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Tiziana Life Sciences PLC (TLSA - NASDAQ)

Foralumab Now in CAR T

Based on our DCF model and a 15% discount rate, Tiziana is valued at approximately $7.50 per ADR share. Our model applies a 15% probability of ultimate approval and commercialization for the portfolio of assets including foralumab and milciclib. The model includes contributions from the United States and global developed markets.

Current Price (9/1/2021)	$1.65
Valuation	**$7.50**

OUTLOOK

Tiziana is a research and development company developing three main candidates for a variety of indications in autoimmune disease, cancer and COVID. The lead candidate, foralumab, is a fully human anti-CD3 antibody, being investigated in multiple sclerosis (MS), Crohn's disease (CD) and COVID, administered intranasally and orally via enteric coated capsules. Milciclib is the second candidate and is being investigated as a combination product in multiple oncology indications. The third candidate, TZLS-501, is an anti-IL-6R receptor antibody expected to be the subject of an IND submitted in 2021. TZLS-501 is being investigated as a treatment for COVID and other pulmonary diseases such as ARDS.

Ph2 foralumab clinical trials for MS and CD are targeted for 2021 & Ph2 combination trials for milciclib in coming quarters. Tiziana differentiates itself in the use of intranasal, oral and inhaled formulations of mAbs that are able to avoid shortcomings of infused & subcutaneous administration.

Our valuation assumes a 2027 regulatory approval and 2028 commercialization of foralumab for both pMS and CD in conjunction with partners.

SUMMARY DATA

52-Week High	**5.44**
52-Week Low	**1.46**
One-Year Return (%)	**-50.0**
Beta	**-0.09**
Average Daily Volume (sh)	**433,687**
Shares Outstanding (mil)	**97.3**
Market Capitalization ($mil)	**160**
Short Interest Ratio (days)	**0.4**
Institutional Ownership (%)	**14.5**
Insider Ownership (%)	**39.5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of GBP)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2020	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2021					0.0 E
2022					0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2019	0.00 A	-0.03 A	0.00 A	-0.03 A	-0.05 A
2020	0.00 A	-0.03 A	0.00 A	-0.09 A	-0.12 A
2021					-0.11 E
2022					-0.10 E

WHAT'S NEW

On September 2nd, Tiziana Life Sciences PLC (NASDAQ: TLSA / LSE: TILS) announced an exclusive licensing agreement with Precision BioSciences (NASDAQ: DTIL) for the exploration and development of foralumab as a lymphodepletion agent to complement Precision's CAR T therapy portfolio. Since our last update, Tiziana also formally declared the start of its corporate reorganization to a Bermuda-incorporated company that will trade exclusively on the NASDAQ, and published an article detailing results from Tiziana's trial of foralumab in mild to moderate COVID-19 patients in Brazil.

Anti-CD3 and CAR T: Joining with Precision

On September 2, 2021, Tiziana announced that it had entered into an exclusive licensing agreement with Precision BioSciences (NASDAQ: DTIL) to evaluate Tiziana's foralumab in conjunction with Precision's allogeneic CAR T portfolio. In this arrangement, foralumab, an anti-CD3 fully human monoclonal antibody, is being investigated as a lymphodepletion agent, an agent that purposely destroys the patient's immune system, including T cells, to make way for CAR T cells. Lymphodepletion is performed before receiving adoptive cell therapy (ACT). The aim is to determine whether or not foralumab can improve the outcome of ACT. Lymphodepletion typically comprises short-course chemotherapy to destroy T, B and NK cells. This can have the effect of debulking the tumor, altering the tumor phenotype, modifying the tumor microenvironment, and modulating the cytokine profile.[1] Common lymphodepletion agents include fludarabine and cyclophosphamide, typically used in combination. These agents have severe side effects and in the case of fludarabine, are associated with neurotoxicity. Foralumab has the potential to either replace or reduce the chemotherapy regimen, thereby improving the side effect profile for patients.

