term extensions available in the U.S and several other jurisdictions.

We have rights to a first patent family that discloses methods of using Foralumab, licensed from NovImmune S.A. (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, and Ukraine. 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 S.A. This patent family comprises four granted U.S. patents one granted European patent, and one granted Eurasian patent. This patent family also includes granted patents in Australia, Brazil, Canada, China, Hong Kong, India, Israel, Japan, Mexico, Republic of Korea, Singapore, South Africa, and Ukraine. An application is pending in the U.S. The patents in this family 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 S.A. This patent family has one pending U.S. application. The patents in this family will expire in January 2032, excluding any patent term adjustment and patent term extensions available in the U.S.

We have rights to a fourth patent family that discloses formulations of Foralumab and dosing regimens for treating various disorders. This patent family has an issued patent in the U.S., and applications pending in the U.S, Australia, Canada, China, Europe, Israel, Hong Kong, and Japan. The patents in this family 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 fifth patent family that discloses methods of using Foralumab for treating central nervous system (CNS) disorders, licensed from Brigham and Women's Hospital, Inc. (which is further described below). This patent family has applications pending in Canada, Europe, Japan, and the United States that, if issued as patents, will expire in June 2038, excluding any patent term adjustment and patent term extensions available in the U.S and several other jurisdictions.

We have rights to a sixth patent family that discloses methods of using Foralumab for treating gastrointestinal, autoimmune, and inflammatory disorders. This family has pending applications in the U.S., and in Europe, Australia, Canada, China, Hong Kong, and Japan. The applications in this family, if issued as patents, will expire in October 2039, excluding any patent term adjustment and patent term extensions that may be available.

We also have rights to international (PCT) applications that disclose methods of using Foralumab in the treatment of coronavirus and methods of using Foralumab to enhance cell adoptive therapies. The patent applications in this family, if issued as patents, will expire in 2041, excluding any patent term adjustment and patent term extensions available in the U.S and several other jurisdictions.

We also have rights to a U.S. provisional application that discloses methods of administering Foralumab subcutaneously for the treatment of various diseases. Any patents issued in this family will expire in April 2042, 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 S.A. This patent family includes, five granted U.S. patents and one granted European patent. This patent family also includes granted patents in Australia, Canada, China, India, Israel, Japan and Mexico. Applications are pending in U.S. and Japan. The patents in this family will expire in May 2029, excluding any patent term extensions available in several jurisdictions, such as Europe.

We have rights to a second patent family that discloses methods of using TZLS-501 to treat coronavirus alone and in combination with Actinomycin D. This patent family includes a pending international (PCT) application and a pending U.S. application. The patent applications in this family, if issued as patents, will expire in March 2041, excluding any patent term extensions available in several jurisdictions.

We also have rights to two patent families related to Actinomycin D (ActD). The first family covers the use of ActD in the treatment of acute myeloid leukemia, and includes granted patents in the U.S., Japan, and Europe and pending applications in the U.S., Australia, and Canada. The patents and patent applications in this family, if issued as patents, will expire in September 2036, 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.

The second ActD family covers nanoparticle formulations of ActD and the use of the same in the treatment of acute myeloid leukemia and myelodysplastic syndrome. In this family, there is a granted U.S. patent and pending applications in the U.S., Europe, Australia, Canada, and Japan. The patent and patent applications in this family, if issued as patents, will expire in September 2037, 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.

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.”

### ***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 to 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 sublicense 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:

<b>Name</b>	<b>Principal activity</b>	<b>Registered address</b>	<b>Percentage shareholding</b>	<b>Country of incorporation</b>
Tiziana Life Sciences Ltd	Clinical stage biotechnology company	107 Cheapside, London EC2V 6DN	100%	England & Wales
Tiziana Pharma Limited	Clinical stage biotechnology company	107 Cheapside, London EC2V 6DN	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- Cagliaria (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.

<b>Location</b>	<b>Tenure</b>	<b>Principal Use</b>	<b>Size</b>
55 Park Lane, Suite 14a, London W1K 1NA, United Kingdom	Annual Lease	Principal Office	652 square feet
5 Penn Plaza 19 <sup>th</sup> Floor New York, United States	Monthly lease	Principal Office	450 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 neurodegenerative diseases such as progressive Multiple Sclerosis (pMS) and Crohn’s disease. As the only fully human engineered human anti-CD3 mAb in clinical development, Foralumab has significant potential advantages such as a shorter treatment duration and reduced immunogenicity. 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. With completion of the intravenous dosing for Phase 2a trial in Crohn’s Disease, Foralumab’s ability to modulate T-cell response enables potential extension into a wide range of other autoimmune and inflammatory diseases, such as GvHD, ulcerative colitis, multiple sclerosis, type-1 diabetes (T1D), inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis

We have completed 2 Phase 1 single-site, double-blind, placebo-controlled trials in healthy volunteers conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA. The first trial was a dose-ranging study with nasally administered Foralumab at 10, 50 and 250 µg per day, consecutively for 5 days for the treatment of progressive multiple sclerosis (pMS). Eighteen subjects received Foralumab treatment and 9 patients received placebo. All nasal doses were well tolerated and no drug-related safety issues were reported at any of the doses. Biomarker analysis showed significant positive immune effects, that were most prominent in the 50 µg cohort with minimal immunomodulatory effects at the 10 µg and 250 µg doses. A Phase 2a trial will be initiated in Q4 2020. The second also conducted at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, was a single-site, double-blind, placebo-controlled, single ascending dose ("SAD") study in healthy subjects in which Foralumab was orally administered at 1.25, 2.5 and 5.0 mg per dose as enteric-coated capsules. The primary endpoint of the Phase 1 study was safety and tolerability of Foralumab in humans. Each cohort comprised of 4 subjects, of whom 3 received Foralumab treatment and 1 received a placebo capsule. All subjects completed the trial without any safety concerns at any of the doses.

A collaborative clinical study was initiated on November 2, 2020, investigating nasally administered Foralumab either alone or in combination with orally administered dexamethasone in COVID-19 patients in Brazil. In view of the importance and urgency, scientific teams at the Harvard Medical School, Santa Casa de Misericórdia de Santos Hospital (Jabaquara, Santos, Brazil) and at our company closely collaborated to facilitate initiation of this study in expedited time frames. The clinical trial was coordinated by the team at INTRIALS, a leading, full-service Latin America Clinical Research Organization, (CRO) based in Sao Paulo City, Brazil. The trial was completed in January 2021. This trial, the first-ever trial on nasal administration of Foralumab for treatment of COVID-19, is of enormous significance because the underlying scientific approach is to modulate immune system, which is dysregulated and crippled to protect against the virus. The results of the trial were All treatments were well-tolerated. There were no grade 3 or 4 severe adverse events ("SAEs") in any of the cohorts. The CT scans of the lungs showed the improvement was approximately double that shown in patients treated with Foralumab as compared to those in the control group. The results of the study were published in the peer-reviewed journal, *Frontiers in Immunology* entitled "Nasal Administration of Anti-CD3 Monoclonal Antibody (Foralumab) Reduces Lung Inflammation and Blood Inflammatory Biomarkers in Mild to Moderate COVID-19 Patients: A Pilot Study" in August 2021. The study served as "proof of concept" that nasal administration of foralumab could be used to treat systemic inflammatory response related to COVID infection and could be used for treatment of other systemic inflammatory diseases. The Company has refocused development of Foralumab for treatment of Crohn's disease (oral treatment) and progressive MS (nasal treatment) utilizing site specific delivery technologies to limit systemic exposure of foralumab which achieving local delivery to inflamed tissue.

On May 25, 2021 we announced that the first expanded access (EA) patient with secondary progressive multiple sclerosis (SPMS) was dosed with nasally administered Foralumab at the Brigham and Women's Hospital (BWH), Harvard Medical School, Boston, MA. Nasal Foralumab 50 mcg (25 mcg/nostril) was administered in 3-week cycles, with 3 times/week dosing for the first 2 weeks followed by 1 week of rest period. This first-ever clinical study in SPMS patients, under an Individual Patient Expanded Access IND, was to continue for six months to evaluate routine safety, tolerability, and neurological behaviors. The study also examined microglial activation, by positron emission tomography (PET), immunological and neurodegenerative markers to assess clinical responses following the dosing regimen On March 10, 2022, we reported positive clinical data in the first SPMS EA patient following completion of six months of treatment with intranasally administered foralumab, at the Brigham and Women's Hospital (BWH), Harvard University, Boston, MA. In addition to being well-tolerated, both biological and clinical improvements were seen in this patient using Tiziana's novel immunotherapy technology, which, importantly overcame the challenge of delivering this antibody across the blood-brain barrier to affect immunomodulation in the brain using nasal administration.

Foralumab was given to an SPMS patient intranasally into each nostril on a regimen of M-W-F for two weeks followed by one week off therapy for a period of six months. This regimen was well-tolerated with associated beneficial clinical and biomarker changes. Importantly, the PET imaging data indicated inhibition of microglial cell activation observed at 3 months following treatment initiation and was sustained at 6 months after treatment start (see Table 1). The reduction in microglial activation was seen in all parts of brain.

**Table 1. Percent Reduction\* in Activated Microglial Cells (AMCs) PET Signal After Starting Intranasal Foralumab as Compared to Baseline, in Whole Brain and Selected Brain Regions**

	<b>WHOLE BRAIN</b>	<b>CEREBRAL CORTEX</b>	<b>THALAMUS</b>	<b>WHITE MATTER</b>	<b>CEREBELLUM</b>
3 MONTHS	-23%	-23%	-20%	-25%	-22%
6 MONTHS	-38%	-38%	-50%	-36%	-38%

\* Percent reduction is based on changes from baseline in SUVR-1, a surrogate index for PET binding potential. SUVR=Standardized Uptake Value Ratio, calculated with reference to a pseudo reference region in cerebral white matter that showed minimal change in PET SUV, across time points.

Consistent with clinical and PET observations, intranasally administered foralumab also downregulated serum levels of pro-inflammatory cytokines, including interferon-gamma (IFN-g), interleukin (IL-18), IL-1 $\beta$  and IL-6, which are associated with multiple sclerosis pathogenesis and progression. Clinical evaluation showed improvement in Timed 25-Foot Walk Test (T25FW), 9-Hole Peg Test (9HPT) and Symbol Digit Modality Test (SDMT). Other published PET studies have shown an increase in activated microglial cells (AMCs) in patients with secondary progressive MS (SPMS), and the increase in AMCs associated with higher scores on the Expanded Disability Status Scale (EDSS), a widely-used scale to measure disability<sup>1,2</sup>. Several FDA-approved drugs, such as TYSABRI<sup>®</sup>, MAYZENT<sup>®</sup> and ZEPOSIA<sup>®</sup> have been shown to suppress microglial activation and exert neuroprotective effects in the central nervous system (CNS) in animal studies but longitudinal assessment of drug effects on microglial activation in exclusive cohorts of SPMS patients are lacking.

Prior to treatment, this patient had continued to experience worsening disease progression despite several MS therapies, including B cell depletion. The patient’s gait and limb strength had been deteriorating over the prior two years. The patient then started on intranasal foralumab, which stabilized his disease course. Tiziana also received FDA authorization to continue treating this patient for an additional 6 months to determine if 12 months of consistent treatment maintains clinical stabilization and provides sustained clinical benefits.

On January 20, 2022, FDA allowed enrollment of a second EA SPMS patient for treatment with intranasal foralumab.

These data were presented in a virtual Key Opinion Leader (KOL) event hosted by Tiziana on March 14<sup>th</sup>, 2022, entitled “Foralumab Clinical Update in Multiple Sclerosis; A Landmark Study with Intranasal Immunotherapy” featuring four Key Opinion Leaders and a live Q&A session.

We plan to continue treatment of EA SPMS patients at Brigham and Women’s Hospital and elsewhere and continue evaluation of foralumab treatment.

We are developing Milciclib, for which we in-licensed the intellectual property from Nerviano, in January 2015, as a potential treatment for pan KRAS mutations in NSCLC patients. 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. To date, Milciclib has been studied in a total of eight completed Phase 1 and Phase 2 clinical trials in a total of 316 patients conducted by Nerviano. In these trials, Milciclib was well-tolerated with minimal adverse events. The last Phase 2a trial was initiated as a monotherapy in patients with HCC in the fourth quarter of 2017 and successfully completed in June 2019. The trial met primary and secondary end points..

Cumulative Patient Exposure in Completed Milciclib Clinical Studies:

<b>Clinical Study</b>	<b>Drug</b>	<b>Indication</b>	<b>Number of Patients Treated</b>
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
		<b>Total Patients Exposed</b>	<b>316</b>

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, 2021, we had received net cash proceeds of \$118.3m 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 \$23.3 million for the year ended December 31, 2021, \$26.1 million for the year ended December 31, 2020 and \$9.3m for the year ended December 31, 2019 respectively. As of December 31, 2021, we had cash and cash equivalents of \$42.2 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***

A collaborative clinical study was initiated on November 2, 2020, investigating nasally administered Foralumab either alone or in combination with orally administered dexamethasone in COVID-19 patients in Brazil. In view of the importance and urgency, scientific teams at the Harvard Medical School, Santa Casa de Misericórdia de Santos Hospital (Jabaquara, Santos, Brazil) and at our company closely collaborated to facilitate initiation of this study in expedited time frames. The clinical trial was coordinated by the team at INTRIALS, a leading, full-service Latin America Clinical Research Organization, (CRO) based in Sao Paulo City, Brazil. The trial was completed in January 2021, and the clinical data from this trial is expected to be available by the first quarter of 2021. This trial, the first-ever trial on nasal administration of Foralumab for treatment of COVID-19, is of enormous significance because the underlying scientific approach is to modulate immune system, which is dysregulated and crippled to protect against the virus. If successful, we believe this approach could be good for treatment of all COVID-19 variants and other viruses.

In addition, on August 18, 2020 the United States Patent and Trademark Office, or USPTO, granted us a patent on use and methods of treatment of Crohn's disease with Foralumab, its proprietary fully human monoclonal antibody, and all other anti-CD3 mAbs. The CD3 (cluster of differentiation 3) is a protein complex on T-cells, which is important for the regulation of the immune system. The patent was published by the USPTO on September 1, 2020 as Patent No. 10,759,858. Recently, we also announced the issuance of the first-ever patent on oral administration of anti-CD3 mAbs for treatment of human diseases (Patent No. 10,688,186). We believe the grant of this additional composition-of-matter and use patent further strengthens our intellectual property, consisting of proprietary technologies on oral and nasal administration of Foralumab and other anti-CD3 mAbs for the treatment of human diseases.

On July 16, 2020, we announced that we had submitted a patent application on the potential use of Foralumab, a fully human anti-CD3 mAbs, to improve success of chimeric antigen receptor T-cell, or CAR-T, therapy for cancer and other human diseases. The patent application conveys inventions related lymphodepletion to improving CAR-T expansion and/or survival using anti-CD-3 mAbs administered either alone or in combination with other co-stimulatory molecules, such as an anti-IL-6R mAb, an anti-CD28 mAb or specific inhibitors of signaling pathways of phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or mammalian target of rapamycin (mTOR).

On July 31, 2020, we announced that we had submitted a patent application for the potential use of nasally administered Foralumab, a fully human anti-CD3 mAb, for the treatment of COVID-19 either alone or in combination with other anti-viral drugs. Recent clinical studies implied that a combination of anti-inflammatory and anti-viral drugs may be more effective to treat patients at different stages of COVID-19 disease.

On June 29, 2020 we announced that we were advancing GMP manufacturing of TZLS-501 with STC Biologics concurrently with the development of inhalation technology using a hand-held nebulizer with Sciarra Laboratories and safety toxicology studies in Cynomolgus monkeys with ITR Canada Laboratories. GMP batches were initiated in January 2021 and completed in March 2021. Safety inhalation toxicology studies were initiated in November 2020 and completed in March 2021. Technological assessment of nebulizers for inhalation treatment of patients was initiated in September 2020 and completed in February 2021.

### **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. Any ad hoc sublicensing revenues have been treated as other income.

#### ***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:

	<b>Year ended December 31,</b>			
	<b>2021</b>	<b>2020</b>	<b>2019</b>	<b>2018</b>
Direct research and development expense by program:	(in thousands)			
Foralumab	\$ 3,372	\$ 1,346	\$ 1,750	\$ 2,261
Milciclib	1,175	364	1,916	2,581
TZLS-0501	8,556	4,167	39	-
ACT-D	74	62	-	-
CAR-T	31	-	-	-
StemPrintER	-	54	9	166
<b>Total direct research and development expense</b>	<b>\$ 13,208</b>	<b>\$ 5,993</b>	<b>\$ 3,714</b>	<b>\$ 5,008</b>
Indirect research and development expense		-	-	502
<b>Total research and development expense</b>	<b>\$ 13,208</b>	<b>\$ 5,993</b>	<b>\$ 3,714</b>	<b>\$ 5,510</b>

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.

