June 9, 2022

Zacks Small-Cap Research (NOTE)

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John D. Vandermosten, CFA
312-265-9588
jvandermosten@zacks.com

scr.zacks.com

10 S. Riverside Plaza, Chicago, IL 60606

Tiziana Life Sciences PLC (TLSA: NASDAQ)

Clinical Improvements for 2nd SPMS Patient

Research Note

Clinical Results for Second SPMS Patient

Tiziana Life Sciences PLC (NASDAQ: TLSA) announced positive clinical results for its second secondary progressive multiple sclerosis (SMPM) patient in a June 8th press release. The ~40 year old individual that was enrolled as the second patient in the trial exhibited clinical improvements on several measures, including positron emission tomography (PET) analysis, neurologic exam and the timed 25-foot walk test after three months of treatment. The results from the second patient are consistent with the results from the first patient which were reported in a March 10 press release. Based on the data gathered from the first two subjects, Tiziana has requested and the FDA has cleared enrollment of eight more eligible SMPS patients to receive intranasal foralumab, a fully human anti-CD3 monoclonal antibody therapy, under the Expanded Access Program.

Patient Response
The second patient was diagnosed with SPMS in 2014 and over the subsequent eight years, the magnitude of his disability increased. After enrolling, the patient was administered three months of treatment with intranasal foralumab at 50 mcg, three times per week for two weeks, followed by one week off of treatment. Improvement was measured by PET imaging and by neurologic examination. A 10-30% reduction in microglial activation was observed in the PET imaging across the thalamus, cortex, white matter and cerebellum, which is similar to the ranges observed in the first patient. See link here for the discussion on the results for the first patient and detailed background on SPMS. In the clinical sphere, investigators observed improvements in the 25-foot walk test and the neurologic exam for patient #2. Both enrollees are continuing their treatment regimen with foralumab and are now in their 13th and 4th months of treatment.

Next Steps
The positive data from the first two patients was shared with the FDA, which granted permission for Tiziana to add eight more SPMS patients to the trial. Reassuring safety results supported the option to use higher levels of dosing, and for all patients going forward, doses may be escalated to up to 100 mcg three times per week[1] to investigate the potential clinical benefits from higher doses. Tiziana expects the third patient to be enrolled in the trial in July 2022 and has several other SPMS patients lined up for screening to enter the trial. Based on company commentary we expect that subsequent enrollees will be added through the Harvard system in order to maintain consistency in monitoring and analysis. Data from all 10 patients is expected in 2023.

While only two patients have contributed to the data so far, the positive response is promising and supports further investigation for this condition that affects near 300,000 individuals around the globe. While there are a few treatments for the specific disorder, the agents act by modulating or suppressing the peripheral immune response and have limited effect on progressive forms of multiple sclerosis.

[1] The regimen is a three times per week for two weeks followed by one week off of treatment.

SPMS Background

Tiziana enrolled its first SPMS subject in May 2021 through the Individual Patient Expanded Access program. The effort is investigating lead candidate, foralumab, in an innovative, intranasal formulation. The biologic is able to bring balance to the immune system by stimulating Tregs and reducing proinflammatory cytokines, characteristics present in a number of neurodegenerative diseases, including multiple sclerosis. In the first patient, investigators observed the upregulation of Tregs and the suppression of cytokines after six months of treatment.

SPMS represents an advanced stage of multiple sclerosis with few treatment options and has a severe impact on a patient. Three-month results released in January of this year provided sufficient evidence of safety and efficacy to justify the enrollment of a second SPMS subject. On March 10, 2022, topline data for the full six months of evaluation was reported, and a key opinion leader (KOL) virtual event was held to further detail results and offer discussion with the study's principal investigators.

Intranasal Foralumab's First SPMS Patient: 3- and 6-Month Data, KOL Discussion

On January 10, 2022, Tiziana provided a progress update for its first patient in the evaluation of intranasal foralumab in SPMS. The first patient enrolled had completed 3 out of 6 months of dosing and analysis of data found that intranasal foralumab was well-tolerated and had produced a favorable clinical response. The brain imaging data, as analyzed by PET, showed reduction in microglial cell activation. Microglial activation has shown correlation with disease severity in multiple sclerosis and its reduction is hoped to remedy the disease. Based on the success of the first patient, Tiziana was allowed by the FDA to enroll a second patient under the Individual Access Program. On March 10th, Tiziana reported 6-month data for its first SPMS patient and subsequently, held a KOL virtual event on March 14th disclosing explicit results. Intranasal foralumab continued to be well tolerated, and data showed sustained inhibition of microglial activation as assessed by PET along with downregulation of pro-inflammatory cytokines. The disease was also stabilized as measured by clinical assessments.