Foralumab may induce tolerance of allogeneic CAR T, or CAR T cells not from the patient's own body, but from a donor, which may attack the patient (host) in what is known as graft-versus-host-disease (GVHD). Allogeneic CAR T has advantages over autologous approaches in that generation of autologous CAR T cells can be challenging, especially in patients of advanced disease due to the length of time needed to generate the cells.[2]

The Cluster of Differentiation 3 (CD3) is a receptor on effector T cells. Precision's processing of T cells uses ARCUS gene editing to knock out the TRAC gene and depletes CD3, producing allogeneic CAR T cells that are greater than 99.9% CD3-negative. Lymphodepletion has been shown to augment T cell adoptive immunotherapy through enhanced intratumoral proliferation. Management has noted the potential of its anti-IL-6 receptor monoclonal antibody (TZLS-501) to be included in CAR T therapy to address cytokine storm syndrome, although this was not discussed as part of the deal with Precision.

Under the terms of the agreement, Precision gained exclusive license to use foralumab as a lymphodepletion agent to complement its CAR T portfolio in the treatment of cancers. Precision will be responsible for development, commercialization, and costs associated with its use of foralumab in exchange for upfront payment, certain milestone payments and royalties to Tiziana. Amounts for upfronts, milestones and royalties were not disclosed; however, some of the milestones are payable upon start of a Phase II and Phase III study and upfront payments will be received shortly after execution of the deal.

Corporate Reorganization

On August 20, Tiziana announced the official commencement of its strategic plan to change its corporate structure by establishing Tiziana Life Sciences as the Bermuda-incorporated, NASDAQ-traded parent of the Tiziana Group, subject to legal and shareholder approval. Existing shareholders, including American Depositary Share (ADS) holders, will have their shares exchanged, two-for-one, for the new parent company and the current company will then become a wholly-owned subsidiary. The new shares are expected to be listed while old shares are delisted from the London Stock Exchange and ADSs are delisted from the NASDAQ. The reorganization is intended to structure Tiziana in a manner more fitting to its US-centric operations, including enhanced trading and coverage characteristics, and reduce cost to shareholders. All outstanding options and warrants pursuant to the 2014 and 2016 Share Option Plans are intended to continue on the same basis but deliver the new shares. Likewise, holders of loan notes are intended to be converted as well.

[1] Lymphodepletion optimization for CAR T-cell therapy (multiplemyelomahub.com)
[2] McCreedy BJ, Senyukov VV, Nguyen KT. Off the shelf T cell therapies for hematologic malignancies. Best Pract Res Clin Haematol. 2018 Jun;31(2):166-175. doi: 10.1016/j.beha.2018.03.001. Epub 2018 Mar 28. PMID: 29909917.

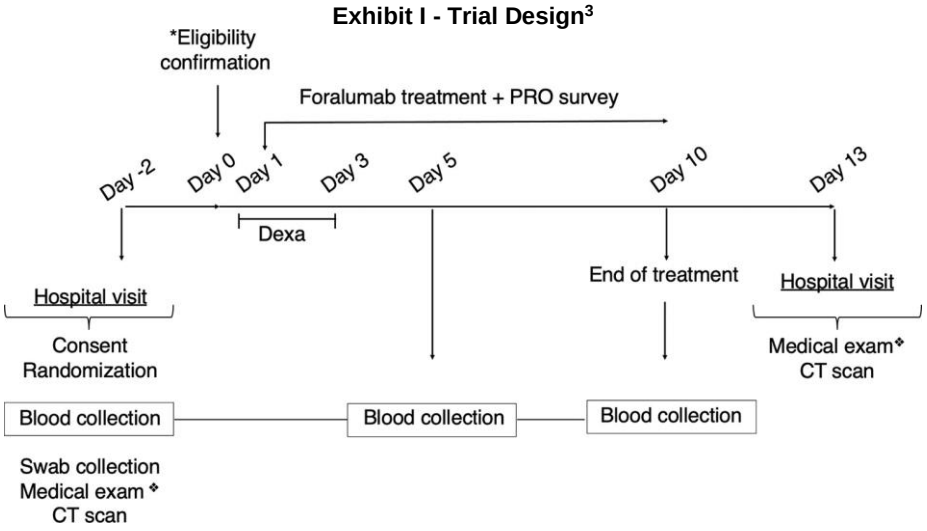
Intranasal Foralumab in Hospitalized, Severe COVID-19

On June 23, 2021, Tiziana announced that it had entered into a collaboration with FHI Clinical to conduct a Phase II trial for intranasal foralumab in hospitalized, severe COVID-19. The Phase II study will be conducted in Brazil, and is intended as a proof-of-concept effort, as well as to evaluate safety, tolerability and efficacy of the candidate in severe COVID-19 and pulmonary inflammation. In the trial, foralumab will be delivered intranasally through a metered atomizing device. The trial will be randomized, placebo-controlled and double-blind. It will expand on the findings of intranasal foralumab in mild to moderate, non-hospitalized COVID-19 patients announced in February and will examine attenuation of pulmonary pathology characteristic of severe COVID-19 patients. Up to seven sites in Brazil will participate in the study, targeting enrollment of 80 patients with CT-confirmed pulmonary involvement. The study will also evaluate foralumab's effect on resolution of symptoms via chest CT, inflammatory biomarkers, T cell subpopulations, safety and mucosal inflammatory response following 14 days of intranasal administration.