#### *Realization Bonus Expenses*

This is an extraordinary expense item for this year and includes the expenses for a realization bonus which became payable in 2020 to the Chairman of the board, triggered by a fundraising event during the year. As the bonus was not settled timely, interest was accrued on the amount due in 2021.

#### *Impairment of an asset*

This is an extraordinary expense item for 2020 and includes the expenses for the impairment of a non-current asset.

#### *Disposal of Intellectual Property*

This is an extraordinary expense item for 2020 and includes the expenses related to the disposal of intellectual property during the year.

#### *Other Income (Expense)*

Other expense consists of interest on a convertible loan note and income received from a partnership agreement.

#### *Taxation*

The tax income 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, 2021 and 2020

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

	Year Ended December 31,		
	2021	2020	Change
	(in thousands)		
Operating Expenses:			
Research and development	\$ (13,208)	\$ (5,993)	\$ (7,215)
General and administrative	\$ (13,311)	\$ (11,203)	\$ (2,108)
Realization bonus	(855)	(13,214)	12,359
Impairment of asset	-	(279)	279
Disposal of Intellectual Property	-	2,663	(2,663)
Total Operating Expenses	<u>\$ (27,374)</u>	<u>\$ (28,026)</u>	<u>\$ 652</u>
Other Income/ (Expense)	717	(312)	1,029
Tax credit	3,240	2,207	1,048
Net Loss	<u>\$ (23,417)</u>	<u>\$ (26,131)</u>	<u>\$ 2,729</u>
Other comprehensive loss:			
Foreign currency translation adjustment	<u>(4,478)</u>	<u>3,474</u>	<u>(7,978)</u>
Total Comprehensive (Loss)	<u>\$ (27,895)</u>	<u>\$ (22,657)</u>	<u>\$ (4,499)</u>

#### Research and Development Expenses

Research and development activities were \$13.2 million for the year ended December 31, 2021 compared to \$6.0 million for the year ended December 31, 2020 an increase of \$7.2 million. The increase in cost is a result of the development of anti-IL-6R monoclonal antibodies (mAbs) compounds and the manufacturing of Foralumab.

#### General and Administrative Expenses

Operating expenses were \$13.3 million for the year ended December 31, 2021 as compared \$11.2 million for the year ended December 31, 2020, an increase of \$2.1 million. The increase in cost is a result of the additional fair value charges of \$3.5m relating to modification of existing options and the issuance of additional options, and additional compliance, professional fees and legal costs of \$1.5m due to increased activity in the Company and the corporate reorganization and establishment of a new Bermudan parent.

#### Realization Bonus Expense

A realization bonus of \$13.2 million became payable during the year ended December 31, 2020 to the chairman of the board. This became payable upon the Company raising funds in excess of \$28m (£20m), which it successfully raised in August 2020. As the bonus was not settled until November 2021, interest of \$0.9m was accrued on the amount due in the year to December 31, 2021.

#### Impairment of asset

There was an asset impairment charge of \$0.3 million for the year ended December 31, 2020. This charge related to the impairment of the Company's investment in SharDNA SPA. No further charges were incurred in the year ended December 31, 2021.

#### Disposal of Intellectual Property

There was a gain of \$2.7m arising on the disposal of the StemPrintER intellectual property in the year ended December 31, 2020. No further disposals were incurred in the year ended December 31, 2021.

## Income Tax Credit

Income tax credits of \$3.2 million and \$2.2 million are recognized for the years ended December 31, 2021 and 2020, respectively. The credits are obtained at a rate of 14.5% of 230% of our qualifying research and development expenditure. The increase in the provision is due primarily to an increase in qualifying research and development expenditure incurred in the year ending December 31, 2021.

## Comparison of Years Ended December 31, 2020 and 2019

The following tables summarizes our results of operations for the years ended December 31, 2020 and 2019:

	Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
Operating Expenses:			
Research and development	\$ (5,993)	\$ (3,714)	\$ (2,279)
General and administrative	\$ (11,203)	\$ (6,207)	\$ (4,996)
Realization bonus	(13,214)	-	(13,214)
Impairment of asset	(279)	-	(279)
Disposal of Intellectual Property	2,663	-	2,663
Total Operating Expenses	<u>\$ (28,026)</u>	<u>\$ (9,921)</u>	<u>\$ (18,105)</u>
Other Income/ (Expense)	(312)	(91)	(221)
Tax credit	2,207	689	1,518
Net Loss	<u>\$ (26,131)</u>	<u>\$ (9,323)</u>	<u>\$ (16,808)</u>
Other comprehensive loss:			
Foreign currency translation adjustment	3,474	(27)	3,501
Total Comprehensive (Loss)	<u>\$ (22,657)</u>	<u>\$ (9,350)</u>	<u>\$ (13,307)</u>

## Research and Development Expenses

Research and development activities were \$6.0 million for the year ended December 31, 2020 compared to \$3.7 million for the year ended December 31, 2019 an increase of \$2.3 million. The increase in cost is a result of the development of anti-IL-6R monoclonal antibodies (mAbs) compounds.

## General and Administrative Expenses

Operating expenses were \$11.2 million for the year ended December 31, 2020 as compared to \$6.2 million for the year ended December 31, 2019, an increase of \$5 million. The increase in cost is a result of the additional fair value charges of \$3.5m relating to modification of existing options and the issuance of additional options, and additional compliance, professional fees and legal costs of \$1.5m due to increased activity in the Company.

## Realization Bonus Expense

A realization bonus of \$13.2 million became payable during the year ended December 31, 2020. This became payable upon the Company raising funds in excess of \$28m (£20m), which it successfully raised in August 2020.

## Impairment of asset

There was an asset impairment charge of \$0.3 million for the year ended December 31, 2020. This charge related to the impairment of the Company's investment in SharDNA SPA.

### *Disposal of Intellectual Property*

There was a gain of \$2.7m arising on the disposal of the StemPrintER intellectual property in the year ended December 31, 2020.

There were proceeds on the disposal of intellectual property of \$2.6 million for the year ended December 31, 2020. This credit related to the disposal of intellectual property with regards to StemPrintER of \$3.9m offset by cash payable to Accustem of \$1.3m.

### *Income Tax Credit*

Income tax credits of \$2.2 million and \$0.7 million are recognized for the years ended December 31, 2019 and 2018, respectively. The credits are obtained at a rate of 14.5% of 230% of our qualifying research and development expenditure. The increase in the provision is due primarily to an increase in qualifying research and development expenditure incurred in the year ending December 31, 2020, plus more qualifying research and development expenditure identified for the year ending December 31, 2019 than was provided for.

## **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, 2021, we had cash and cash equivalents of \$42.2 million.

Through December 31, 2021, we had received net cash proceeds of \$0.2 million from the exercise of warrants.

### *Cash Flows*

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

	<b>Year ended December 31,</b>		
	<b>2021</b>	<b>2020</b>	<b>2019</b>
Net cash used in operating activities	\$ (21,762)	\$ (11,335)	\$ (6,796)
Net cash used in investing activities	(23)	(123)	(4)
Net cash provided by financing activities	130	75,346	1,680
Effect of exchange rate changes on cash and cash equivalents	(1,983)	1,736	16
Net (decrease)/increase in cash and cash equivalents	<u>\$ (21,655)</u>	<u>\$ 63,888</u>	<u>\$ (5,120)</u>

### *Net Cash Used in Operating Activities*

Our use of cash in each of the years ended December 31, 2021, and 2020, 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 \$21.8 million during the year ended December 31, 2021 increased by \$10.5 million compared to the year ended December 31, 2020.

Our use of cash in each of the years ended December 31, 2020, and 2019, 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 \$11.3 million during the year ended December 31, 2020 increased by \$4.5 million compared to the year ended December 31, 2019.

### *Net Cash Used in Investing Activities*

During the year ended December 31, 2021, we used \$0.02 million of cash in investing activities for the purchases of property and equipment offset by a finance lease receivable.

### *Net Cash Provided by Financing Activities*

During the years ended December 31, 2021 and 2020, net cash provided by financing activities was \$0.1 million and \$75.3 million, respectively, consisting of net cash proceeds from our sale and issuance of ordinary shares and ADS's, convertible loan notes and the exercise of options and warrants.

During the years ended December 31, 2020 and 2019, net cash provided by financing activities was \$75.3 million and \$1.7 million, respectively, consisting of net cash proceeds from our sale and issuance of ordinary shares and ADS's, convertible loan notes and the exercise of options 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.

#### **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, 2021 and 2020.

As at December 31, 2021

(in thousands)	Total	Less than 1 Year	Between 1 and 5 Years	More than 5 Years
Borrowings	\$ -	\$ -	\$ -	\$ -
Operating lease obligations	24	-	-	-
Total	<u>\$ 24</u>	<u>\$ -</u>	<u>\$ -</u>	<u>\$ -</u>

As at December 31, 2020

(in thousands)	Total	Less than 1 Year	Between 1 and 5 Years	More than 5 Years
Borrowings	-	-	-	-
Operating lease obligations	\$ 555	\$ 265	\$ 290	-
Total	<u>\$ 555</u>	<u>\$ 265</u>	<u>\$ 290</u>	<u>-</u>

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 May 2, 2022.

Name	Age	Position
Gabriele Marco Antonio Cerrone MBA (2)	50	Executive Chairman
Willy Simon (1,2,3)	70	Non-Executive Director
John Brancaccio (1), (3)	74	Non-Executive Director
Dr. Kunwar Shailubhai MBA	65	Chief Executive Officer, Chief Scientific Officer and 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 May 2, 2022:

<b>Name</b>	<b>Position</b>
Jules S. Jacob	Executive Director, CMC & Non-Clinical Development
Dr. Vaseem A. Palejwala	Senior Director, Clinical operations
Keeren Shah	Finance Director

**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 ten biotechnology companies in oncology, infectious diseases and molecular diagnostics, and has listed seven of these companies on Nasdaq two to the Main Market and AIM Market in London. Mr. Cerrone co-founded Cardiff Oncology, Inc., an oncology company and served as its Co-Chairman; he 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 also co-founded FermaVir Pharmaceuticals, Inc. and served as Chairman of the Board 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 Myers Squibb Co in 2012. Mr. Cerrone is the Executive Chairman and Founder of Tiziana Life Sciences Ltd, an oncology focused therapeutics company; Co-Founder of Rasna Therapeutics Inc., a company focused on the development of therapeutics for leukaemias; Co-Founder of Hepion Pharmaceuticals, Inc.; Executive Chairman and Co-Founder of Gensignia Life Sciences, Inc., a molecular diagnostics company focused on oncology using microRNA technology; Non-Executive Chairman and Founder of Accustem Sciences Limited; and founder of BioVitas Capital Ltd. Mr. Cerrone graduated from New York University’s Stern School of Business with a master’s degree 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. He is a banker and worked at Kredietbank N.V. and Citibank London before serving as an executive member of the Board of Generale Bank NL from 1997 to 1999 and as the chief executive of Fortis Investment Management from 1999 to 2002. He acted as chairman of Bank Oyens & van Eeghen from 2002 to 2004. He was chairman of AIM-traded Velox3 plc (formerly 24/7 Gaming Group Holdings plc) until 2014 and had been a director of Playlogic Entertainment Inc., a Nasdaq OTC listed company. Willy Simon has been the chairman of Bever Holdings, a company listed in Amsterdam, since 2006 and Chairman of Ducat Maritime since 2015. He is also a non-executive director of OKYO Pharma Ltd.

**John Brancaccio – Non-Executive Director**

John Brancaccio, a retired CPA, has served as a director of our company since July 2020. From April 2004 until May 2017, Mr. Brancaccio was the Chief Financial Officer of Accelerated Technologies, Inc., an incubator for medical device companies. Mr. Brancaccio served as a director of Callisto Pharmaceuticals, Inc. from April 2004 until its merger with Synergy Pharmaceuticals, Inc. in January 2013 and was a director of Tamir Biotechnology, Inc. (formerly Alfacell Corporation) until 2019, as well as a director of Hepion Pharmaceuticals, Inc. since December 2013, Rasna Therapeutics, Inc. since September 2016, Cardiff Oncology, Inc. since December 2005 and Okyo Pharma Ltd since June 2020. Mr. Brancaccio served as a director of Synergy from July 2008 until April 2019.

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

Dr. Kunwar Shailubhai 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.

**Jules S. Jacob – Executive 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. Vaseem A. Palejwala – Senior 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.

### **Keeren Shah – Finance Director**

Keeren Shah serves as our Finance Director. Ms. Shah currently also serves as the CFO of Accustem Sciences Inc, OKYO Pharma Ltd and Rasna Therapeutics Inc., having previously served as the Group Financial Controller for these businesses from June 2016 to July 2020. Prior to joining the Company, Ms. Shah spent 10 years at Visa, Inc. as a Senior Leader in its finance team where she was responsible for key financial controller activities, financial planning and analysis, and core processes as well as leading and participating in key transformation programmes and Visa Inc.'s initial public offering. Before joining Visa, Ms. Shah has also held a variety of finance positions at other leading companies including Arthur Andersen and BBC Worldwide. She holds a Bachelor of arts with honours in Economics and is a member of the Chartered Institute of Management Accountants.

### **Family Relationships**

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

## **B. Compensation**

### **Total Compensation for the Executive Chairman and Non-Executive Directors**

The table below sets out the total remuneration received by the Executive Chairman and the Non-Executive Directors for the year ended December 31, 2021.

<b>Name</b>	<b>Position</b>	<b>Fees earned or paid in cash (\$000)</b>	<b>Bonus earned or paid in cash (\$000) (2)</b>	<b>Options awarded (\$000) (1)</b>	<b>Other (\$000)</b>	<b>Total (\$000)</b>
Gabriele Cerrone	Executive Chairman	330	855	-	-	1,185
Willy Simon	Non – Executive Director	59	-	-	4	63
John Brancaccio	Non – Executive Director	59	-	-	-	59

- (1) Represents the fair value of incentive stock options granted during the year to December 31, 2021 using an appropriate valuation model for computing stock-based compensation expense as of the date of grant.
- (2) The Chairman's first realization bonus of \$13.50m was satisfied on 5 August 2020, and the Chairman is unconditionally entitled to the immediate delivery of 4,763,995 new ordinary shares credited as fully paid in lieu of a cash payment. Due to late delivery of the shares, additional interest shares were issued worth \$855k during 2021.

## Narrative Disclosure to the Compensation table

### *Gabriele Cerrone*

On June 9, 2016 we entered into an agreement with our Executive Chairman, Gabriele Cerrone. Under the agreement, Mr Cerrone was to hold office as Chairman for £80,000 per annum. The agreement was to expire no earlier than 24 April 2018 and was to continue thereafter until terminated by either party giving written notice of 12 months. Mr Cerrone was also eligible to receive an annual bonus of up to 50% of his base salary, such bonus amount to be determined at the discretion of the Board of Directors.

Additionally, Mr Cerrone was also eligible to receive two realization bonuses as follows:

- (a) in the event that, either: (i) the Group raises, in one or a series of transactions, new equity capital in excess of £20,000,000 (after expenses); or (ii) there is a sale, in one or a series of transactions, of all or substantially all of the assets (calculated on the basis of book values) of the Group Companies (or a licence of the same on an exclusive or non-exclusive basis), where the Enterprise Value equals or exceeds £150,000,000; or (iii) there is a change of control where the Enterprise Value equals or exceeds £150,000,000, in which case the Realisation Bonus will be the amount equal to the Enterprise Value multiplied by two and a half (2.5) per cent
- (b) In the event that, during this Agreement, either: (i) there is a sale, in one or a series of transactions, of all or substantially all of the assets (calculated on the basis of book values) of the Group ( or a licence of the same on an exclusive or non-exclusive basis ), where the Enterprise Value equals or exceeds £300,000,000; or (ii) there is either a change of control where the Enterprise Value equals or exceeds £300,000,000, the Chairman will be entitled to receive an additional Realization Bonus in the amount equal to the Enterprise Value multiplied by three and a half (3.5) per cent.

The Enterprise Value means: (i) in the case of a change of control resulting in consideration payable to the Group (for example, on a sale of its assets or licensing transaction), the total cash and non-cash consideration received by the Group; or (ii) in the case of a change of control resulting in consideration payable to the shareholders of the ordinary shares in the issued share capital of the Group from time to time, the total cash and non-cash consideration payable to the Shareholders.

The first realization bonus was satisfied on 5 August 2020, and the Chairman is unconditionally entitled to the immediate delivery of 4,763,995 new ordinary shares credited as fully paid in lieu of a cash payment. The number of shares to be issued is fixed. Due to the delayed delivery of shares, additional shares were granted in lieu of interest.

