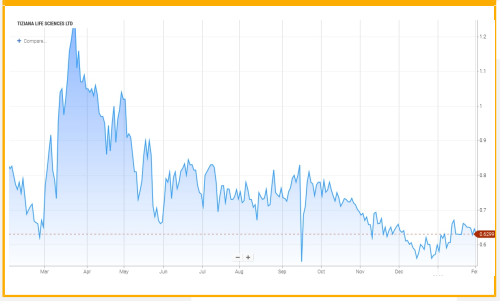
TIZIANA LIFE SCIENCES PLC (NASDAQ:TLSA)

28 July 2023

Healthcare

52-WEEK HIGH	**$1.37**
52-WEEK LOW	**$0.51**
PRICE	**$0.72**
MARKET CAP MLN	$72.42

Share Price



Major Shareholders

Shares in issue	102,272,614
Avg Three-month trading volume	215,013
Primary Index	NASDAQ
Next Key Announcement	FY 22 results

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Tiziana Moving forward in MS and AD

Key trials in SPMS and AD due to start shortly

Tiziana is close to being able to start the important phase IIa study with its lead product, intranasal foralumab, in non-active secondary progressive multiple sclerosis (SPMS) and is well advanced in its plan to initiate a separate study in Alzheimer's disease (AD).

Within the next two months, Tiziana expects to both receive FDA regulatory clearance for its trial protocol in SPMS and hold the initial investigator meeting, which will effectively represent the start the trial. This in turn should put it in a position to enrol the first patients in early Q4.

Tiziana is currently completing the enrolment of patients into its expanded access protocol (EAP) of foralumab in SPMS and expects to recruit the final four patients in August. Next month should also see it obtain the six-month PET scans on the second cohort of four patients (numbers 3-6), which it is hoped may show evidence of clinical improvement over time. We understand that these data may feature in a poster presentation of the ECTRIMS scientific conference in October.

Details of the design of the study in SPMS recently emerged in a key opinion leader presentation for investors. The study is expected to enrol 54-patients and will test two doses of foralumab versus a placebo given over 12 weeks. The study will use imaging as the primary endpoint, with fatigue as a key secondary endpoint.

This design represents a refinement of an earlier plan and has the advantage that it may render the important clinical proof-of-concept data earlier than was previously envisaged, potentially as soon as late 2024. The data are likely to be important as they may provide the basis for Tiziana to seek a partnering deal and/or seek funding.

Meanwhile, in AD, the company hopes to obtain the IND (regulatory clearance to conduct a trial) for the planned exploratory clinical study of foralumab in this indication as well as the outcome of its grant application with a philanthropic/patient advocacy group over the next two months. This study may start in early 2024.

Preclinical work with foralumab remains underway in other indications, including prevention/delay on onset of Type 1 diabetes. This work is examining whether the molecule could be developed as a potential alternative to Sanofi 's recently-approved Tzield. Foralumab has the same mechanism of action and could offer safety/efficacy and dosing administration advantages.

Tiziana is also conducting preparatory work for a potential study of foralumab in so-called "long-Covid". However, this would, in our view, require additional equity or non-dilutive funding.

Two key indications for foralumab

The initiation of the phase II trial in SPMS is an important event as the data are likely to be a key value inflection point in stock market terms. Presentation of further results at scientific meetings from the expanded access protocol in H2 23 should both raise the profile of foralumab and provide important third-party validation from peer review. Tiziana remains funded into 2024 with cash on 31 December 2022 of US$18.1mln

Gabriele Cerrone, interim chief executive and executive chair. He has a track record of corporate financing having listed nine companies, seven on NASDAQ and two in London. He is the former chair of Trovagene, Gensignia, Rasna, Contravir and Okyo. He is also the co-founder and director of two NASDAQ-listed companies that brought drugs from the discovery through to US Food & Drug Administration approval: Synergy Pharmaceuticals and Siga Technologies.

Matthew Davis MD, chief operating officer and chief medical officer. Previously, he was chief scientific officer and chief medical officer at Endo Pharmaceuticals. Prior to that, Dr Davis was chief medical officer for Lupin Inc. and URL Pharma, Inc. where he led three NDA approvals. He was also on the executive team that sold URL Pharma to Takeda.

Investment case focussed on SPMS

Tiziana's investment case centres around the potential of foralumab as a treatment for CNS indications, primarily in MS. The company is poised to start a phase II trial in non-active SPMS, the data from which are likely to be important in its ablity to secure a licensing agreement/partnership with a pharmaceutical or larger biotech company that would to ultimately commercialise the product.

Late-stage assets in MS can have high values in licensing or M&A deals, as evidenced by Sanofi's $3.7bn equity value acquisition of Principia Biopharma in 2020. That company had two BTK inhibitors that were then at the end of phase II studies, one of which now known as tolebrutinib, is in three phase III trials for MS.

MS is a large market (projected >$40bln by 2028) but is a highly competitive field. However, non-active SPMS represents a niche where there is almost no competition. *Non-active* SPMS is the most advanced stage of this disease where patients continue to deteriorate but do not experience the characteristic sudden flares associated with earlier stages of the disease. Generally, these patients will have exhausted all other therapeutic options.

No product is specifically approved for non-active SPMS. There are two drugs approved for the slightly less advanced stage of *active* secondary progressive disease (where flares still occur): Ocrevus (ocrelizumab, Roche), which is given by infusion (and is considered the more effective drug) and Mayzent (siponimod, Novartis), an oral product. Both products have strong side effects.