FHI Clinical is a subsidiary of FHI 360, specializing in clinical development of drugs for infectious diseases. FHI Clinical is involved with COVID-19 trials in all phases for vaccines and therapeutics, as well as observational studies to characterize SARS-CoV-2 infection. FHI Clinical has a network of clinical sites across 16 countries and 43 states in the US.

On August 17th, Tiziana informed via press release that a peer-reviewed article had been published featuring data from the foralumab trial in mild to moderate COVID-19 patients in Brazil, announced in February. The article was published in *Frontiers in Immunology* titled "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." Again, the study was a collaboration with teams from Harvard Medical School and INTRIALS, a CRO based in São Paulo. The aim of the study was to assess safety of intranasal foralumab and its potential efficacy in treating immune hyperactivity and lung inflammation associated with mild/moderate COVID-19 patients. 39 patients were randomized into three cohorts: control, 100 µg foralumab + dexamethasone, and foralumab monotherapy.

Exhibit I - Trial Design[3]



Foralumab was well tolerated and all patients completed the study. No serious adverse events (SAEs) were observed. 11 patients experienced an adverse event including headache (n=4), burning in the nostril (n=1), retrosternal pain (n=2), pustular lesions and itching in cervical area (n=1), dysuria (n=1), tachycardia associated with anxiety (n=1), and insomnia (n=1). On the efficacy front, foralumab treatment resulted in significant reduction in lung inflammation, as observed with CT scans, which revealed improvement in clearance of lung infiltrates versus baseline. The CT data were correlated by reduction in levels of inflammatory markers such as IL-6 levels (69%; p=0.03) and CRP[4] (85%; p=0.03) at day 10. Management anticipates initiation of Phase II proof-of-concept study in Brazil to further evaluate

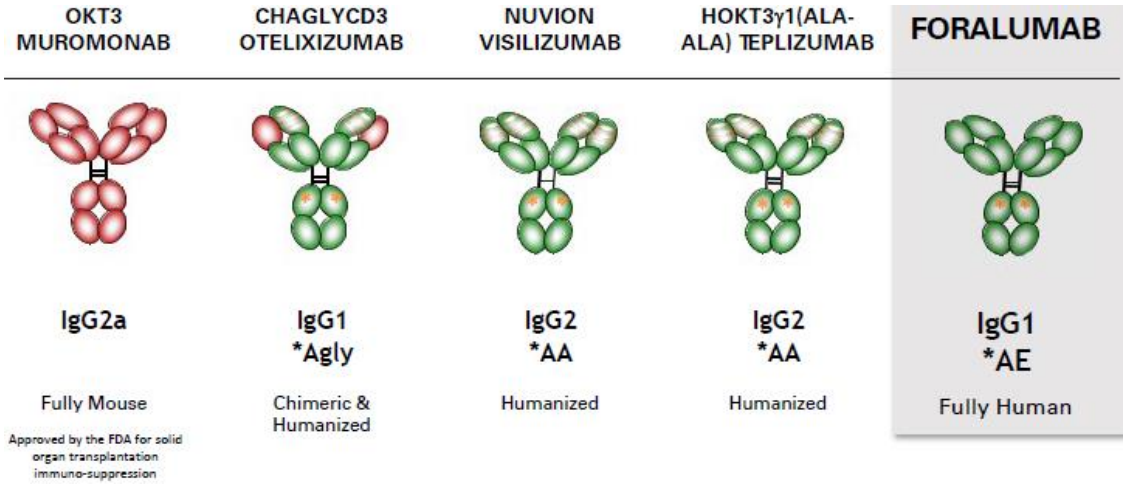
Foralumab

Foralumab is an anti-CD3 monoclonal antibody that reduces T cell activation and cytokine release by enhancing the production of IL-10, TGF-β and partial exhaustion of T cells. It specifically acts on the epsilon (ε) chain of the CD3-