On October 9, 2020, we entered into an amended agreement with Mr Cerrone, increasing his base salary to £240,000 per annum. All other terms and conditions remained the same.

### *Non -Executive Director remuneration*

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.

## Compensation of Executive Directors

The table below sets the remuneration of each of the Executive Directors and Senior Managers for the financial year ended December 31, 2021.

Name	Position	Fees earned or paid in cash (\$000)	Bonus earned or paid in cash (\$000)	Options awarded (\$000) (1)	Total (\$000)
Kunwar Shailubhai	Executive Director	600	210	-	810
Tom Adams (2)	Executive Director	413	-	3,664	4,077

(1) Represents the fair value of incentive stock options granted during the year to December 31, 2021 using an appropriate valuation model for computing stock-based compensation expense as of the date of grant.

(2) Dr. Adams passed away on January 9, 2022.

### Narrative Disclosure to the Compensation table

#### *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 \$600,000 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.

### Outstanding Equity Awards at Fiscal Year-End

The following table provides information regarding all outstanding equity awards for our directors, executive officers, and non-executive directors, as of December 31, 2021:

Name	Ordinary Shares Underlying Options	Exercise Price Per Ordinary Share (£)	Grant Date	Expiration Date
Gabriele Cerrone	1,830,775	0.35	25/06/2014	25/06/2024
	3,259,403	0.35	06/05/2020	05/05/2028
Kunwar Shailubhai	2,500,000	0.35	06/05/2020	05/05/2028
	4,700,000	0.35	06/05/2020	05/05/2030
	1,400,000	0.35	06/05/2020	05/05/2030
Willy Simon	250,000	147.5	25/08/2020	24/08/2030
John Brancaccio	250,000	147.5	25/08/2020	24/08/2030

### The Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc) Employee Share Option Plan with Non-Employee Sub-Plan and US Sub-Plan

The Tiziana Life Sciences Ltd (formerly 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.

### *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 Tiziana Life Sciences Ltd 2021 Equity Incentive Plan**

On October 20, 2021, Tiziana adopted the Tiziana Life Sciences Ltd 2021 Equity Incentive Plan (the “Plan”) which operates over common shares in Tiziana. The purpose of the Plan is to assist the Company and its Subsidiaries in attracting and retaining valued Employees, Consultants and Non-Employee Directors by offering them a greater stake in the Company’s success and a closer identity with it, and to encourage ownership of the Company’s shares by such Employees, Consultants and Non-Employee Directors. Any employee, director or consultant of Tiziana Life Sciences Ltd or any of its subsidiaries is eligible to receive Awards under the Plan. The Plan will be administered by the Compensation Committee of the Board (the “Compensation Committee”). Awards granted to nonemployee members of the Board will be administered by the full Board.

The Plan was approved by the shareholders of the Company, no new awards will be granted under the Tiziana Life Sciences plc Employee Share Option Plan with Non-Employee Sub-Plan and US Sub-Plan with California Supplement, as amended and/or restated from time to time (collectively, the “Prior Equity Plan”).

Subject to adjustment as provided in the Plan, the maximum number of shares that may be issued pursuant to Awards under the Plan is 15,000,000 shares (the “Cap”). The Cap will be increased by the number of shares corresponding (as determined by the Compensation Committee) to the securities underlying the portion of an award granted under the 2016 Plan that is cancelled, terminated or forfeited or lapses, in any case, on or after the effective date of the Plan. No more than 15,000,000 shares issued under the Plan may be issued pursuant to the exercise of incentive stock options.

Under the Plan, awards may be in the form of options, share appreciation rights, restricted stock, restricted stock units, performance stock, performance stock units, and other share-based awards. Each Award will be evidenced by an Award agreement containing the terms and conditions applicable to such Award.

### *UK Supplemental Plan*

The UK Supplemental plan shall apply to any Award granted to a Participant who is resident in the United Kingdom for tax purposes at the time the Award is granted or on the occurrence of any taxable event in respect of the Award and to any Participant who is not resident in the United Kingdom at such time(s) but who is granted the Award in respect of duties performed in the United Kingdom (a “UK Participant”).

### *Additional Terms for UK Participants*

*Employer National Insurance Contributions Indemnity.* In the case of any Award to a UK Participant in the form of Options, Restricted Stock, Restricted Stock Units, Performance Stock, Performance Stock Units or Other Share-Based Award, if required by the Board, it shall be a condition of such Award that the UK Participant irrevocably agrees that the Company and/or any applicable Subsidiary may recover from the UK Participant the whole or any part of any employer National Insurance Contributions, Apprenticeship Levy or other social security contributions for which the Company and/or any applicable Subsidiary is liable to account in respect of the Award, in each case to the extent permitted by applicable law, and/or that the UK Participant shall enter into such election (using a form approved by HM Revenue & Customs) as may be required for the whole or any part of such taxes to be transferred to the UK Participant.

*Date of Termination.* For the purposes of the Plan (and the corresponding provisions in any Award Agreement) the termination of employment of a UK Participant for Cause or as the result of the UK Participant's resignation shall be deemed to occur on the earlier of (i) the date on which the UK Participant's employment terminates, and (ii) the date on which the UK Participant gives or receives notice of the termination of employment.

*Bankruptcy.* Unless otherwise provided in an Award Agreement, the unvested portion of a Participant's Award shall be immediately forfeited with no compensation or other payment due to the Participant upon the Participant (i) being declared bankrupt, (ii) making an application for an interim order or any proposal for a voluntary arrangement within Part VIII of the Insolvency Act 1988, or (iii) proposing any form of compromise with his creditors or any class of creditors.

*Tax Election.* In the case of an Award to a UK Participant in the form of Options, Restricted Stock, Restricted Stock Units, Performance Stock, Performance Stock Units or Other Share-Based Award, unless the Board determines otherwise, it shall be a condition of the Award that the UK Participant enters into a joint tax election with his or her employer pursuant to Section 431(1) of the Income Tax (Earnings and Pensions) Act 2003 in respect of any Shares acquired pursuant to such Award, such election to be made no later than 14 days following the date on which such Shares are acquired.

*Relationship to Employment Contract.* The rights of a UK Participant under the terms of his or her office or employment with the Company or any Subsidiary shall not be affected by the Plan, this Supplement or any Award Agreement. The value of any benefit realised by a UK Participant in respect of an Award shall not be taken into account in determining any pension or similar entitlement.<sup>21</sup>

*Limitation on Claims.* A UK Participant shall have no right to compensation or damages on account of any loss in respect of an Award where the loss arises (or is claimed to arise), in whole or in part, from termination of office or employment with, or notice to terminate office or employment given by or to, the Company or any Subsidiary. This exclusion of liability shall apply however termination of office or employment, or the giving of notice, is caused, and however compensation or damages are claimed. A UK Participant shall have no right to compensation or damages from the Company or any Subsidiary on account of any loss in respect of an Award where the loss arises (or is claimed to arise), in whole or in part, from any Change in Control, any company ceasing to be a Subsidiary or the transfer of any business from the Company or any Subsidiary to any other person

## 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.

In connection with the migration to Bermuda, Tiziana adopted a Code of Business Conduct and Ethics which covers a broad range of matters including the handling of conflicts of interest, compliance issues and other corporate policies such as insider trading and equal opportunity and non-discrimination standards. Tiziana’s Code of Business Conduct and Ethics applies to all directors, executive officers and employees of Tiziana. Tiziana publishes its Code of Business Conduct and Ethics on its website ([www.tizianalifesciences.com](http://www.tizianalifesciences.com)).

- We do not 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 Bye-laws will provide alternative quorum requirements that are generally applicable to meetings of shareholders.
- We do not 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 following section titled “Description of Bye-laws and Memorandum of Association”

### Description of Bye-laws and Memorandum of Association

The following description includes a summary of specified provisions of our memorandum of association and our Bye-laws. This description is qualified by reference to our memorandum of association and our Bye-laws which are incorporated by reference as exhibits to this annual report.

## **Preemptive Rights**

Our Bye-laws do not provide shareholders with pro rata preemptive rights to subscribe for any newly issued common shares. Additionally, the Companies Act does not provide shareholders with a statutory preemptive right.

## **Repurchase of Shares**

Our board of directors may exercise all of the powers to purchase for cancellation or acquire our shares as treasury shares in accordance with the Companies Act. On a reacquisition of shares, such shares may be cancelled (in which event, our issued but not our authorized capital will be diminished accordingly) or held as treasury shares. Such purchases may only be effected out of the capital paid up on the purchased shares or out of the funds otherwise available for dividend or distribution or out of the proceeds of a fresh issue of shares made for the purpose.

## **Alteration of Share Capital**

We may, if authorized by a resolution of our shareholders, increase, divide, consolidate, subdivide, change the currency denomination of, diminish or otherwise alter or reduce the share capital in any manner permitted by the Companies Act.

## **Variation of Rights**

If at any time we have more than one class of shares, the rights attaching to any class, unless otherwise provided for by the terms of issue of the relevant class, may be varied with the sanction of a resolution passed by a majority of the votes cast at a general meeting of the relevant class of shareholders at which a quorum consisting of at least two persons holding or representing one-third of the issued shares of the relevant class is present. Our Amended and Restated Bye-laws specify that the creation or issue of shares ranking equally with existing shares will not, unless expressly provided by the terms of issue of existing shares, vary the rights attached to existing shares. In addition, the creation or issue of preference shares ranking prior to common shares will not be deemed to vary the rights attached to common shares or, subject to the terms of any other series of preference shares, to vary the rights attached to any other series of preference shares.

## **Transfer of Shares**

Our board of directors may in its absolute discretion and without assigning any reason refuse to register the transfer of a share which is not fully paid. Our board of directors may also refuse to recognize an instrument of transfer of a share unless it is accompanied by the relevant share certificate and such other evidence of the transferor's right to make the transfer as our board of directors shall reasonably require. The board shall refuse to register a transfer unless all applicable consents, authorizations and permissions of any governmental body or agency in Bermuda have been obtained. Subject to these restrictions, a holder of common shares may transfer the title to all or any of its common shares by completing a form of transfer in the form set out in our Bye-laws (or as near thereto as circumstances admit) or in such other common form as the board may accept. The instrument of transfer must be signed by the transferor and transferee, although in the case of a fully paid share our board of directors may accept the instrument signed only by the transferor.

Notwithstanding anything to the contrary in the Amended and Restated Bye-laws, our shares may be transferred without a written instrument if transferred by an appointed agent and in any form or manner which is in accordance with the rules or regulations of an appointed stock exchange (which includes the Nasdaq Capital Market) on which the shares are listed or admitted to trading.



## **General Meetings**

An annual general meeting will be held each year in accordance with the requirements of the Companies Act and our Bye-laws at such time and place as our board of directors appoints. Our board of directors or the chairman may also, whenever in its judgment it is necessary, convene general meetings other than annual general meetings which are called special general meetings. Bermuda law and the Bye-laws provide that a special general meeting must be called upon the request of shareholders holding not less than one-tenth of the paid-up capital of the Company carrying the right to vote at general meetings. Any annual general meeting and special general meeting must be called by, respectively, not less than twenty-one (21) days and five (5) days' prior notice in writing. A notice of meeting must include the place, day and time of the meeting and, in the case of an annual general meeting, that the election of directors will take place thereat and any other business to be conducted at the meeting, and, in the case of a special general meeting, the general nature of the business to be considered at the meeting. This notice requirement is subject to the ability to hold such meetings on shorter notice if such notice is agreed: (i) in the case of an annual general meeting by all of the shareholders entitled to attend and vote at such meeting; or (ii) in the case of a special general meeting by a majority in number of the shareholders entitled to attend and vote at the meeting holding not less than 95% in nominal value of the shares entitled to vote at such meeting. A shareholder may appoint a proxy to attend and vote at the general meeting by providing notice in writing to us at our registered office or at such other place or in such manner as specified in the notice of the general meeting.

The chairman, if present, and if not, the chief executive officer, if present, and if not, the president, if present, and if not, any person appointed by our board of directors will act as chairman of the meeting. In their absence and if no one is appointed by our board of directors as chairman of such meeting, a chairman of the meeting will be appointed or elected by those present at the meeting and entitled to vote.

## **Board and Shareholder Ability to Call Special Meetings**

Our Bye-laws provide that (a) the president or the chairman of the Company (if any) or any two Directors or any Director and the Secretary or the Board may convene a special general meeting whenever in their judgment such a meeting is necessary and (b) the board of directors must convene a special general meeting at the request of shareholders holding not less than one-tenth of the paid-up share capital of the Company with the right to vote at general meetings.

## **Shareholder Meeting Quorum**

Our Bye-laws provide that at any general meeting of shareholders, At any general meeting two or more persons present throughout the meeting and representing in person or by proxy in excess of 33 1/3% of the total voting rights of all issued and outstanding shares in the Company shall form a quorum for the transaction of business.

## **Voting Rights**

Subject to any restrictions for the time being lawfully attached to any class of shares, every shareholder who is present in person or by proxy at a general meeting shall be entitled to one vote on a show of hands and be entitled to one vote for every share of which he is a holder on a vote taken by poll, and any question proposed for the consideration of the shareholders at any general meeting shall be decided by the affirmative votes of a majority of the votes cast in accordance with the Bye-laws, and in the case of an equality of votes, the resolution will fail.

## **Shareholder Action by Written Consent**

The Bye-laws provide that no action required to be taken or which may be taken at any general meeting of Members may be taken without a meeting, and the power of Members to consent in writing, without a meeting, to the taking of any action is specifically denied.

## **Access to Books and Records and Dissemination of Information**

Members of the general public have a right to inspect the public documents of a company available at the office of the Registrar of Companies in Bermuda. These documents include the company's memorandum of association, including its objects and powers, and certain alterations to the memorandum of association. The shareholders have the additional right to inspect the bye-laws of the company, minutes of general meetings and the company's audited financial statements, which must be presented to the annual general meeting. The register of members of a company is also open to inspection by shareholders and by members of the general public without charge. The register of members is required to be open for inspection for not less than two hours in any business day (subject to the ability of a company to close the register of members for not more than thirty days in a year). A company is required to maintain its share register in Bermuda but may, subject to the provisions of the Companies Act, establish a branch register outside of Bermuda. A company is required to keep at its registered office a register of directors and officers that is open for inspection for not less than two hours in any business day by members of the public without charge. A company is also required to file with the Registrar of Companies in Bermuda a list of its directors to be maintained on a register, which register will be available for public inspection subject to such conditions as the Registrar may impose and on payment of such fee as may be prescribed. Bermuda law does not, however, provide a general right for shareholders to inspect or obtain copies of any other corporate records.

## **Removal of Directors**

Our Amended and Restated Bye-laws provide that shareholders entitled to vote for the election of directors may, at any special general meeting convened and held in accordance with the Amended and Restated Bye-laws, remove a director only with cause, by the affirmative vote of shareholders holding at least a majority of the total voting rights of all shareholders having the right to vote at such meeting, provided that the notice of any such meeting convened for the purpose of removing a director must contain a statement of the intention so to do and be served on such director not less than 14 days before the meeting and at such meeting the director will be entitled to be heard on the motion for such director's removal.

## **Proceedings of Board of Directors**

Our Bye-laws provide that our business is to be managed and conducted by our board of directors. Bermuda law permits individual and corporate directors and there is no requirement in the Bye-laws or Bermuda law that directors hold any of our shares. There is also no requirement in the Bye-laws or Bermuda law that our directors must retire at a certain age.

The remuneration of our directors is determined by the board of directors from time to time at a duly authorized meeting. Our directors may also be paid all travel, hotel and other expenses properly incurred by them in connection with our business or their duties as directors.

Provided a director discloses a direct or indirect interest in any contract or arrangement or proposed contract or arrangement with us as required by Bermuda law, such director is entitled to vote in respect of any such contract or arrangement in which he or she is interested and/or be counted in the quorum for the meeting at which such contract or arrangement is to be voted on.

## **Amalgamations, Mergers and Business Combinations**

The amalgamation or merger of a Bermuda company with another company or corporation (other than certain affiliated companies) requires the amalgamation or merger agreement to be approved by the company's board of directors and by its shareholders. Unless the company's bye-laws provide otherwise, the approval of 75% of the shareholders voting at such meeting is required to approve the amalgamation or merger agreement, and the quorum for such meeting must be two persons holding or representing more than one-third of the issued shares of the company. The Amended and Restated Bye-laws provide that an amalgamation, consolidation or a merger (other than with a wholly owned subsidiary or as described below) that has been approved by the board must only be approved by a majority of the votes cast at a general meeting of the shareholders at which the quorum shall be two or more persons present in person and representing in person or by proxy in excess of 50% of all issued and outstanding common voting shares. Any other amalgamation or merger or other business combination (as defined in the Amended and Restated Bye-laws) not approved by our board must be approved by the holders of not less than 66 2/3% of all votes attaching to all shares then in issue entitling the holder to attend and vote on the resolution.