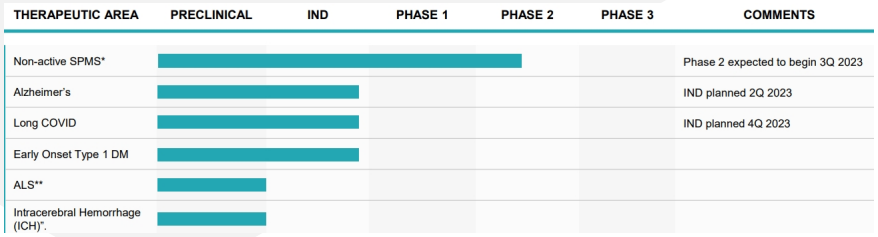
Given the unmet need, in this form of MS, Tiziana was allowed by regulators - somewhat unusually - to treat a small number of patients under an expanded access protocol (EAP). This will shortly complete enrolment with 10 patients, with data presented so far being encouraging albeit anecdotal. All the patients in this study received 50mcg foralumab three times a week for two weeks followed by one week off. The dose can be increased to 100mcg on the same schedule if needed. (The new phase II study will test both of these doses versus placebo).

In January, Tiziana reported that after 11 months of dosing, additional clinical improvements had been seen in the second patient on the EAP. On the EDSS (expanded disability status scale, a standard MS scoring system), a score on enrolment of 6.0 had fallen (improved) to 5.0, by which point the patient could walk 200 metres without a cane.

Imaging results showed a reduction in microglial activation; microglial cells are the brain's immune cells and cause MS, so lower activation is encouraging. Inflammation in the brain drives disease pathology in MS. The results were also consistent with previously reported data from the first SPMS patient. In June this year, Tiziana announced that it had observed a reduction in microglial activation, per PET scans, in five of the six patients treated at that point (the sixth may have missed doses due to Covid infection).

Although MS is the focus of the investment case, Tiziana is conducting activities in more than five different indications, as shown in the R&D schematic below.

Development pipeline for foralumab



Non-active SPMS study schematic

Alzheimer's disease

Tiziana is also advancing plans to take foralumab into a phase IIa study in mild to moderate Alzheimer's disease, partly backed by grant funding expected from a foundation. The study could start in early 2024 and is likely to have a three-month treatment period, so could render data in 2026.

The company believes foralumab may reduce the known neuro-inflammatory component of the disease, caused by the activation of microglia triggered by amyloid beta plaques that are a hallmark of Alzheimer's. As the two drugs recently approved for AD both target amyloid, foralumab could be complementary to this approach. Tiziana's collaborators have presented supporting data on foralumab at various scientific meetings. We understand a scientific paper is in preparation on this that has been submitted for publication in a prestigious journal.

Key timelines for MS and AD indications

EAP	Enrolment of pts 7-10	August
	6 month data on pts 3-6	mid Aug
	Poster presentation at ECTRIMS	Oct
Phase IIa study SPMS	FDA feedback on trial protocol	mid-Sept
	Investigator meeting	end-Sept
	First patient in	Q4
	Last patient in	Q3 24 *
	Primary outcome data	Q4 24*
Alzheimer's disease	IND for AD trial	August
	Outcome of grant application	mid-Aug
	Possible journal publication	Q4
	Study initiation	Q1 24*
	Study outcome	2025*

* date estimated by Proactive Investors

Preclinical work in T1D...

Tiziana is conducting a preclinical project to explore the potential of foralumab in the delay of onset of Type 1 diabetes (T1D). This follows the approval of Sanofi/Provention Bio's Tzield (teplizumab) for this indication in 2022. Both Tzield and foralumab are anti-CD3 monoclonal antibodies., although Tzield is humanised and given systemically and intravenously whereas foralumab is fully human.

Tzield is given by 30 min IV infusion once per day over 14 days, with the dose-escalating from 65mcg/m^2 to 1,030 mcg/m^2 (equivalent to c 1.1mg/day for a typical 10 year old child). Typically, it would be given to children/adolescents who have shown the initial symptoms, caused by the autoimmune attack on their pancreatic islet cells (which produce insulin). Treatment with Tzield has been shown to delay the onset of T1D by a median of two years. Tiziana is considering using the same treatment regime to that expected to be used in MS (and potentially AD). The intranasal route of administration used by Tiziana could be more convenient for patients but also may allow it to be positioned differently, possibly as a maintenance therapy in patients who have previously received Tzield.

Provention Bio was recently the subject of an agreed takeover offer from Sanofi valued at $2.9bln.

...and Long-Covid

Plans are also taking shape to conduct a phase II study of foralumab in post-COVID-19 syndrome (or "long-Covid"), potentialyl starting in 2024 (subject to funding). So far, few details have been disclosed. The programme is based on the hypothesis that a key pathogenic component of long-Covid is the activation of microglial cells. There are numerous patients who experience persistent fatigue, neurological or other debilitating symptoms consequent to Covid infection and in some patients, these symptoms have not resolved more than two years after the original infection.

Foralumab has been previously studied in Covid patients. During the pandemic, a pilot study of foralumab (100ug/day for 10 consecutive days) in 39 COVID-19 patients was conducted in Brazil, which showed a reduction of serum IL-6 and C-reactive protein, inflammatory biomarkers.

Given the large number of people exposed during the Covid pandemic, this represents a potentially large market opportunity and there is very little competing development activity. There are probably only two active development by other pharma/biotech companies: temelimab from GeNeuro and Vyvgart (efgartimod) from Argenx. Both are in Phase 2 studies.

Finances and cash

Cash on 31 December 2022 was US$18.1mln. Tiziana states that it has sufficient cash reserves to initiate the phase II trial in MS.

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