[3] https://doi.org/10.3389/fimmu.2021.709861
[4] C-reactive protein

TCR complex. Foralumab immunogenicity is negligible as it is a fully human antibody, unlike its earlier counterparts with rodent elements. Due to its unique structure, it stimulates only minor cytokine release *in vivo* while maintaining CD3/TCR modulation and T-cell depletion, further contributing to its overall safety in intravenous use.[5]

Exhibit II – Evolution of Anti-CD3 mAbs[6]



Appointment of Dr. Kevin Schutz as VP of Regulatory Affairs

Tiziana announced the appointment of Kevin Schutz, Pharm.D. as its Vice-President of Regulatory Affairs on June 21, 2021. Dr. Schutz will lead interactions between Tiziana and regulatory entities as Tiziana progresses its clinical studies in the US, Europe and Asian countries. Dr. Schutz brings over 19 years of pharmaceutical industry experience including 14 years in Regulatory Affairs. Dr. Schutz' experience is in multiple fields including neurology, pulmonology, and other indications that Tiziana is currently considering. Tiziana's work in secondary progressive multiple sclerosis (SPMS) aligns well with Dr. Schutz' background. Over the course of his career, Dr. Schutz has worked with the FDA, EMA and PMDA (Japan).

UK Calls for 'Take-Home' Treatments for COVID-19, Tiziana Responds

In a June 17th press release, Tiziana informed that, in response to the United Kingdom COVID Therapeutics Advisory Panel's initiative to investigate therapies that can be delivered at home, Tiziana had submitted an application for a grant to support further development of nasally-administered foralumab in non-hospitalized COVID-19 patients. The grant application followed Tiziana results from a successfully-completed trial in Brazil that demonstrated take-home nasal-spray foralumab's immunomodulatory effects in COVID-19 patients, as evident in CT scans and inflammation markers including interleukin-6 and C-reactive protein.

Nasally-administered Foralumab Trial in SPMS Patient

On May 25, 2021, Tiziana announced that it had initiated a trial through the Individual Patient Expanded Access Program (EAP) of foralumab in a Secondary Progressive Multiple Sclerosis (SPMS) patient. This follows a previous release in late March that first introduced the effort that was cleared under the EAP. The first SPMS patient was dosed on May 24, 2021 with treatment to be administered over the following six months to examine long-term safety, tolerability and clinical response. Previous clinical work has been conducted in healthy volunteers and COVID-19 patients demonstrating the well-tolerated safety of nasally-administered foralumab, dosed up to 10 consecutive days, with no apparent severe adverse events. Treatment in these investigations also produced anti-inflammatory effects.

The SPMS patient will be treated at Brigham and Women's Hospital Harvard Medical School and will receive 50 mcg, or 25 mcg/nostril, in 3-week cycles. Dosing will be three times a week for the first two weeks followed by one week of rest in a repeating cycle that will continue for six months. The patient will be monitored during the period evaluating routine safety, tolerability and neurological behaviors. In addition, the study will also track microglial activation and will assess treatment response through immunological and neurodegenerative markers.

[5] Dean Y, Dépis F, Kosco-Vilbois M. Combination therapies in the context of anti-CD3 antibodies for the treatment of autoimmune diseases. Swiss Med. Wkly 142, w13711 (2012).
[6] Source: Tiziana Life Sciences Corporate Presentation, January 2021.

Multiple Sclerosis and Its Subtypes

Multiple sclerosis (MS) is a neurological condition that affects the central nervous system (CNS), specifically white matter. The immune system mistakenly inflames and damages myelin, the insulating layer that wraps and protects axonal processes of nerves in the brain and spinal cord. Damage to the myelin sheaths of neurons prevents communication throughout the CNS and blocks effective transmission of electrical signals leading to various neurological findings. This autoimmune, inflammatory disease typically presents itself in the third or fourth decade of life. The causes of MS are unknown. Researchers have speculated that it may be related to virus and bacteria exposure, geographic location, genetics or immunological malfunctions. MS is clinically classified into four types: relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), primary-progressive multiple sclerosis (PPMS) and progressive-relapsing multiple sclerosis (PRMS). SPMS occurs when symptoms arise during a stage in remission and are not resolving with treatments, in contrast to PPMS which occurs when there are no periods of remission and the disease progresses.