### *Dissenter's Rights*

Under Bermuda law, in the event of an amalgamation or merger of a Bermuda company with another company or corporation, including a public Bermuda company, a shareholder of the Bermuda company who did not vote in favor of the amalgamation or merger and is not satisfied that fair value has been offered for such shareholder's shares may, within one month of notice of the shareholders meeting, apply to the Supreme Court of Bermuda to appraise the fair value of those shares. These approval rights did not apply to the Business Combination because the Company was not a party to any amalgamation or merger contemplated by the Business Combination.

## **Limitations on Director Liability and Indemnification of Directors and Officers**

Section 98 of the Companies Act provides generally that a Bermuda company may indemnify its directors, officers and auditors against any liability which by virtue of any rule of law would otherwise be imposed on them in respect of any negligence, default, breach of duty or breach of trust, except in cases where such liability arises from fraud or dishonesty of which such director, officer or auditor may be guilty in relation to the company. Section 98 further provides that a Bermuda company may indemnify its directors, officers and auditors against any liability incurred by them in defending any proceedings, whether civil or criminal, in which judgment is awarded in their favor or in which they are acquitted or granted relief by the Supreme Court of Bermuda pursuant to section 281 of the Companies Act.

The Bye-laws provide that the directors, resident representative, secretary and other officers acting in relation to any of the affairs of the Company or any subsidiary thereof and the liquidator or trustees (if any) acting in relation to any of the affairs of the Company or any subsidiary thereof and every one of them shall be indemnified and secured harmless out of the assets of the Company from and against all actions, costs, charges, losses, damages and expenses which they or any of them shall or may incur or sustain by or by reason of any act done, concurred in or omitted in or about the execution of their duty, or supposed duty, or in their respective offices or trusts, and no indemnified party shall be answerable to the acts, receipts, neglects or defaults of the others of them or for joining in any receipts for the sake of conformity, or for any bankers or other persons with whom any moneys or effects belonging to the Company shall or may be lodged or deposited for safe custody, or for insufficiency or deficiency of any security upon which any moneys of or belonging to the Company shall be placed out on or invested, or for any other loss, misfortune or damage which may happen in the execution of their respective offices or trusts, or in relation thereto, provided that this indemnity shall not extend to any matter in respect of any fraud or dishonesty in relation to the Company which may attach to any of the indemnified parties. We may also enter into an indemnification agreement with any director or officer of the Company.

In addition, the Bye-laws provide that the Company may (i) purchase and maintain insurance for the benefit of any director or officer against any liability incurred by such person under the Companies Act in his or her capacity as a director or officer of the Company or indemnifying such director or officer in respect of any loss arising or liability attaching to him or her by virtue of any rule of law in respect of any negligence, default, breach of duty or breach of trust of which the director or officer may be guilty in relation to the Company or any of its subsidiaries and (ii) advance moneys to a director or officer for the costs, charges and expenses incurred by the director or officer in defending any civil or criminal proceedings against him or her, on condition that the director or officer shall repay the advance if any allegation of fraud or dishonesty in relation to the Company is proved against him or her.

## **Class Actions and Derivative Suits**

Class actions and derivative actions are generally not available to shareholders under Bermuda law. The Bermuda courts, however, would ordinarily be expected to permit a shareholder to commence an action in the name of a company to remedy a wrong to the company where the act complained of is alleged to be beyond the corporate power of the company or illegal, or would result in the violation of the company's memorandum of association or bye-laws. Furthermore, consideration would be given by a Bermuda court to acts that are alleged to constitute a fraud against the minority shareholders or, for instance, where an act requires the approval of a greater percentage of the company's shareholders than that which actually approved it.

When the affairs of a company are being conducted in a manner which is oppressive or prejudicial to the interests of some part of the shareholders, one or more shareholders may apply to the Supreme Court of Bermuda, which may make such order as it sees fit, including an order regulating the conduct of the company's affairs in the future or ordering the purchase of the shares of any shareholders by other shareholders or by the company.

## **Amendment of Memorandum of Association and Bye-laws**

Bermuda law provides that the memorandum of association of a company may be amended by a resolution passed at a general meeting of shareholders. Our Amended and Restated Bye-laws provide that no bye-law shall be rescinded, altered or amended, and no new bye-law shall be made, unless it shall have been approved by a resolution of our board of directors and by a resolution of our shareholders.

Under Bermuda law, the holders of an aggregate of not less than 20% in par value of the company's issued share capital or any class thereof have the right to apply to the Supreme Court of Bermuda for an annulment of any amendment of the memorandum of association adopted by shareholders at any general meeting, other than an amendment which alters or reduces a company's share capital as provided in the Companies Act. Where such an application is made, the amendment becomes effective only to the extent that it is confirmed by the Bermuda court. An application for an annulment of an amendment of the memorandum of association must be made within 21 days after the date on which the resolution altering the company's memorandum of association is passed and may be made on behalf of persons entitled to make the application by one or more of their number as they may appoint in writing for the purpose. No application may be made by shareholders voting in favor of the amendment.

## **Capitalization of Profits and Reserves**

Pursuant to our Bye-laws, our board of directors may (i) capitalize any part of the amount of our share premium or other reserve accounts or any amount credited to our profit and loss account or otherwise available for distribution by applying such sum in paying up unissued shares to be allotted as fully paid bonus shares pro-rata (except in connection with the conversion of shares) to the shareholders; or (ii) capitalize any sum standing to the credit of a reserve account or sums otherwise available for dividend or distribution by paying up in full, partly paid or nil paid shares of those shareholders who would have been entitled to such sums if they were distributed by way of dividend or distribution.

## **Certain Provisions of Bermuda Law**

### *Share Certificates*

In accordance with Bermuda law, share certificates are only issued in the names of companies, partnerships or individuals. In the case of a shareholder acting in a special capacity (for example as a trustee), certificates may, at the request of the shareholder, record the capacity in which the shareholder is acting. Notwithstanding such recording of any special capacity, we are not bound to investigate or see to the execution of any such trust.

### *Membership*

Under the Companies Act, only those persons who agree to become members of a Bermuda company and whose names are entered on the register of members of such company are deemed members. A Bermuda company is not bound to see to the execution of any trust, whether express, implied or constructive, to which any of its shares are subject and whether or not the company had notice of such trust. Accordingly, persons holding shares through a trustee, nominee or depository will not be recognized as members of a Bermuda company under Bermuda law and may only have the benefit of rights attaching to the shares or remedies conferred by law on members through or with the assistance of the trustee, nominee or depository.

## 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. John Brancaccio and Mr. Simon, and that each of these directors is “independent” as that term is defined under Nasdaq rules.

In accordance with our Articles, at the first general meeting which is held after the date of adoption of the Bye-laws for the purpose of electing Directors, the Class I Directors shall be elected for a three year term of office, the Class II Directors shall be elected for a two year term of office and the Class III Directors shall be elected for a one year term of office. At each succeeding annual general meeting, successors to the class of Directors whose term expires at that annual general meeting shall be elected for a three-year term. If the number of Directors is changed, any increase or decrease shall be apportioned among the classes so as to maintain the number of Directors in each class as nearly equal as possible, and any Director of any class elected to fill a vacancy shall hold office for a term that shall coincide with the remaining term of the other Directors of that class, but in no case shall a decrease in the number of Directors shorten the term of any Director then in office. A Director shall hold office until the annual general meeting for the year in which his term expires.

The Class of the members of the Board of Directors is as follows:

<b>Name</b>	<b>Class</b>	<b>Year Current Term Began</b>	<b>Year Current Term Expires</b>
Gabriele Cerrone	I	2021	2024
Kunwar Shailubhai	II	2021	2023
John Brancaccio	II	2021	2023
Willy Simon	III	2021	2022

## 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. Brancaccio and Mr. Simon, assists the board of directors in overseeing our accounting and financial reporting processes. Mr. Brancaccio 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. Brancaccio 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 and Mr. Simon. Mr. Simon 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.

None of our non-employee directors have any service contracts with Tiziana Life Sciences Ltd or any of our subsidiaries that provide for benefits upon termination of employment.

## **D. Employees**

As of December 31, 2021, we had 14 full time employees. Eight of our employees were engaged in research and development and six employees were engaged in management, administration and finance. Five are located in England and nine are located in the United States. None of our employees are members of labor unions. 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 29, 2022 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 29, 2022 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.

Name and address of beneficial owner	Number of Ordinary Shares Beneficially Owned	
	Shares	%
<b>5% or Greater Shareholders:</b>		
Gabriele Cerrone <sup>(1)</sup>	39,348,461	38.13
<b>Executive Officers and Directors:</b>		
Gabriele Cerrone <sup>(1)</sup>	39,348,461	38.13
Willy Simon	8,250	*
Kunwar Shailubhai <sup>(2)</sup>	2,740,000	2.61
John Brancaccio	-	-
All directors and executive officers as a group (4 persons) <sup>(3)</sup>	42,093,711	39.82

\* 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 915,388 stock options which are currently exercisable or exercisable within 60 days of May 2, 2022.

(2) Consists of 2,740,000 stock options which are currently exercisable or exercisable within 60 days of May 2, 2022

(3) Includes of 3,452,888 stock options which are currently exercisable or exercisable within 60 days of May 2, 2022



## **B. Related Party Transactions**

The following is a description of related party transactions we have entered into since January 1, 2020, 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.

### **Employment Agreements**

We have entered into employment agreements with our Chief Executive Officer, and director agreements with our remaining board members. For further details on these agreements, see Item 6 entitled "Directors, Senior Management and Employees."

We have entered into certain related party transactions as disclosed in Note 8 and Note 23 to the Consolidated Financial Statements in Item 18 of this report.

## **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, 2020.

## ITEM 9: THE LISTING

### A. Listing Details

The principal trading market for our ordinary shares is NASDAQ where our ordinary shares have been listed since October 21, 2021. Prior to this date Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc) was listed on main market (LSE) of the London Stock Exchange, where our ordinary shares have been listed since January 21, 2021 and , prior to January 20, 2021, the AIM market of the London Stock Exchange 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 had been trading on LSE under the symbol “TILS” since January 21, 2021 until October 20, 2021 and on AIM under the symbol “TILS” since April 24, 2014 until January 20, 2021.

The following table presents, for the periods indicated, the reported high and low sale prices, including intra-day sales, of our ordinary shares of Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc) on LSE and 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 April 22, 2022, which was £1.00 to \$1.2848.

	Price Per Ordinary Share £		Price Per Ordinary Share \$	
	High	Low	High	Low
<b>Year Ended December 31, 2021</b>				
First Quarter	1.95	0.90	2.51	1.16
Second Quarter	1.01	0.71	1.30	0.91
Third Quarter	0.76	0.51	0.98	0.66
Fourth Quarter (to October 20, 2022)	0.59	0.49	0.76	0.63
<b>Year Ended December 31, 2020</b>				
First Quarter	1.73	0.24	2.22	0.30
Second Quarter	1.20	0.33	1.54	0.42
Third Quarter	3.00	0.99	3.85	1.27
Fourth Quarter	2.06	0.72	2.65	0.93
<b>Year Ended December 31, 2019</b>				
First Quarter	0.64	0.43	0.82	0.55
Second Quarter	0.76	0.44	0.98	0.57
Third Quarter	0.70	0.48	0.90	0.62
Fourth Quarter	0.50	0.41	0.64	0.53
<b>Year Ended December 31, 2018</b>				
First Quarter	1.49	0.82	1.91	1.05
Second Quarter	0.88	0.37	1.13	0.48
Third Quarter	1.45	0.37	1.86	0.48
Fourth Quarter	1.47	0.63	1.89	0.81
<b>Year Ended December 31, 2017</b>				
First Quarter	2.10	1.66	2.70	2.13
Second Quarter	2.40	1.65	3.08	2.12
Third Quarter	1.75	1.42	2.25	1.82
Fourth Quarter	1.80	1.39	2.31	1.79

On October 20, 2021, the last reported sale price of our ordinary shares on LSE was £0.59 per ordinary share (\$0.76 per ordinary share based on the exchange rate set forth above).

Our American Depositary Shares, or ADSs, issued under Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc) have been trading on the Nasdaq Global Market under the symbol “TLSA” since November 20, 2018. These were swapped for common shares in Tiziana Life Sciences Ltd on October 21, 2021. The following table sets forth, for the periods indicated, the reported high and low closing sale prices of our common shares on the Nasdaq Global Market in U.S. dollars. The common share prices have been adjusted to reflect the 2:1 stock split that took place in October 2019.

	Price Per Common Share \$	
	High	Low
<b>Monthly:</b>		
November 2018	2.118	1.57
December 2018	1.7699	1.34
January 2019	1.42	1.1121
February 2019	1.35	1.14
March 2019	1.218	1.0
April 2019	1.9069	1.1
May 2019	1.7734	1.2835
June 2019	1.848	1.44
July 2019	1.6226	1.3
August 2019	1.47	1.2382
September 2019	1.544	1.0713
October 2019	1.436	0.69
November 2019	1.408	1.08
December 2019	1.252	0.944
January 2020	3.27	0.9514
February 2020	0.956	0.8572
March 2020	2.104	0.684
April 2020	1.36	0.72
May 2020	2.644	1.128
June 2020	2.74	2.152
July 2020	6.99	2.604
August 2020	5.62	3.53
September 2020	3.93	3.01
October 2020	4.96	3.32
November 2020	4.05	2.48
December 2020	2.59	1.86
January 2021	4.73	2.45
February 2021	4.54	2.98
March 2021	3.24	2.65
April 2021	3.29	2.31
May 2021	2.63	2.10
June 2021	2.61	2.21
July 2021	2.35	1.82
August 2021	2.10	1.52
September 2021	2.08	1.45
October 2021	1.66	1.40
November 2021	1.63	1.25
December 2021	1.25	0.89

On April 29, 2022, the last reported sale price of our common share on the Nasdaq Global Market was \$1.02.

**B. Plan of Distribution**

Not applicable.

**C. Markets**

Our common shares 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 of Association and Bye-laws**

We incorporate by reference into this Annual Report the description of our memorandum of association and Bye-laws contained in Form 8-K filed with the SEC on October 21, 2021.

**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**

The permission of the Bermuda Monetary Authority is required, under the provisions of the Exchange Control Act 1972 of Bermuda and related regulations, for all issuances and transfers of shares (which includes our common shares) of Bermuda companies to or from a non-resident of Bermuda for exchange control purposes, other than in cases where the Bermuda Monetary Authority has granted a general permission. The Bermuda Monetary Authority, in its notice to the public dated June 1, 2005, has granted a general permission for the issue and subsequent transfer of any securities of a Bermuda company from and/or to a non-resident of Bermuda for exchange control purposes for so long as any “Equity Securities” of the company (which include our common shares) are listed on an “Appointed Stock Exchange” (which include Nasdaq). In granting the general permission the Bermuda Monetary Authority accepts no responsibility for our financial soundness or the correctness of any of the statements made or opinions expressed in this annual report.

Although the Company is incorporated in Bermuda, as an exempted company it is classified as a non-resident of Bermuda for exchange control purposes by the Bermuda Monetary Authority. Other than transferring Bermuda Dollars out of Bermuda, there are no restrictions on the Company’s ability to transfer funds into and out of Bermuda or to pay dividends in currency other than Bermuda Dollars to non-residents of Bermuda who are holders of our common 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 Common shares by U.S. Holders. This discussion applies to U.S. Holders that purchase our Common shares pursuant to this offering and hold such Common shares 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 Common shares 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 Common shares 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 Common shares, the U.S. federal income tax consequences relating to an investment in such Common shares 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 Common shares.

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 Common shares or that any such position would not be sustained. Persons considering an investment in our Common shares should consult their own tax advisors as to the particular tax consequences applicable to them relating to the purchase, ownership and disposition of our Common shares, 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 Common shares, 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 Common shares, and (2) any gain recognized on a sale, exchange or other disposition, including, under certain circumstances, a pledge, of our Common shares, 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 Common shares. 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 Common shares, 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 Common shares, unless we cease to meet the requirements for PFIC status and the U.S. Holder makes a “deemed sale” election with respect to our Common shares. If the election is made, the U.S. Holder will be deemed to sell our Common shares 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 Common shares 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 Common shares 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 Common shares if a valid “mark-to-market” election is made by the U.S. Holder for our Common shares. An electing U.S. Holder generally would take into account as ordinary income each year, the excess of the fair market value of our Common shares held at the end of such taxable year over the adjusted tax basis of such Common shares. The U.S. Holder would also take into account, as an ordinary loss each year, the excess of the adjusted tax basis of such Common shares 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 Common shares 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 Common shares 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 Common shares 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 Common shares 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 Common shares 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 Common shares.