As disclosed in the March 10th release, between the 3-month and 6-month timepoints, the patient demonstrated greater reduction in activated microglial cells versus baseline based on changes from baseline in Standardized Uptake Value Ratio (SUVR-1).[2] Pro-inflammatory cytokines that were observed to be downregulated included interferon-gamma, interleukin 18, IL-1beta and IL-6. Clinical measures of disease progression included Timed 25-Foot Walk Test, 9-Hole Peg Test, and Symbol Digit Modality Test, all of which showed improvement. The FDA authorized the patient to continue on intranasal foralumab for another 6 months, and Tiziana will continue to measure efficacy and safety data over this extended timeframe. The March 14th KOL event quantified the microglial PET signal in several parts of the brain as shown below.

Exhibit I - 6-Month Reduction in Microglial PET Signal from First SPMS Patient[3]

	Whole Brain	Cerebral Cortex	Thalamus	White Matter	Cerebellum
3 Months	-23%	-23%	-20%	-25%	-22%
6 Months	-38%	-38%	-50%	-36%	-38%
Incremental Δ	-15%	-15%	-30%	-11%	-16%

Proposed Phase Ib Foralumab Trial: Crohn's Disease

Tiziana expects to launch a double-blind, multiple ascending dose study of orally administered foralumab to assess the safety of foralumab in patients with mild to moderate Crohn's Disease, with the first patient to be enrolled in late June. 2.5 mg and 5 mg doses in take-home capsules will be administered for five consecutive days and will be evaluated for safety and tolerability. Sixteen subjects are expected to be enrolled with two dose groups and a 3:1 active to placebo ratio in each group. During the five day hospitalization period for the subjects enrolled, vital signs will be evaluated, laboratory values will be recorded and adverse events and other physical findings will be measured to assess the safety and tolerability of the agent. Secondary endpoints include measurement of systemic circulation of foralumab and pharmacokinetics, change from baseline in inflammation response and incidence of detectable anti-drug antibody. Exploratory endpoints will include change in T-cell subsets in blood from baseline and detection of foralumab in stool samples.

[2] SUVR-1 is calculated with reference to a pseudo reference region in white matter that showed minimal change in PET SUV across time points
[3] Tiziana Life Sciences

Annual Report

Tiziana filed its annual report, Form 20-F, for the fiscal year ended December 31, 2021 on May 23rd. The report summarized the financial flows and balances for the year. No revenues were reported and $27.4 million in operational expenses were recognized. Net loss for 2021 was ($23.4) million or ($0.24) per share. Cash at year end was $42.2 million compared to cash of $65.8 million at the end of 2020. Cash burn over the 12-month period was ($21.8) million with only minimal cash used in financing as repayment of leasing liabilities was partially offset by contributions from warrant exercise.

The $13.2 million in research and development expense was spent to support programs in TZLS-0501 ($8.6 million) for COVID, foralumab ($3.4 million) in SPMS and Crohn's and Milciclib ($1.2 million) in cancer indications. In terms of activities, research and development funds were primarily allocated to monoclonal antibody development activities and manufacturing foralumab. General and administrative expenses were $13.3 million for the year with the year over year increase in expense on recognition of option value and additional compliance, professional fees and legal costs compared with the prior year.

Exhibit II – Tiziana Pipeline[4]

	Subject	PC	IND	Phase 1/IAP	Phase 2	Phase 3
FORALUMAB *Fully human anti-CD3 mAb*	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	
ANTI IL-6 RECEPTOR *Fully human mAb*	Inhalation	Pulmonary Fibrosis			3Q-2022 IND Submission	
MILCICLIB *Pan-CDK inhibitor*	Oral	Milciclib + Gemcitabine in NSCLC Kras+ mutants			2Q-2022 IND Submission	

Milestones

- First Crohn's patient enrolled – June 2022
- Submit IND for foralumab in Type 1 Diabetes – July 2022
- Submit IND for Milciclib in non-small cell lung cancer (NSCLC) – July 2022
- Enroll third patient in SPMS trial – July 2022
- Submit IND for Anti IL-6 (TZLS-501) for pulmonary fibrosis – Fall 2022
- Topline data from SPMS trial - 2023

Summary

Tiziana has shown early success with its first two patients in the SPMS trial with clinical benefit observed after three months in the second patient. Additional SPMS subjects will be added as the year progresses and we expect to see topline data from the study next year. In other programs, we expect to see an IND submission for foralumab in Type 1 Diabetes, for Milciclib in NSCLC and for TZLS-501 in pulmonary fibrosis later this year.

[4] Source: April 2022 Tiziana Corporate Presentation. Note-some timing details have been updated since the April presentation.

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