In the Space: Teplizumab FDA Advisory Committee Meeting

Foralumab rival teplizumab was reviewed in an FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting, with related briefing documents posted on May 25. The advisory committee meeting was held on May 27 to review Provention Bio's (NASDAQ: PRVB) candidate. The meeting discussed potential merits of teplizumab, which, like foralumab, is an anti-CD3 monoclonal antibody (mAb). In contrast to foralumab, teplizumab is indicated in type 1 diabetes and contains some murine elements, while fully human foralumab is indicated in a multitude of conditions with a focus on multiple sclerosis, Crohn's Disease and COVID-19 symptoms. On July 6th, Provention announced that it had received a Complete Response Letter (CRL) from the FDA for Teplizumab. The reasons for the rejection were attributable to incomplete pharmacokinetic (PK) comparability between a previous version of the product and Teplizumab. The agency also cited issues related to product quality in the CRL according to Provention's press release at the facility where the product is being manufactured. Provention plans to re-submit after obtaining the necessary PK data related to comparability and after affirming that the deficiencies at the fill and finish manufacturing facility have been addressed.

Key reasons to own Tiziana shares:

- **Multiple Phase II-ready assets pursuing unmet needs**
  - **Fully human anti-CD3 mAb - foralumab**
    - **Multiple Sclerosis**
    - **Crohn's Disease**
    - **COVID-19 / ARDS**
  - **Pan-CDK inhibitor - milciclib**
    - **Non-small cell lung carcinoma (NSCLC)**
    - **Hepatocellular carcinoma (HCC)**
  - **Fully human anti-IL-6 receptor mAb – TZLS-501**
    - **ARDS, ILD, COVID-19 and other diseases**
    - **IND development underway**
- **Oral, nasal and inhaled administration of antibodies**
  - **Improved ease of use**
  - **No need for hospital-based infusion**
  - **Lower doses required for efficacy**
  - **Reduced systemic exposure and toxicity**
  - **Fewer side effects with reduced systemic exposure and toxicity**
  - **Focused distribution at the target organs in CD and severe lung disorders**
  - **Higher lung drug retention and efficacy while minimising toxicity to other organs**
- **Validation of intranasal foralumab technology in Phase I COVID-19 trial**
  - **Phase II trial announced**

Summary

Since our last update, Tiziana has entered into an exclusive license agreement with Precision BioSciences to advance its anti-CD3 antibody in allogeneic CAR T therapy for lymphodepletion therapy. Tiziana will receive upfronts, milestones and royalties as part of the agreement. Tiziana also formally declared the commencement of its corporate reorganization to a Bermuda-incorporated company that will trade exclusively on the NASDAQ, and published an article detailing results from Tiziana's trial of foralumab in mild to moderate COVID-19 patients in Brazil.

We initiated on Tiziana in April, a research and development company advancing three candidates for a variety of indications including autoimmune disease, cancer and COVID. The lead candidate, foralumab, is a fully human anti-CD3 antibody, being investigated in multiple sclerosis (MS), Crohn's disease (CD), COVID-19 and now in allogeneic CAR T lymphodepletion. Milciclib is the second candidate and is being investigated as a combination product in multiple oncology indications. The third candidate, TZLS-501, is an anti-IL-6R receptor antibody expected to be the subject of an IND submitted in 2021. TZLS-501 is being investigated as a treatment for COVID and other pulmonary diseases such as ARDS. We maintain our target price of $7.50 per share.