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 Common shares, the consequences to them of an investment in a PFIC, any elections available with respect to the Common shares and the IRS information reporting obligations with respect to the purchase, ownership and disposition of Common shares 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 Common shares 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 Common shares. To the extent the distribution exceeds the adjusted tax basis of the U.S. Holder's Common shares, 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 Common shares 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 Common shares 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 Common shares 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 advisers 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 Common shares 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 Common shares***

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 Common shares 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 Common shares. 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 Common shares 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 Common shares 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 Common shares. 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 Common shares.

## **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 Common shares, 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 Common shares 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 Common shares 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 COMMON SHARES 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.**

## **Bermuda Tax Considerations**

Under present Bermuda law, no Bermuda withholding tax on dividends or other distributions, or any Bermuda tax computed on profits or income or on any capital asset, gain or appreciation will be payable by us or applicable to our operations, and there is no Bermuda tax in the nature of estate duty or inheritance tax applicable to our shares, debentures or other obligations held by non-residents of Bermuda.

## *Tax Assurance*

We have obtained an assurance from the Minister of Finance of Bermuda under the Exempted Undertakings Tax Protection Act 1966 that, in the event that any legislation is enacted in Bermuda imposing any tax computed on profits or income, or computed on any capital asset, gain or appreciation or any tax in the nature of estate duty or inheritance tax, such tax shall not, until March 31, 2035, be applicable to us or to any of our operations or to our shares, debentures or other obligations except insofar as such tax applies to persons ordinarily resident in Bermuda or is payable by us in respect of real property owned or leased by us in Bermuda.

## *Taxation of Shareholders*

Shareholders should seek advice from their tax advisor to determine the taxation to which they may be subject based on the shareholder's circumstances.

## **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.

Members of the general public have a right to inspect the public documents of a company available at the office of the Registrar of Companies in Bermuda. These documents include the company’s memorandum of association, including its objects and powers, and certain alterations to the memorandum of association. The shareholders have the additional right to inspect the bye-laws of the company, minutes of general meetings and the company’s audited financial statements, which must be presented to the annual general meeting. The register of members of a company is also open to inspection by shareholders and by members of the general public without charge. The register of members is required to be open for inspection for not less than two hours in any business day (subject to the ability of a company to close the register of members for not more than thirty days in a year). A company is required to maintain its share register in Bermuda but may, subject to the provisions of the Companies Act, establish a branch register outside of Bermuda. A company is required to keep at its registered office a register of directors and officers that is open for inspection for not less than two hours in any business day by members of the public without charge. A company is also required to file with the Registrar of Companies in Bermuda a list of its directors to be maintained on a register, which register will be available for public inspection subject to such conditions as the Registrar may impose and on payment of such fee as may be prescribed. Bermuda law does not, however, provide a general right for shareholders to inspect or obtain copies of any other corporate records.

## **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 US Dollar. 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.

The currencies of our subsidiaries are generally their functional currencies. In translating the financial statements of those subsidiaries or branches whose functional currency is other than the U.S. dollar, assets and liabilities are converted into U.S. dollars using the rates of exchange in effect at the balance sheet dates, and revenues and expenses are converted using the average foreign exchange rates for the period. 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**

Not applicable.

## 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

*Evaluation of Disclosure Controls and Procedures*

#### **Disclosure Controls and Procedures**

The Company's management, with the participation of the Company's Chief Executive Officer and Finance Director, have evaluated the effectiveness of the Company's disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")) as of December 31, 2020. Based on that evaluation, the Company's Chief Executive Officer and the Company's Finance Director have concluded that as of December 31, 2020, due to the existence of the material weaknesses in the Company's internal control over financial reporting described below, the Company's disclosure controls and procedures were not effective.

#### **Management's Annual Report on Internal Control over Financial Reporting**

The Company's management is responsible for establishing and maintaining adequate internal controls over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. The Company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with International Financial Reporting Standards (IFRS) as issued by the International Accounting Standards Board (IASB), and IFRIC interpretations as applicable to companies reporting under IFRS.

Because of their inherent limitations, internal controls over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of management, the Company's Chief Executive Officer and the Company's Finance Director, the Company conducted an evaluation of the effectiveness of its internal control over financial over financial reporting based on the framework described in Internal Control-Integrated Framework issued by the Commission of Sponsoring Organizations of the Treadway Commission, as revised in 2013. Based on that evaluation, management has concluded that the Company did not maintain effective internal control over financial reporting as of the period ended December 31, 2021 due to the existence of the material weaknesses in internal control over financial reporting described below.

#### Material Weaknesses

A deficiency in internal control over financial reporting exists when the design or operation of a control does not allow management or employees, in the normal course of performing their assigned functions, to prevent or detect misstatements on a timely basis. A material weakness is a deficiency, or a combination of deficiencies, in internal controls over financial reporting, such that there is a reasonable possibility that a material misstatement of the Company's annual or interim financial statements will not be prevented or detected on a timely basis.

Management has determined that the Company did not maintain effective internal control over financial reporting as of the period ended December 31, 2021 due to the existence of the following material weaknesses identified by management. The material weaknesses identified below did not result in a material misstatement of our consolidated financial statements, and management believes that our consolidated financial statements present fairly the consolidated financial position, results of operations and cash flows for the periods covered. However, management recognizes that the failure of the internal control over financial reporting to operate effectively as described below could have resulted in a material misstatement which may not have been detected by our controls:

#### Lack of Accounting Resources

Due to the limited financial resources available for expenditure other than research and development, the Company had a lack of accounting resources resulting in over reliance on key staff, professional opinions, a weakness in monitoring controls and other oversight procedures, which resulted in corrected misstatements.

#### Control Environment

The Company did not maintain an effective control environment. The control environment, which is the responsibility of senior management, sets the tone of the organization, influences the control consciousness of its people, and is the foundation for all other components of internal control over financial reporting. Our control environment was ineffective because:

- We did not timely develop and communicate an employee handbook for employees to consult in the event an issue arises

## Remediation efforts

Management intends to remediate this item in the following manner:

- i. Additional funds have been made available to enable the Company to address its lack of accounting resources.
- ii. Periodic assessments will be performed to evaluate the sufficiency of the Company's accounting resources and needs for recruiting additional personnel, in addition to providing our accounting personnel with regular training over applicable IFRS accounting standards, complex accounting and financial reporting subject matter, and SEC reporting.
- iii. Develop and maintain an Employee Handbook, for employees to reference.

We intend to complete the remediation of the material weaknesses discussed above as soon as practicable, but we can give no assurance that we will be able to do so. Designing and implementing effective disclosure controls and procedures is a continuous effort that requires us to anticipate and react to changes in our business and the economic and regulatory environments and to devote significant resources to maintain a financial reporting system that adequately satisfies our reporting obligations. The remedial measures that we have taken and intend to take may not fully address the material weaknesses that we have identified, and material weaknesses in our disclosure controls and procedures may be identified in the future. Should we discover such conditions, we intend to remediate them as soon as practicable. We are committed to taking appropriate steps for remediation, as needed.

## **ITEM 16A: AUDIT COMMITTEE FINANCIAL EXPERT**

The members of our audit committee are Mr. John Brancaccio and Mr. Willy Simon. Mr. John Brancaccio 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. John Brancaccio 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.

	<b>Year Ending December 31,</b>	
	<b>2021</b>	<b>2020</b>
	(in thousands)	
Audit fees	203	85
Other assurance services	13	77
<b>Total</b>	<b>216</b>	<b>162</b>

**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 Bermuda law. In accordance with generally accepted business practice, our Bye-laws 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 Bermuda law, we are not required to seek shareholder approval to allot ordinary shares in connection with applicable employee equity compensation plans. We will follow Bermuda 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.

**ITEM 16I: DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS**

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
3.2	<a href="#">Memorandum of Association of Tiziana Life Sciences Ltd, adopted as of October 20, 2021 (incorporated by reference to Exhibit 3.1 to Form 8-K12B filed on October 21, 2021).</a>
3.3	<a href="#">Amended and restated bye-laws of Tiziana Life Sciences Ltd, adopted as of October 20, 2021 (incorporated by reference to Exhibit 3.2 to Form 8-K12B filed on October 21, 2021).</a>
4.1	<a href="#">License Agreement relating to Milciclib between Nerviana Medical Services S.r.l. and Tiziana Life Sciences PLC, dated January 2015 (incorporated by reference to Exhibit 10.1 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.2	<a href="#">License and Sublicense Agreement relating to CD3 (NI-0401) between Novimmune SA and Tiziana Life Sciences PLC, dated December 2014, incorporated by reference to Exhibit 10.2 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.3	<a href="#">License and Sublicense Agreement relating to IL-6r (NI-1201) between Novimmune SA and Tiziana Life Sciences PLC, dated December 2016. (incorporated by reference to Exhibit 10.3 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.4	<a href="#">License Agreement relating to a novel formulation of Foralumab in a medical device for nasal administration between The Brigham and Women's Hospital, Inc. and Tiziana Life Sciences plc, dated April 2018. (incorporated by reference to Exhibit 10.4 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.5	<a href="#">Annual Lease for 55 Park Lane, Suite 14a, London W1K 1NA, United Kingdom, dated June 29, 2018 (incorporated by reference to Exhibit 4.5 to Form 20-F filed on June 17, 2020).</a>
4.7	<a href="#">Annual Lease for 3084 Old Easton Road, Doylestown, Pennsylvania, United States, as amended, dated October 1, 2018. (Incorporated by reference to Exhibit 10.6 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.8	<a href="#">Tiziana Life Sciences plc Employee Share Option Plan, with Non-Employee Sub-Plan and US Sub-Plan, adopted by the Board on 23 March 2016 and approved by shareholders on June 30, 2016. (Incorporated by reference to Exhibit 4.7 to Form 20-F filed on April 4, 2019).</a>
4.9	<a href="#">Amended and Restated Service Agreement dated July 11, 2019, between the Registrant and Dr. Kunwar Shailubhai (incorporated by reference to Exhibit 10.9 to Amendment No. 2 to Form F-1 filed on July 11, 2019).</a>
4.10	<a href="#">Form of Deed of Indemnity for board members. (Incorporated by reference to Exhibit 10.10 to Amendment No. 1 to Form F-1 filed on August 23, 2018).</a>
4.12	<a href="#">Tiziana Life Sciences Ltd 2021 Equity Incentive Plan (incorporated by reference to Exhibit 10.3 to Form 8-K12B filed on October 21, 2021).</a>
8.1*	<a href="#">List of Subsidiaries.</a>
12.1*	<a href="#">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.</a>
12.2*	<a href="#">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.</a>
13.1*	<a href="#">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.</a>
13.2*	<a href="#">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.</a>
15.1*	<a href="#">Consent of Mazars LLP.</a>
101.INS	Inline XBRL Instance Document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document.
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).

\* 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 LTD**

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

Date: May 20, 2022

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**TIZIANA LIFE SCIENCES LTD**

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

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

*Opinion on the Consolidated Financial Statements*

We have audited the accompanying Consolidated Balance Sheets of Tiziana Life Sciences Ltd and its subsidiaries (the Group) as of December 31, 2021 and 2020, together with the related Consolidated Statements of Operations and Comprehensive Loss, Consolidated Statements of Shareholders' Equity, and Consolidated Statements of Cash Flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as "the consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Group as of December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

*Basis for Opinion*

These consolidated financial statements are the responsibility of the Group'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 Group is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, 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 Group'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.

/s/ Mazars LLP

Mazars LLP

We have served as the Group's auditor since 2016.

London, England

May 20, 2022



TIZIANA LIFE SCIENCES LTD

**Consolidated Balance Sheets**  
(In thousands)

	<b>Year ended</b>	
	<b>December 31,</b>	
	<b>2021</b>	<b>2020</b>
	\$	\$
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents	42,186	65,824
Prepayments and other receivables	1,301	785
Finance lease receivable	-	152
Taxation receivable	4,736	3,047
Related party receivables	456	368
Total current assets	<u>48,679</u>	<u>70,176</u>
Property and Equipment, net	17	3
Right of use asset	-	357
Intangible asset	130	120
Total non-current assets	<u>147</u>	<u>480</u>
<b>Total assets</b>	<u><b>48,826</b></u>	<u><b>70,656</b></u>
<b>LIABILITIES AND SHAREHOLDERS' EQUITY</b>		
Liabilities:		
Current liabilities:		
Accounts payable and accrued expenses	6,181	5,590
Lease Liability	-	265
Financial liability	-	324
Related party payable	1,355	1,716
Other liabilities	10	85
Total current liabilities	<u>7,546</u>	<u>7,980</u>
Lease Liability (Non-Current)	-	290
<b>Total liabilities</b>	<u><b>7,546</b></u>	<u><b>8,270</b></u>
Shareholders' Equity:		
Called up share capital (102,272,614 shares are issued and outstanding; 2020: 97,306,144)	102	97
Share premium	15,596	-
Share based payment reserve - Options	13,797	8,624
Share based payment reserve - warrants	697	697
Merger relief reserve	118,697	118,697
Shares to be issued reserve	-	13,503
Translation reserve	454	5,414
Retained earnings	<u>(108,063)</u>	<u>(84,646)</u>
Total shareholders' equity	<u>41,280</u>	<u>62,386</u>
<b>Total liabilities and shareholders' equity</b>	<u><b>48,826</b></u>	<u><b>70,656</b></u>

The accompanying notes are an integral part of these consolidated financial statements.

TIZIANA LIFE SCIENCES LTD

**Consolidated Statements of Operations and Comprehensive Loss**  
(In thousands, except loss per share)

	Year ended December 31,		
	2021	2020	2019
	\$	\$	\$
Revenue			
Other revenue	-	-	-
Gross Profit	-	-	-
Research and Development	(13,208)	(5,993)	(3,714)
Operating Expenses	(13,311)	(11,203)	(6,207)
Realization bonus	(855)	(13,214)	-
Impairment of other non-current asset	-	(279)	-
Gain from disposal of intellectual property	-	2,663	-
Total operating expenses	<u>(27,374)</u>	<u>(28,026)</u>	<u>(9,921)</u>
Loss from operations	(27,374)	(28,026)	(9,921)
Other income/(expense):			
Finance Income/(expense)	(176)	(312)	(91)
Other income	893	-	-
Total other income/(expense)	<u>717</u>	<u>(312)</u>	<u>(91)</u>
Loss from operations before income taxes	<u>(26,657)</u>	<u>(28,338)</u>	<u>(10,012)</u>
Income tax credit	<u>3,240</u>	<u>2,207</u>	<u>689</u>
Loss for the year	<u>(23,417)</u>	<u>(26,131)</u>	<u>(9,323)</u>
Other Comprehensive loss:			
Currency translation	<u>(4,478)</u>	<u>3,474</u>	<u>(27)</u>
Comprehensive loss	<u>(27,895)</u>	<u>(22,657)</u>	<u>(9,350)</u>
Basic and diluted loss per share attributable to common shareholders	\$ (0.24)	\$ (0.16)	\$ (0.07)

The accompanying notes are an integral part of these consolidated financial statements.

TIZIANA LIFE SCIENCES LTD

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	Retained Earnings	Shares to be issued Reserve	Translation Reserve	Total Equity
	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
<b>Balance at 1 January 2019</b>	<b>97</b>	-	<b>3,854</b>	<b>1,874</b>	-	<b>118,697</b>	<b>(50,721)</b>	-	<b>1,967</b>	<b>75,768</b>
Convertible loan note issued	-	-	-	-	1,850	-	-	-	-	1,850
Convertible loan note interest	-	-	-	-	52	-	-	-	-	52
Share based payment (options)	-	-	1,309	-	-	-	-	-	-	1,309
Share based payment (warrants)	-	-	-	545	(545)	-	-	-	-	-
Total transactions with owners	-	-	1,309	545	1,357	-	-	-	-	3,211
<b>Comprehensive income</b>										
Loss for the period	-	-	-	-	-	-	(9,323)	-	-	(9,323)
Translation	-	-	-	-	-	-	-	-	(27)	(27)
Total comprehensive income	-	-	-	-	-	-	(9,323)	-	(27)	(9,350)
<b>Balance at 31 December 2019</b>	<b>97</b>	-	<b>5,163</b>	<b>2,419</b>	<b>1,357</b>	<b>118,697</b>	<b>(60,044)</b>	-	<b>1,940</b>	<b>69,629</b>
Issue of share capital (Loan conversion)	-	-	-	-	(2,304)	-	-	-	-	(2,304)
Convertible loan note issued	-	-	-	-	163	-	-	-	-	163
Convertible loan note interest	-	-	-	-	272	-	-	-	-	272
Share based payments charge (warrants)	-	-	-	324	(298)	-	-	-	-	26
Share based payment (options)	-	-	5,105	-	-	-	-	-	-	5,105
Options forfeited in the year	-	-	(35)	-	-	-	-	-	-	(35)
Exercise of options	-	-	(1,609)	-	-	-	1,529	-	-	(80)
Exercise of warrants	-	-	-	(2,046)	810	-	-	-	-	(1,236)
Shares to be issued in lieu of cash realization bonus	-	-	-	-	-	-	-	13,503	-	13,503
Total transactions with owners	-	-	3,461	(1,722)	(1,357)	-	1,529	13,503	-	15,414
<b>Comprehensive income</b>										
Loss for the period	-	-	-	-	-	-	(26,131)	-	-	(26,131)
Translation	-	-	-	-	-	-	-	-	3,474	3,474
Total comprehensive income	-	-	-	-	-	-	(26,131)	-	3,474	(22,657)
<b>Balance at 31 December 2020</b>	<b>97</b>	-	<b>8,624</b>	<b>697</b>	-	<b>118,697</b>	<b>(84,646)</b>	<b>13,503</b>	<b>5,414</b>	<b>62,386</b>
Issue of share capital	2	759	-	-	-	-	-	-	-	761
Share based payment charge (options)	-	-	5,173	-	-	-	-	-	-	5,173
Shares issued in lieu of cash realization bonus	3	14,837	-	-	-	-	-	(13,503)	(482)	855
Total transactions with owners	5	15,596	5,173	-	-	-	-	(13,503)	(482)	6,789
<b>Comprehensive income</b>										
Loss for the period	-	-	-	-	-	-	(23,417)	-	-	(23,417)
Translation	-	-	-	-	-	-	-	-	(4,478)	(4,478)
Total comprehensive income	-	-	-	-	-	-	(23,417)	-	(4,478)	(27,895)
<b>Balance at 31 December 2021</b>	<b>102</b>	<b>15,596</b>	<b>13,797</b>	<b>697</b>	-	<b>118,697</b>	<b>(108,063)</b>	-	<b>454</b>	<b>41,280</b>

The accompanying notes are an integral part of these consolidated financial statements.

TIZIANA LIFE SCIENCES LTD

Consolidated Statements of Cash Flows  
(In thousands)

	Year ended December 31,		
	2021	2020	2019
<b>CASH FLOWS FROM OPERATING ACTIVITIES:</b>			
Loss from operations before income taxes	\$ (26,657)	\$ (28,338)	\$ (10,012)
Adjustments to reconcile net loss to net cash used in operating activities:			
Convertible loan interest accrued	163	272	50
Shares issued in lieu of fees	-	466	105
Share based payment – options	5,173	5,070	1,266
Share based payment – warrants	-	26	-
Bonus to be settled in equity	855	13,503	-
Depreciation	8	5	5
(Gain)/ loss on foreign exchange	(1,899)	237	165
Lease adjustment	-	-	-
Depreciation of right-of-use asset	133	86	248
(Gain)/loss on disposal of right of use asset	(28)	-	71
Proceeds from finance lease reclassified as an investing activity	(152)		
Cash inflow from taxation	1,415	-	1,021
Impairment of SharDNA SPA	-	296	-
Gain from disposal of intellectual property	-	(2,663)	-
Net (increase) in related party receivables	(88)	(31)	(287)
Net (decrease)/increase in related party payables	(685)	1,145	436
Net (increase)/decrease in operating assets/other receivables	516	(437)	159
Net (decrease) in operating liabilities /other liabilities	(516)	(972)	(23)
Net cash used in operating activities	(21,762)	(11,335)	(6,796)
<b>CASH FLOWS FROM INVESTING ACTIVITIES</b>			
Purchase of PPE	(22)	(3)	(4)
Purchase of Act D	-	(120)	-
Proceeds from finance lease	152	-	-
Net cash used in investing activities	130	(123)	(4)
<b>CASH FLOWS FROM FINANCING ACTIVITIES:</b>			
Proceeds from issuance of ordinary shares	-	71,157	-
Proceeds from issuance of convertible loan notes	-	163	1,880
Proceeds from issuance of warrants	129	3,364	-
Proceeds from issuance of options	-	939	-
Repayment of leasing liabilities	(152)	(277)	(200)
Net cash provided by financing activities	(23)	75,346	1,680
Net (decrease)/increase in cash and cash equivalents	(21,655)	63,888	(5,120)
Cash and cash equivalent, beginning of period	65,824	200	5,304
Exchange difference	(1,983)	1,736	16
Cash and cash equivalent, end of period	42,186	65,824	200

## TIZIANA LIFE SCIENCES LTD

### Notes to Consolidated Financial Statements

#### 1. GENERAL INFORMATION

Tiziana Life Sciences Ltd is a public limited company incorporated in Bermuda and at the year end was quoted on the NASDAQ Capital Market (NASDAQ: TLSA). The previous parent, Tiziana Life Sciences plc, delisted from the main market of the London Stock Exchange (LSE: TILS) on October 21, 2021. The address of its registered office is given on page 1. 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 for the Company is also US dollars (\$) indicative of the primary economic environment in which the Company operates.

#### 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 (IASB), and IFRIC interpretations as applicable to companies reporting under IFRS. These accounts have been prepared under the historical cost convention except for the following items:

- Financial instruments – fair value through profit or loss
- Financial instruments – fair value through other comprehensive income

##### **Going Concern**

The Group incurred losses during the year and has net assets 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. As the Group is pre-revenue, the Directors expect the Group 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 going forward will need to continue to secure additional investment to fund the clinical trials.

The Directors have prepared cash flow projections that include the costs associated with the continued clinical trials and additional investment to fund that operation. Based on those projections, the directors conclude that the company will be able to meet its liabilities as they fall due until at least June 2023, with a cash surplus of approximately \$15m projected at this date. Accordingly, the Directors believe it appropriate that the financial statements have been prepared on a going concern basis.

##### ***New and Revised Standards***

##### ***Standards in effect in 2021***

There are no new IFRS standards, amendments to standards or interpretations that are mandatory for the financial year beginning on January 1, 2021, that are relevant to the Group and that have had any impact in the year to December 31, 2021. New standards, amendments to standards and interpretations that are not yet effective, which have been deemed by the Group as currently not relevant, and hence are not listed here

## **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 Group has undertaken a group reorganisation exercise during the year to December 31, 2021. As part of this process, Tiziana Life Sciences Ltd (a Bermudan entity) was inserted above Tiziana Life Sciences Limited (formerly Tiziana Life Sciences Plc) in the Group's structure. As both entities were under common control of Planwise Ltd, the transaction does not constitute a business combination under IFRS 3 'Business combinations' and instead has been accounted for as a group reorganization, using the pooling of interest method. This results in assets and liabilities being measured at their carrying amount in Tiziana Life Sciences Limited (formerly Tiziana Life Sciences Plc) but share capital being that of Tiziana Life Sciences Ltd (a Bermudan entity). Merger accounting has been used to account for this transaction (See note 15 for details).

On 21 October 2021, Tiziana Life Sciences Ltd. (the 'Company') acquired the entire shareholding of the former Tiziana Life Sciences Plc and its related subsidiaries, by a way of a share for share exchange with Tiziana Life Sciences Ltd becoming the Group's immediate parent company.

On 21 October 2021, the Company was admitted for listing on the NASDAQ Capital Market Exchange and the former Tiziana Life Sciences Plc was delisted from the London Stock Exchange.

This Annual Report 20-F is the first set of annual financial statements presented for the newly formed Group and the prior period comparison is that of the former Tiziana Life Sciences Plc. The underlying structure of the Group is unchanged and as such the Consolidated Income Statement, Consolidated Statement of Financial Position, Consolidated Statement of Changes in Equity and Consolidated Statement of Cash Flows have been presented on a consistent basis as if the group reorganisation had taken place at the start of the earliest period presented (see note 15).

## **Segment reporting**

Operating segments are reported in a manner consistent with the internal reporting provided to the Board. 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 the year represents the total of current taxation and deferred taxation. The charge in respect of current taxation is based on the estimated taxable profit for the year. Current tax is provided at amounts expected to be paid (or recovered) using the tax rates and laws that have been enacted or substantively enacted by the balance sheet date.

Deferred tax is provided in full, using the liability method, on temporary differences arising between the tax bases of assets and liabilities and their carrying amounts in the consolidated financial statements. Deferred tax is determined using tax rates (and laws) that have been enacted or substantially enacted by the balance sheet date and expected to apply when the related deferred tax is realized, or the deferred liability is settled. Deferred tax assets are recognized to the extent that it is probable that the future taxable profit will be available against which the temporary differences can be utilized.

Research and Development tax credits are provided for in the year that the costs are incurred. These are estimated based on eligible research and development expenditure. Any differences that are rebated are recognized in the following year, when the cash is received from the UK tax authorities.

## **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 presentational 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 made which provide the right to perform research are carefully evaluated to determine whether such payments are to fund research or acquire an asset. Licence fees expenses are recognised as incurred.

## **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 recognised 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**

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 (FVTPL) 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.

## **Warrants**

Warrants are issued by the Group in return for services and as part of a financing transaction.

### *Warrants issued in return for services.*

These warrants fall within scope of IFRS 2. The Company recognises that the fair value at the date of grant of these warrants should be expensed to the Statement of Income and recognised over the life of the service for which the warrant was provided. These warrants have been valued by reference to the equity instruments granted as they are all tied to Convertible loan notes. The measurement date is therefore the date that the Convertible loan note was entered into.

### *Warrants issued as part of a financing transaction.*

Warrants issued as part of a financing transaction fall outside the scope of IFRS 2. These are classified as equity instruments because a fixed amount of cash is exchanged for a fixed amount of equity. The fair value is recognised within equity and is not remeasured.



## Share capital

Ordinary shares of the Company are classified as equity.

## Property, plant and equipment

### (i) Recognition and measurement

Items of property, plant 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 capitalised as part of that equipment.

When parts of an item of property, plant and equipment have different useful lives, they are accounted for as separate items (major components) of property, plant and equipment.

Gains and losses on disposal of an item of property, plant and equipment are determined by comparing the proceeds from disposal with the carrying amount of property, plant and equipment, and are recognised in profit or loss.

### (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 recognised in profit or loss on a straight-line basis over the estimated useful life of each part of an item of property, plant and equipment. Leased assets are depreciated over the shorter of the lease term and their useful lives unless it is reasonably certain that the Group 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.

Fixtures and fittings	5 years
IT and equipment	3 years
Right of use asset	Economic life of contractual relationship

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.

### *Impairment of non-financial assets*

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 at a pre-tax discount rate.

### **Leases**

All leases are accounted for by recognizing a right-of-use asset and a lease liability except for:

- Leases of low value assets; and
- Leases with a duration of 12 months or less.

IFRS16 was adopted 1 January 2019 without restatement of comparative figures. The following policies apply subsequent to the date of initial application, 1 January 2019.

The Group has leases for its offices. Each lease is reflected on the balance sheet as a right-of-use asset and a lease liability. The Group does not have any leases of low value assets. Variable lease payments which do not depend on an index or a rate (such as lease payments based on a percentage of Group sales) are excluded from the initial measurement of the lease liability and asset. The Group classifies its right-of-use assets in a consistent manner to its property, plant and equipment (see Note 12).

For leases over office buildings and factory premises the Group must keep those properties in a good state of repair and return the properties in their original condition at the end of the lease. The expected costs of returning to original condition is considered negligible.

At lease commencement date, the Group recognises a right-of-use asset and a lease liability in its consolidated statement of financial position. The right-of-use asset is measured at cost, which is made up of the initial measurement of the lease liability, any initial direct costs incurred by the Group, an estimate of any costs to dismantle and remove the asset at the end of the lease, and any lease payments made in advance of the lease commencement date (net of any incentives received).

The Group depreciates the right-of-use asset on a straight-line basis from the lease commencement date to the earlier of the end of the useful life of the right-of-use asset or the end of the lease term. The Group also assesses the right-of-use asset for impairment when such indicators exist.

At the commencement date, the Group measures the lease liability at the present value of the lease payments unpaid at that date, discounted using the Group's incremental borrowing rate because as the lease contracts are negotiated with third parties it is not possible to determine the interest rate that is implicit in the lease. The incremental borrowing rate is the estimated rate that the Group would have to pay to borrow the same amount over a similar term, and with similar security to obtain an asset of equivalent value. This rate is adjusted should the lessee entity have a different risk profile to that of the Group.

Lease payments included in the measurement of the lease liability are made up of fixed payments (including in substance fixed), variable payments based on an index or rate, amounts expected to be payable under a residual value guarantee and payments arising from options reasonably certain to be exercised.

Subsequent to initial measurement, the liability will be reduced by lease payments that are allocated between repayments of principal and finance costs. The finance cost is the amount that produces a constant periodic rate of interest on the remaining balance of the lease liability.

Short term leases exempt from IFRS 16 are classified as operating leases. Payments made under operating leases are recognised in profit and loss on a straight-line basis over the term of the lease.

### ***The Group as a lessor***

As a lessor the Group classifies its leases as either operating or finance leases. A lease is classified as a finance lease if it transfers substantially all the risks and rewards incidental to ownership of the underlying asset and classified as an operating lease if it does not.

During the course of 2021, the Group continued to sublet one of its office spaces until October 2021. This has been recognised as a finance lease receivable for the value of the sublease.

### **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 recognised valuation model in order to calculate the fair value of the awards.

Where employees and directors 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).

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 an –equity 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 recognised in prior periods if fewer share options ultimately are exercised than originally estimated.

Upon exercise of share options/warrants, the proceeds received are allocated to share capital with any excess being recorded as share premium. A corresponding debit is made to the share based payment reserve.

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 recognised for services received over the remainder of the vesting period is recognised 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**

The Group issues Convertible loan notes which can be classified as equity or a liability depending on whether the fixed for fixed condition is met or not.

*Where the fixed for fixed condition is met*

The Group classifies convertible loan notes that meet the fixed for fixed condition as equity instruments and records the principal of the loan note as a equity in a Convertible loan note reserve. The accrued interest on the principal amount 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 the fixed for fixed condition is not met*

The Group classifies convertible loan notes that do not meet the fixed for fixed condition as liability instruments and records the principal of the loan note as a debt liability in the liabilities section of the statement of financial position. 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.

### **Sub License Income**

In September 2021 the Company signed a collaboration agreement signed with Precision Biosciences, Inc. under which \$750k was recognized as an upfront payment in accordance with the contract for the on grant of an exclusive license to use foralumab as a lymphodepletion agent in conjunction with Precision Biosciences, Inc's allogeneic CAR T therapeutics for the treatment of cancers.

### **Other Intangible Assets**

Other intangible assets that are acquired by the Group are stated at cost less accumulated impairment losses.

At each balance sheet date non-financial assets are assessed to determine whether there is an indication that the asset or the asset's cash generating unit may be impaired. If there is such an indication the recoverable amount of the asset or asset's cash generating unit is compared to the carrying amount.

## **3. CRITICAL ACCOUNTING JUDGEMENT**

The preparation of financial information in accordance with generally accepted accounting practice, in the case of the Group being International Financial Reporting Standards as issued by the IASB, 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.

The following are considered to be critical accounting estimates:

### ***Share-based payments***

The Group accounts for share-based payment transactions for employees in accordance with IFRS 2 Share-based Payment, which requires the measurement of the cost of employee services received in exchange for the options on our ordinary shares, based on the fair value of the award on the grant date.

The Directors selected the Black-Scholes-Merton option pricing model as the most appropriate method for determining the estimated fair value of our share-based awards without market conditions. For performance-based options that include vesting conditions relating to the market performance of our ordinary shares, a Monte Carlo pricing model was used in order to reflect the valuation impact of price hurdles that have to be met as conditions to vesting.

The Company makes estimates as to the useful life of an option award, the expected price volatility of the underlying share, risk free interest rate for the term of the award and correlations and volatilities of the shares of peer group companies. The Company also makes estimates as to the vesting period for awards that have performance based criteria.

The resulting cost of an equity incentive award is recognised as expense over the requisite service period of the award, which is usually the vesting period. Compensation expense is recognised over the vesting period using the straight-line method and classified in the consolidated statements of comprehensive income.

The assumptions used for estimating fair value for share-based payment transactions are disclosed in note 27 to our consolidated financial statements.

#### 4 OTHER INCOME

The Group's other income is made up of the following:

	<b>Year Ended December 31,</b>		
	<b>2021 \$'000</b>	<b>2020 \$'000</b>	<b>2019 \$'000</b>
Sublicense income	750	-	-
Other	143	-	-

Sublicense income has been classified as other income as the counterparty is not considered a customer but an entity we are collaborating with.