PROJECTED FINANCIALS

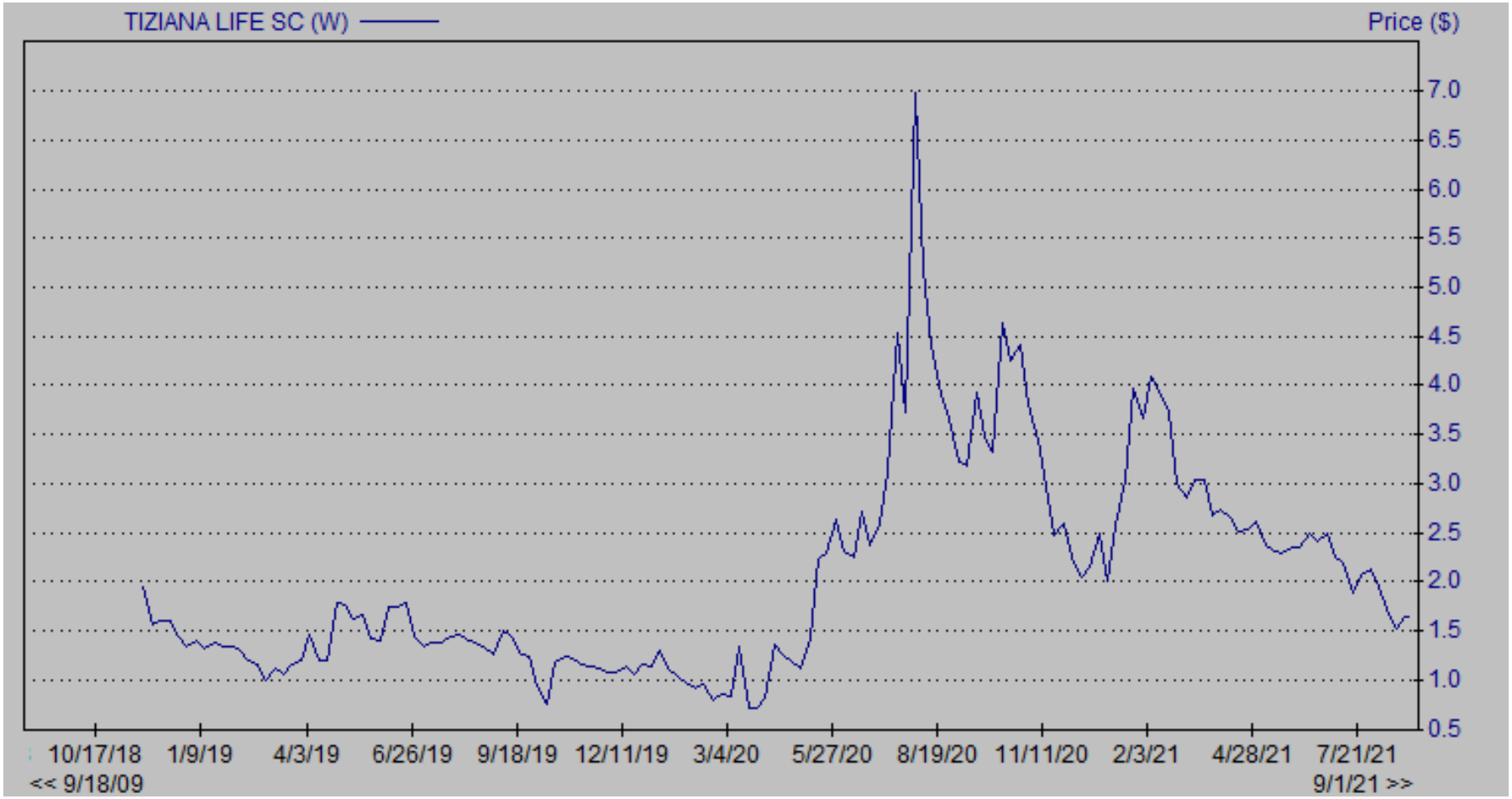
Tiziana Life Sciences PLC - Income Statement

Tiziana Life Sciences Plc	2019 A	1H A	2H A	2020 A	2021 E	2022 E
Total Revenues (£UK)	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
Research & Development	£2,910	£760	£3,907	£4,667	£19,312	£20,801
General & Administrative	£4,864	£3,169	£5,555	£8,724	£5,895	£5,968
Income from operations	-£7,774	-£3,929	-£9,462	-£13,391	-£25,207	-£26,769
Other Expense	£72	-£5	£8,681	£8,676	£0	£0
Pre-Tax Income	-£7,846	-£3,924	-£18,143	-£22,067	-£25,207	-£26,769
Provision for Income Tax	-£540	£0	-£1,719	-£1,719	£0	£0
Tax Rate	0.0%	0.0%	0.0%	7.8%	0.0%	0.0%
Net Income	**-£7,306**	**-£3,924**	**-£16,424**	**-£20,348**	**-£25,207**	**-£26,769**
Reported EPS	**-£0.054**	**-£0.026**	**-£0.09**	**-£0.12**	**-£0.11**	**-£0.10**
Basic Shares Outstanding	136,483	150,224	187,907	169,065	220,000	260,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

HISTORICAL STOCK PRICE

Tiziana Life Sciences PLC – Share Price Chart[7]



[7] Source: Zacks Research System

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