#### 5. OPERATING LOSS

The Group's operating losses are stated after charging the following:

	<b>Year Ended December 31,</b>		
	<b>2021 \$'000</b>	<b>2020 \$'000</b>	<b>2019 \$'000</b>
License fee	(1,047)	706	553
Realization bonus	855	13,503	-
Foreign exchange gain related to the realization bonus	-	(289)	-
Depreciation of Property, Plant and Equipment	8	5	5
Depreciation (Right-of-use asset)	133	86	245
Foreign exchange (gain)/losses	(1,899)	239	165

License fees relating to 2019 and 2020 were waived in the current year as a result of negotiations by the Group.

A realization bonus of \$13.5 million became payable during the year ended December 31, 2020 to the chairman of the board. This became payable upon the Company raising funds in excess of \$28m (£20m), which it successfully raised in August 2020. As the bonus was not settled until November 2021, interest of \$0.9m was accrued on the amount due in the year to December 31, 2021.

#### 6. 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.

An analysis of the Group's other income by location is shown below:

	<b>UK \$'000</b>	<b>USA \$'000</b>	<b>Total \$'000</b>
	Sublicense income	750	-

## 7. EMPLOYEES

Group	Year ended December 31,		
	2021 \$'000	2020 \$'000	2019 \$'000
Staff costs comprised:			
Directors' salaries (including bonus)	2,526	14,666	1,145
Employees' wages, salaries and bonus	1,856	1,058	696
Social security costs	176	194	609
Recruitment fees	242	17	-
Share based payment charge	5,173	5,105	1,266
	<u>9,973</u>	<u>21,040</u>	<u>3,716</u>
The average monthly number of employees, including directors, employed by the group during the year was:			
Research and Development	8	3	5
Corporate and administration	5	8	4
	<u>13</u>	<u>11</u>	<u>9</u>

## 8. REMUNERATION OF KEY MANAGEMENT PERSONNEL

\$'000	Year ended December 31,											
	2021				2020				2019			
	Directors' fee	Bonus	Salary	Share based payments	Directors' fee	Bonus	Salary	Share based payments	Directors' fee	Salary	Share based payments	Bonus
G. Cerrone (1)	330	855	-	624	170	13,588	-	155	102	-	296	182
R. Dalla Favera	-	-	-	-	-	-	-	-	3	-	-	-
Willy Simon	59	-	-	93	49	-	-	31	48	-	-	-
Gregor MacRae	-	-	-	-	27	-	-	-	-	-	-	-
J Brancaccio	59	-	-	93	22	-	-	31	-	-	-	-
K. Shailubhai	-	210	600	492	-	210	600	2,069	-	600	695	210
T Adams	-	-	413	2,197	-	-	-	-	-	-	-	-
	<u>448</u>	<u>1,065</u>	<u>1,013</u>	<u>3,499</u>	<u>268</u>	<u>13,798</u>	<u>600</u>	<u>2,286</u>	<u>153</u>	<u>600</u>	<u>991</u>	<u>392</u>

(1) Gabriele Cerrone's 2021 bonus is the interest charged on his 2020 bonus due to delayed issuance of shares ; his 2020 bonus includes a \$13.2m realization bonus; his 2019 bonus covers the period June 9, 2016 to December 31, 2019

All bonuses are short term. No post-employment or termination payments were made.

The following share options were granted to directors in the following periods:

	Year ended December 31,		
	2021 Number of options	2020 Number of options	2019 Number of options
G. Cerrone	-	1,800,000	-
K. Shailubhai	-	-	-
L. Zanbeletti	-	-	-
W.Simon	-	250,000	-
J. Brancaccio	-	250,000	-
T Adams	3,500,000	-	-
	<u>3,500,000</u>	<u>2,300,000</u>	<u>-</u>

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 share options were exercised by directors in the year. 2,319,225 share options were exercised by directors in the year to 31 December 2020 for an intrinsic gain of \$4.1m.

The Company made \$24k (2020: \$10k, 2019: \$16k) of payments to a defined contribution pension schemes on behalf of directors or employees.

## 9. FINANCE COSTS

	Year ended December 31,		
	2021 \$'000	2020 \$'000	2019 \$'000
<b>Group</b>			
<b>Finance Income</b>			
Finance income received on net investment in lease	-	8	1
<b>Total finance income</b>	<b>-</b>	<b>8</b>	<b>1</b>
<b>Finance Expense</b>			
Finance charge accrued on convertible loan notes	163	303	61
Interest expense on lease liabilities	13	17	31
<b>Total finance expenses</b>	<b>176</b>	<b>320</b>	<b>92</b>
<b>Net finance expense recognized in Statement of Comprehensive Income</b>	<b>176</b>	<b>312</b>	<b>92</b>

## 10. TAXATION

	Year Ended December 31,		
	2021 \$'000	2020 \$'000	2019 \$'000
<b>Group</b>			
Current year tax (credit)	(3,255)	(1,546)	(661)
Adjustments due to prior periods	(15)	(661)	(28)
<b>Total tax (credit) for the period</b>	<b>(3,240)</b>	<b>(2,207)</b>	<b>(689)</b>

The tax charge for the year is different from the standard rate of corporation tax in the United Kingdom of 19%. The difference can be reconciled as follows:

Loss before taxation	(26,657)	(28,337)	(10,013)
Loss charged at standard rate of corporation tax 19%	(5,065)	(5,384)	(1,903)
Movement in unrecognized deferred tax	1,722	1,316	(241)
Expenses not deductible for taxation	1,550	4,986	1,727
Adjustments due to prior periods	(15)	(661)	(28)
Research and development claim	(1,401)	(665)	(285)
Income not taxable for tax purposes	(61)	(1,741)	
Consolidation adjustment in relation to foreign exchange movements	-	(58)	(41)
	<b>(3,313)</b>	<b>(2,207)</b>	<b>(689)</b>

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 for the prior period. 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, 2021 is \$11,591k (2020 is \$6,182k; 2019; \$3,517k).



## 11. 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,		
	2021	2020	2019
(Loss) attributable to equity holders of the company (\$000)	(23,417)	(26,131)	(9,323)
Weighted average number of ordinary shares in issue	97,932,055	97,306,144	97,306,144
<b>Basic loss per share (cents per share)</b>	<b>(23.9)</b>	<b>(26.85)</b>	<b>(9.58)</b>

As the Group is reporting a loss from continuing operations for the year then, in accordance with IAS 33, share options, warrants and convertible loan notes 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.

## 12. PROPERTY, IT AND EQUIPMENT

Details of the Groups property, IT and equipment are as follows:

\$000	Furniture and fixtures	IT equipment	Total
<b>Cost</b>			
At 1 January 2020	16	38	54
Additions	-	1	1
Disposals	-	-	-
<b>At 31 December 2020</b>	<b>16</b>	<b>39</b>	<b>55</b>
<b>Depreciation</b>			
At 1 January 2020	12	35	47
Charge in year	3	2	5
<b>At 31 December 2020</b>	<b>15</b>	<b>37</b>	<b>52</b>
<b>Net Book Value as at 31 December 2020</b>	<b>1</b>	<b>2</b>	<b>3</b>

\$000	Furniture and fixtures	IT equipment	Total
<b>Cost</b>			
At 1 January 2021	16	39	55
Additions		22	22
Disposals			
<b>At 31 December 2021</b>	<b>16</b>	<b>61</b>	<b>77</b>
<b>Depreciation</b>			
At 1 January 2021	15	37	52
Charge in year	1	7	8
<b>At 31 December 2021</b>	<b>16</b>	<b>44</b>	<b>60</b>
<b>Net Book Value as at 31 December 2021</b>	<b>-</b>	<b>17</b>	<b>17</b>

### 13. OTHER RECEIVABLES

<u>\$000</u>	<u>Year ended</u> <u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
VAT Receivable	80	82
Receivable due for options exercised	-	191
Security deposits receivable	35	135
Prepayments	1,186	375
	<u>1,301</u>	<u>785</u>

There are no differences between the carrying amount and fair value of any of the trade and other receivables above.

### 14. FINANCE LEASE RECEIVABLE

In November 2019, the Group subleased one of its leased office spaces in its entirety. The sublease ran for the remaining term of the original lease, until October 2021. The sublease had been classified as a finance lease receivable

<u>Finance lease receivable</u>	<u>31 Dec</u> <u>2021</u>	<u>31 Dec</u> <u>2020</u>
	<u>\$000</u>	<u>\$000</u>
Current	-	152
Non-current	-	-
	<u>-</u>	<u>152</u>

## 15 SHARE CAPITAL AND SHARE PREMIUM

### Group

On 21 October 2021, the Company acquired the entire shareholding of Tiziana Life Sciences Plc and its subsidiaries through a share for share exchange transaction. On this date Tiziana Life Sciences Ltd became the Group's parent company. This transaction does not constitute a business combination under IFRS 3 "Business combinations" and has been accounted for as a group reorganization. Merger accounting has been applied to account for the insertion of the new company. Due to a share consolidation, the effect of this was a decrease in share capital of the Company with an offset posted to the merger reserve. As a common control transaction, the Group has elected to present the comparative information as if this transaction had occurred before the start of the comparative period. The share capital arising on the share for share exchange has been presented as share capital in the comparative period.

	Nominal Value		Share Capital		Share Premium	Merger Reserve
	£/\$		Shares	\$000	\$000	\$000
<b>At January 1 2021 per 20-F annual report</b>	£	0.03	194,612,289	10,794	111,821	-
<b>Group Reorganization</b>						
Elimination of share capital in Tiziana Life Sciences Plc	£	0.03	(194,612,289)	(10,794)	(111,821)	122,615
Shares issued pursuant to share for share exchange and consolidation	\$	0.001	97,306,144	97	-	(97)
Elimination of other reserves in Tiziana Life Sciences Plc						(3,821)
<b>Restated at 1 January 2021</b>	\$	0.001	97,306,144	97	-	118,697
Shares issued in the period:						
Conversion of warrants	\$	0.001	136,854	-	156	-
Conversion of Loan	\$	0.001	1,866,907	2	603	-
Issued in lieu of cash bonus	\$	0.001	2,962,709	3	14,837	-
<b>At 31 December 2021</b>			102,272,614	102	15,596	118,697

### Ordinary Shares

Ordinary shares have a par value of \$0.001. 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.

## 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.

	2021		2020		2019	
	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	67	17,024	113	16,379	107	18,617
Granted	166	5,210	111	3,870	-	-
Forfeited	-	-	(52)	(300)	(152)	(2,238)
Exercised	-	-	(25)	(2,925)	-	-
Outstanding at 31 December	90	22,234	67	17,024	113	16,379
Exercisable at 31 December	54	7,616	65	6,249	67	5,521

During the year ending 31 December 2021 no options were exercised. 2,925,725 options were exercised during the year ending 31 December 2020. No options were exercised in the year to 31 December 2019.

The total outstanding fair value charge of the share option instruments is deemed to be approximately \$12,339k (2020: \$7,046k; 2019: \$5,237k).

The total expenses recognized for the year ending 31 December 2021 arising from share based payment transactions is \$5,173k (2020: \$5,105k; 2019: \$1,266k).

Share options outstanding at the end of the year have the following expiry dates and exercise prices:

Grant Date	Expiry Date	Exercise Price	Share Options as at 31 December 2021 ('000)
26 June 2014	26 June 2024	\$ 0.47	1,831
30 April 2018	30 April 2028	\$ 1.10	1,300
6 May 2020	5 May 2028	\$ 0.47	12,393
23 July 2020	26 July 2030	\$ 2.11	1,000
25 August 2020	24 August 2030	\$ 1.98	500
02 February 2021	01 February 2031	\$ 1.36	1,250
02 February 2021	01 February 2031	\$ 1.98	3,500
08 October 2021	08 October 2031	\$ 0.72	460
<b>Total</b>			<b>22,234</b>

### Fair value of options granted

The Directors have used the Black-Scholes-Merton option pricing model to estimate the fair value of all of the options granted during the year to December 31, 2021, applying the assumptions below.

Historical volatility is based on the historical volatility of the Company itself.

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.

The model inputs for options granted during the year ended 31 December 2021 valued under the Black-Scholes-Merton Valuation model included:

	<b>2 February 2021</b>	<b>8 October 2021</b>
Grant date share price	\$ 2.116	\$ 0.719
Exercise share price	\$ 1.357/1.983	\$ 0.719
Risk free rate	-0.10% to -0.02%	0.32% to 0.65%
Expected volatility	101% to 162%	83% to 122%
Option life	10 years	10 years
Weighted average share price	\$ 1.818	\$ 0.719
Weighted average fair value per share option	\$ 0.862	\$ 0.319

The model inputs for options granted during the year ended 31 December 2020 valued under the Black-Scholes-Merton Valuation model included:

	<b>6 May 2020</b>	<b>23 July 2020</b>
Grant date share price	\$ 0.853	\$ 2.184
Exercise share price	\$ 0.478	\$ 2.150
Risk free rate	0.04% to 0.05%	0.04% to 0.05%
Expected volatility	92% to 117%	92% to 117%
Option life	10 years	10 years
Weighted average share price	\$ 0.853	\$ 2.184
Weighted average fair value per share option	\$ 0.478	\$ 2.150

For the options issued in August 2020 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 award is 4 years and is based on managements' assessment of when the market condition is likely to be achieved; and
- a range of fair value's per share were produced and management have determined the most appropriate value based on their knowledge of the market and vesting conditions being fulfilled.

#### *Modification of share based payments.*

In May 2020, the Company reduced the exercise price for options issued to employees and directors to \$0.48 (£0.35). This was approved by shareholders at a General Meeting held on May 6, 2020.

The fair value of the modified options at the date of modification was determined using the option pricing models as described above. The incremental fair value was recognised as an expense over the period from the modification date to the end of the vesting period. The expense for the original option grant will continue to be recognised as if the terms had not been modified.

The fair value of the modified options was determined using the same models and principles as described above.

## Group and Company Warrants

No warrants were issued in 2021. For warrants issued in 2020, the Directors have estimated the fair value of the warrants using the Black-Scholes valuation model and assumptions below:

	<u>January</u> <u>2020</u>		<u>21 January</u> <u>2020</u>		<u>1 June</u> <u>2020</u>	
Grant date share price	£	0.43	£	0.43	£	1.15
Exercise share price	£	0.42	£	0.35	£	0.70
Risk free rate		0.64%		0.40%		0.04%
Expected volatility		61.7%		84.7%		111%

	<u>2021</u> <u>\$000</u>	<u>2020</u> <u>\$000</u>	<u>2019</u> <u>\$000</u>	
Outstanding at 1 January		697	2,418	1,873
Granted		-	324	545
Transfer to share premium on exercise of warrants		-	(2,046)	-
Outstanding at 31 December		<u>697</u>	<u>697</u>	<u>2,418</u>

A share-based payment charge for the year of \$0 (2020: \$26k, 2019: \$0) has been expensed in the statement of comprehensive income.

## **17. CONVERTIBLE DEBT INSTRUMENT CLASSIFIED AS A LIABILITY**

### Group and Company

#### **Convertible Loan Notes 2016**

A convertible loan note of \$273k 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 the Noteholder 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 as a result of the fact that the Company is obligated to repay the capital amount and the interest of the loan, and the Noteholder has the right to settle the obligation via a cash settlement and is not limited to settling the obligation in shares in the Company. The loan note was converted during the course of the year to December 31, 2021, with accelerated interest until October 2028 recognized by board approval.

#### **Accounting for the convertible debt instrument**

The net proceeds received from the issue of the Convertible Loan Note have been recorded as a debt liability in the balance sheet and the accrued interest charged to the income statement and the debt liability. The loan was converted in November 2021. The liability for the convertible debt instrument is;

#### **Convertible Loan Note Classified as a Liability**

	<u>Year ended</u> <u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
	<u>\$000</u>	<u>\$000</u>
Convertible loan notes b/f	324	313
Accrued interest	163	11
Conversion of loan note	(487)	-
	<u>-</u>	<u>324</u>

## 18. CONVERTIBLE INSTRUMENTS CLASSIFIED AS EQUITY

On October 31, 2019, the Company decided to raise convertible equity finance from supportive existing shareholders. \$1,850,000 was raised from the issuance of Convertible Loan Notes. The Loan Notes are short term instruments and carry a coupon of 16% per annum and are convertible (together with all accrued interest) into ordinary shares of nominal value £0.03 each in the capital of the Company at a conversion price of 42p, they are not convertible into cash. The Loan Notes are convertible on the third anniversary of the date of issue of the Notes, or at the election of the noteholder on completion of the next non-qualifying equity financing or on the making of a takeover offer for the Company (as defined in the City Code on Takeovers and Mergers), and such election may be made on an immediate basis or conditional on any such takeover offer being declared, or becoming, unconditional.

The warrants issued in connection with the Loan Notes entitle the holders to subscribe for one additional share per conversion share at the same price of 42p. The warrants may be exercised for a period of up to 5 years from their date of issue.

The principal amount of the Convertible Equity Instrument that was recorded as in the convertible loan note reserve prior to conversion is as follows:

	<u>2021</u> <u>\$000</u>	<u>2020</u> <u>\$000</u>	<u>2019</u> <u>\$000</u>
Par value of Convertible loan notes issued	-	1,850	1,850
Less: Fair value of warrants issued to note holders	-	(545)	(545)
Exchange rate adjustment	-	209	-
	<u>-</u>	<u>1,514</u>	<u>1,305</u>
Accrued interest	-	348	52
Less: convertible loan note conversion	-	(2,523)	-
Exercise of warrants	-	661	-
	<u>-</u>	<u>-</u>	<u>1,357</u>

## 19. RESERVES

The share-based payment reserve for warrants represent the cost to issue warrants in the future based on their grant date fair value.

The share-based payment reserve for options represents the cost to issue share-based compensation, primarily share options, based on their grant date fair value.

The convertible loan note reserve represents the proceeds received on issuance of convertible loan notes classified as equity instruments, accrued interest and the fair value of the debt component, in respect of loans that are yet to convert.

Retained earnings represent the cumulative profits/(losses) of the entity which have not been distributed to shareholders. This reserve has been credited as part of the capital reduction exercise described below.

The shares to be issued reserve represents the equity shares that are to be issued to the Chairman in lieu of his realization bonus, which became payable during the course of the year to 31 December 2020.

The translation reserve represents the unrealised gains or losses from the foreign currency translation of Companies within the Group.

The merger reserve arises on consolidation as a result of the share for share exchange transaction that took place this year described in note 15. It represents the difference between the share capital issued and the aggregate carrying value of assets and liabilities and other reserves of the previous parent on the merger date.

## 20. 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 summarised 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 minimising the exposure to financial markets. The Group does not engage in the trading of financial assets for speculative purposes.

## 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 minimise 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 by 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:

\$000	2021		
	Less than 3 months	3 to 12 months	Total
Trade payables	2,873	1,533	4,406
Related party payables	1,355	-	1,355
Total	4,228	1,533	5,761

\$000	2020		
	Less than 3 months	3 to 12 months	Total
Trade payables	2,620	746	3,366
Related party payables	-	2,040	2,040
Total	2,620	2,786	5,406

## 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 Barclays 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 either the year ended 31 December 2021 or 31 December 2020.

## Foreign Currency risk

The group operates internationally although the majority of its operations are based in the United Kingdom and the United States, and the majority of assets and liabilities are denominated in US Dollars, with a small amount denominated in Pound Sterling. It therefore is exposed to some foreign exchange risk arising from exposure to various currencies primarily the Pound Sterling. The Group monitors currency exchange rates and makes judgments as to whether to enter into currency hedging contracts. Currently no such hedging contracts are in place.

### Sensitivity analysis

A reasonably possible strengthening (weakening) of the US dollar, or Sterling against all other currencies at 31 December 2021 would have affected the measurement of the financial instruments denominated in a foreign currency and affected equity and profit and loss by the amounts shown below. This analysis assumes that all other variables remain constant.

December 31, 2021	Profit or loss and equity	
	Strengthening	Weakening
USD (5% movement)	90	(90)

## 21. CAPITAL RISK MANAGEMENT

For the purpose of the Group's capital management, capital includes called up share capital, share premium, share based payments for options, share based payments for warrants, convertible loan note reserve, and all other equity reserves attributable to the equity holders of the parent as reflected in the statement of financial position.

The Company's objectives when managing capital are to safeguard the Company's ability to continue as a going concern and to maximise shareholder value through the optimisation of the equity balance.

The Group adjusts its capital structure in light of changes in economic conditions and expected business demands on capital. The Group may also return capital to shareholders or issue additional shares.



## 22. TRADE AND OTHER PAYABLES

Group	Year ended December 31,	
	2021	2020
	\$000	\$000
Trade payables	4,406	3,366
Accruals	1,775	2,224
	<u>6,181</u>	<u>5,590</u>

## 23. OTHER NON-CURRENT ASSETS

In June 2016, the Board approved the purchase of the data repository of DNA samples from SharDNA (an Italian entity in liquidation) for EUR 258k, approximately \$279k.

Management recognize that the transaction is not the purchase of a business, but the purchase of key assets owned by SharDNA. These assets are owned by Tiziana Life Sciences Ltd (formerly Tiziana Life Sciences plc).

The validity to the sale of the assets has been confirmed by the Italian judicial system however the Company is still unable to utilise these assets until the resolution of the outstanding data protection legal action. This action is unlikely to be resolved for another 2 years so the Company decided to impair the asset resulting in an impairment charge of \$279k during the year ending December 31, 2020.

## 24. RELATED PARTY TRANSACTIONS

The ultimate controlling party of the Group is Planwise Group Ltd.

Rasna Therapeutics Inc is a related party as the entity is controlled by a person that has significant influence over the Group. Rasna is also party to a Shared Services agreement with Tiziana whereby Rasna is charged for shared services such as the payroll and rent. During 2020, Tiziana extended a loan to Rasna for \$72,000 at an interest rate of 8% per annum. As of December 31, 2021, \$106k (2020: \$78k, 2019: \$5k) was owed to Tiziana Life Sciences Ltd in respect of the loan and shared services agreement. The total charged under the shared services agreement in the year ending 31 December 2021 was \$11k.

In addition to the above, on April 16, 2020, Tiziana also acquired all of the intellectual property relating to a nanoparticle-based formulation of Actinomycin D (Act D; a.k.a. Dactinomycin), from Rasna to expand its pipeline for a consideration of an initial \$120k upfront payment and milestone payments of up to an additional aggregate \$630k (also see note 26). There were no milestone payments due in the year ending 31 December 2021.

OKYO Pharma Ltd is a related party as the entity is controlled by a person that has significant influence over the Group. OKYO is also party to a Shared Services agreement with Tiziana whereby OKYO is charged for shared services such as the payroll and rent. As of December 31, 2021, \$42k (2020: \$27k, 2019 \$28k) was owed to Tiziana Life Sciences Ltd in respect of this agreement. The total charged under the shared services agreement in the year ending 31 December 2021 was \$98k.

Gensignia Lifesciences Inc is a related party as the entity is controlled by a person that has significant influence over the Group. As of December 31, 2021, \$295k (2020: \$348k, 2019: \$320k) was owed to Tiziana Life Sciences Ltd in respect of a loan facility, which is past due Interest is due on the loan however the board have waived all interest charges to date. However the board are considering mechanism's for settlement and believe this to be likely. There were no transactions during the year to December 31, 2021.

Accustem Sciences Inc is a related party as the entity is controlled by a person that has significant influence over the Group. Accustem is also party to a Shared Services agreement with Tiziana whereby the Company is charged for shared services such as payroll and rent As of December 31, 2021, \$1,341k (2020: \$1,346k) was the net amount owed to Accustem, made up of cash payable of \$1,355k less shared service costs of \$14k.

## 25. LEASES

All leases are accounted for by recognising a right-of-use asset and a lease liability except for:

- Leases of low value assets; and
- Leases with a duration of 12 months or less.

IFRS16 was adopted 1 January 2019 without restatement of comparative figures. The following policies apply subsequent to the date of initial application, 1 January 2019.

The Group has leases for its offices. Each lease is reflected on the balance sheet as a right-of-use asset and a lease liability. The Group does not have leases of low value assets. Variable lease payments which do not depend on an index or a rate (such as lease payments based on a percentage of Group sales) are excluded from the initial measurement of the lease liability and asset. The Group classifies its right-of-use assets in a consistent manner to its property, plant and equipment (see Note 12).

For leases over office buildings and factory premises the Group must keep those properties in a good state of repair and return the properties in their original condition at the end of the lease.

During the course of 2021, the Group entered into new lease agreements on all of its offices. The new leases all have a term shorter than 12 months so the Group has applied the exemption allowed by paragraph 5a in IFRS16 in respect of short term leases.

	<b>31 Dec 2021</b>	<b>31 Dec 2021</b>
	<b>\$000</b>	<b>\$000</b>
Right-of-use assets		
At 1 January 2021	357	433
Depreciation	(133)	(91)
Disposal of lease	(224)	-
Exchange differences		15
	<u>-</u>	<u>357</u>
	<u>-</u>	<u>357</u>
Lease Liabilities		
At 1 January 2021	555	820
Interest expense	13	18
Lease payments	(164)	(321)
Exchange differences	-	(38)
Disposal of lease	(394)	-
	<u>-</u>	<u>555</u>
	<u>-</u>	<u>555</u>

## 26. DEMERGER OF SUBSIDIARY

The Company's demerger of its subsidiary, Stemprinter Sciences Ltd, to allow for the creation of a separate business occurred by way of a demerger under English law. It happened in two distinct steps. In the first step, in September 2020, Tiziana transferred all the ownership rights and intellectual property relating to the StemPrintER project, in the form of patents and a license, to a Tiziana subsidiary, Stemprinter Sciences Limited. In the second step, on October 5, 2020, the Company sold Stemprinter Sciences Limited to Accustem Sciences Ltd.

In September 2020, the Company transferred all the ownership rights and intellectual property relating to StemPrintER™ along with \$1.4 million (£1.0 million) in cash to its newly formed wholly owned subsidiary, StemPrinter Sciences Limited. This was the first step in the creation of the separate business by way of a demerger under English law.

In this first step, the transfer of all the ownership rights and intellectual property was treated as an asset transfer (acquired IPR&D). The treatment as a separate asset acquisition at this stage reflected the fact that, immediately prior to transfer, the Company carried out only limited maintenance type activity on the StemPrintER project and the concentration of fair value was in the StemPrintER intellectual property asset.

Stemprinter Sciences Limited recorded the ownership rights and intellectual property a separately acquired an intangible asset in its books at cost under IAS 38, with cost (as defined in the IFRS Glossary), including the fair value of the other consideration given (i.e., shares issued in exchange for intellectual property). temprinter Sciences Limited therefore was also required to record the equity capital issued for the StemPrintER asset acquired at fair value as set out in IFRS 13. Prior to the transfer, the intellectual property was an internal project within the Company and was not classified as an asset on the Company's balance sheet or a separate line of business.

The Company tracked the expenses incurred in maintaining this project in the form of patent maintenance fees, CRO fees and project consultancy fees, the total amounts for which between 2014 and the transfer date were £2,073,930. The Company used the aggregate amount of these expenses as its determination of fair value (as further discussed below) to credit an account in the books of Stemprinter Sciences Limited by \$2,83,246 (£2,073,930). Tiziana received 3,070,000 shares in Stemprinter Sciences Limited as consideration for the asset transfer. Tiziana also contributed capital and resources, consisting of \$1.4 million (£1.0 million) in cash.

In the second step of the transaction, on October 5, 2020, Accustem Sciences Ltd entered into an agreement with the Company to acquire Stemprinter Sciences Limited, including the ownership rights and intellectual property relating to StemPrintER™ and cash of \$1.4 million (£1.0 million) contained within the entity. In exchange for the transfer of ownership (shares in Stemprinter Sciences Limited), Accustem Sciences Ltd allotted 194,612,288 ordinary shares of £0.01 par value to Tiziana shareholders on a one for one basis based on the Tiziana ownership as at October 30, 2020. Stemprinter Sciences Limited was a consolidated subsidiary of Tiziana Life Sciences plc until October 5, 2020.

The Demerger was effected by Tiziana declaring a special dividend on the Tiziana Shares which was satisfied by the transfer to Accustem of the entire issued share capital of Stemprinter Sciences Limited, the company to which all the relevant assets relating to StemPrintER had been transferred.

In order for the Demerger to be effective, the Company cancelled \$5,461,000 (£4,000,000) from its Share Premiium account in order to create a distributable reserve in the Company to facilitate the special dividend to shareholders. This was approved by the High Court on October 26, 2020.

As at December 31, 2021, \$1.4 million (£1.0 million) is a payable by Tiziana to Accustem Sciences Ltd.

## 27. 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 commercialisation of the products of this research and development, pre-clinical, clinical and commercial milestone obligations are not detailed until there is a reasonable certainty that the obligation will become payable.

- Milciclib project research future payments relate to the achievement of clinical milestones or the payment of royalties.

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) \$1,000,000 upon initiation of the first Phase II clinical trial, this is currently being negotiated with BMS.
- (b) \$4,000,000 upon FPD of the first Phase 3 registration trial in HCC.
- (c) \$3600,000 upon first patient enrollment into a Phase II human clinical trial
- (d) Upon the first NDA equivalent in: thymic carcinoma, \$900,000; HCC, \$9,000,000; breast cancer, \$15,000,000.

- Foralumab project – Future payments relate to the achievement of clinical milestones or the payment of royalties. Diligence obligations are payable to BMS/Medarex should the project continue to commercialisation. \$750,000 has been accrued in respect of diligence obligations due to Medarex for 2021.

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

- (a) \$300,000 upon enrolment of first patient in a Phase I human clinical trial of the first Phase II Clinical trial, this is currently being negotiated with BMS.
- (b) \$1,500,000 upon initiation of the first Phase III clinical trial
- (c) \$2,000,000 upon filing of the first BLA, or equivalent
- (d) \$2,000,000 upon approval of the first BLA, or equivalent

We are obligated to pay Brigham's Women's Hospital the following hospital milestone payments:

- (a) \$300,000 upon first patient enrollment into a Phase I human clinical trial
  - (b) \$300,000 upon first patient enrollment into a Phase II human clinical trial
  - (c) \$1,500,000 upon first patient enrollment into a Phase III human clinical trial
  - (d) \$3,000,000 upon first commercial sale of a product
- ACT D - Tiziana will need to make milestone payments of up to \$630k depending on the issuance of a US patent from any US patent application in Transferred IP relating to nanoparticle formulations of Act D and upon the successful completion of a Phase II clinical efficacy trial.

## 28. POST BALANCE SHEET EVENTS

On 13 January 2022, the Company announced that Dr. Thomas Adams passed away on January 9, 2022. He had served as a member of Tiziana Life Science's Board of Directors since February 2021.

On 24 January 2022, the Company announced that its Board of Directors has today authorized the Company's management to implement a stock repurchase program for up to \$5 million of the Company's common shares at any time. The term of the board authorization is until December 31, 2022. The repurchase program may be suspended or discontinued at any time and will be funded using the Company's working capital.

## Subsidiaries of Tiziana Life Sciences Ltd

<b>Legal Name of Subsidiary</b>	<b>Jurisdiction of Organization</b>
Tiziana Life Sciences Ltd	England & Wales
Tiziana Pharma Limited	England & Wales
Tiziana Therapeutics Inc.	United States of America
Longevia Genomics S.r.l.	Italy

## CERTIFICATION

I, Kunwar Shailubhai, certify that:

1. I have reviewed this annual report on Form 20-F of Tiziana Life Sciences Ltd;
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: May 20, 2022

/s/ Kunwar Shailubhai

Kunwar Shailubhai  
Chief Executive Officer

## CERTIFICATION

I, Keeren Shah, certify that:

1. I have reviewed this annual report on Form 20-F of Tiziana Life Sciences Ltd;
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: May 20, 2022

/s/ Keeren Shah

Keeren Shah

Finance Director

**CERTIFICATION**

The certification set forth below is being submitted in connection with Tiziana Life Sciences Ltd's Annual Report on Form 20-F for the fiscal year ended December 31, 2021 (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 Ltd, 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 Ltd

Date: May 20, 2022

/s/ Kunwar Shailubhai

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Name: Kunwar Shailubhai

Chief Executive Officer



**CERTIFICATION**

The certification set forth below is being submitted in connection with Tiziana Life Sciences Ltd's Annual Report on Form 20-F for the fiscal year ended December 31, 2021 (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.

Keeren Shah, Finance Director of Tiziana Life Sciences Ltd, certifies that, to the best of her 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 Ltd

Date: May 20, 2022

/s/ Keeren Shah

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Name: Keeren Shah

Finance Director

**Consent of Independent Registered Public Accounting Firm**

The Board of Directors of Tiziana Life Sciences Ltd:

We consent to the incorporation by reference of our report dated May 20, 2022 with respect to the consolidated balance sheets for the years ended December 31, 2021 and December 31, 2020 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, 2021, and the related notes, for Tiziana Life Sciences Ltd, which report appears in the December 31, 2021 annual report on Form 20-F.

/s/ Mazars LLP.

Mazars LLP  
London  
May 20, 2022