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Tiziana Life Sciences PLC (TLSA: NASDAQ)

TLSA: Six Month SPMS Results

Research Note

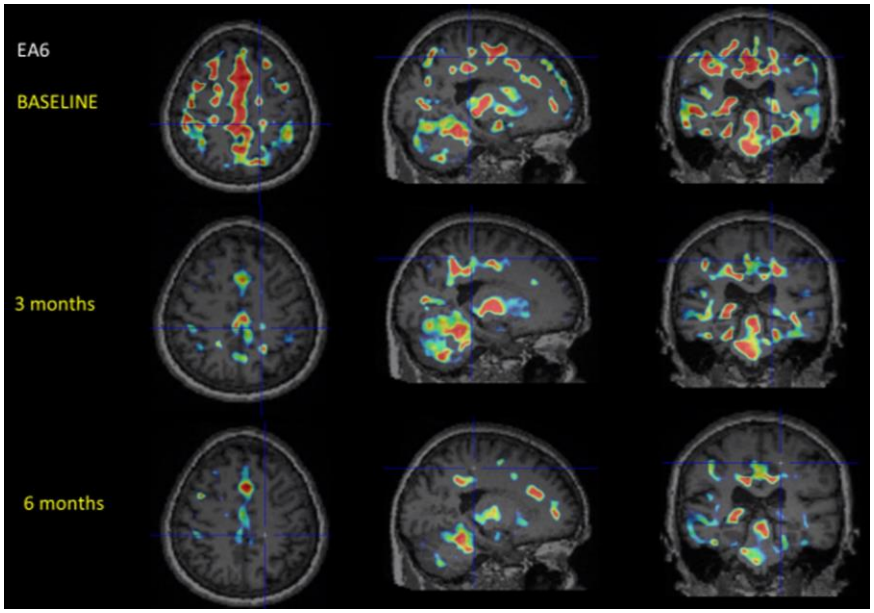
In a series of press releases released over the first half of October, Tiziana Life Sciences PLC (NASDAQ: TLSA) announced impressive results for its expanded access (EA) cohort of six patients who were receiving intranasal foralumab to treat non-active Secondary Progressive Multiple Sclerosis (na-SPMS). The six-month results span multiple parameters and demonstrated a positive result in five of the six subjects. Parallel work on these subjects showed an improvement in microglial activation as measured in Positron Emission Tomography (PET) scans. The achievements in the EA program provide additional validation for the start of a Phase IIa clinical trial of intranasal foralumab in na-SPMS subjects. Tiziana announced the initiation of the study in late September which is expected to enroll its first subjects before year end. The FDA has allowed at-home dosing of intranasal foralumab for MS subjects, which should dramatically simplify treatment for the autoimmune disorder and reduce the burden on enrollees. In parallel with the work being done in na-SPMS, Tiziana continues to report results from its Alzheimer's disease (AD) programs including publication of study results in the journal Proceedings of the National Academy of Sciences (PNAS). Finally, Tiziana announced that it has appointed William A Clementi as Chief Development Officer who will oversee pipeline development.

Six Month Data for SPMS

In a series of press releases published in mid-October, Tiziana updated stakeholders on the results from its six-patient EA study in na-SPMS at the six-month mark. Trial participants had been nasally administered the anti-CD3 monoclonal antibody foralumab over a six-month period. The first update identified a qualitative reduction in microglia activation while the second identified overall improvements in the enrolled patients' measures for multiple sclerosis (MS).

Five of six patients evinced a reduction in microglial activation as measured by positron emission tomography (PET) scans over a six-month period. Activated microglia are thought to contribute to the pathogenesis of neuroinflammatory and neurodegenerative diseases such as MS, AD and amyotrophic lateral sclerosis (ALS). Three of the four most recently added patients dosed in the program produced scans that suggest a qualitative reduction in the microglial PET signal. This helps to confirm the assessment that foralumab produced an improvement in microglial activation for the first two EA subjects. The results further confirm the trend observed in the three-month PET scan and continue to support the start of the Phase II study. Tiziana provided PET imaging of the last enrolled subject at baseline, three months and six months showing the reduction in microglial activation over the period. See the following exhibit for an illustration of this progress.

Exhibit I – Expanded Access Subject Six PET Scan Illustrating Microglial Activation[1]



Additional work with the EA subjects produced favorable results at the six-month mark. Several metrics were used to evaluate the condition of the na-SPMS patients and compare their status over the course of the study. The measures used include Expanded Disability Status Scale (EDSS), Pyramidal Scores, Timed 25-Foot Walk Test (T25FW) and Modified Fatigue Impact Scale. Each factor was directionally measured for the six subjects evaluated. Notable is that na-SPMS is a degenerative disease which worsens over time and stabilization is considered to be a favorable outcome. The clinical trial managers compiled a matrix that depicts the data for each of the patients which we include below. A dash (-) indicates stability over the six-month period while a down arrow (↓) denotes improvement.

Exhibit II – Expanded Access Patients' Scoring on MS-Related Metrics at Six Months[2]

	EDSS	Pyramidal score	T25FW	MFIS
EA1	–	↓	–	–
EA2	↓	–	↓	↓
EA3	–	–	↓	–
EA4	↓	–	–	↓
EA5	–	↓	↓	↓
EA6	–	–	–	↓

Of the four measures, fatigue (MFIS) improved for the largest number of subjects (4/6) compared to the other metrics. This debilitating symptom of MS is a result of damage to the central nervous system and can dramatically impact a person's quality of life.

While the results from the PET scans and the various MS-related metrics were supportive for additional clinical work, the much-heralded Phase II clinical trial was initiated in September. Initial work with the expanded access patients took place at the Brigham and Women's Hospital, which will continue to be used for the Phase IIa as well as six to ten new clinical sites.

[1] Tiziana press release, October 13, 2023. Tiziana Announces Positive Qualitative Six-Month PET Scan Results With Intranasal Foralumab Treating Multiple Sclerosis Patients Diagnosed With Non-Active Secondary Progressive MS (na-SPMS)
[2] Tiziana Press Release, October 16, 2023. Tiziana Life Sciences Announces Positive Six-Month Clinical Results in Multiple Sclerosis Patients Treated with Intranasal Foralumab.

Poster na-SPMS Expanded Access Trial Outcomes

A poster was developed to summarize the results from the non-active secondary progressive MS (SPMS) expanded access (EA) trial that recently produced favorable data. It was presented at the 39th Congress of the European Committee for Treatment and Research of Multiple Sclerosis (ECTRIMS) that was held in Milan, Italy, from October 11th to 13th, 2023. The title of the piece is Treatment of six non-active secondary progressive MS with nasal anti-CD3 monoclonal antibody (foralumab): safety, biomarker, and disability outcomes. It summarizes the results of the trial discussed above that examined three female and three male na-SPMS patients who were administered a two week on / one week off treatment cycle of 50 µg/day of nasal foralumab, three times per week.

The poster summarized study results finding that there were no severe treatment related adverse events (TRAEs), that all six patients experienced improvement in at least one metric (see Exhibit II) and five of six showed improvement in microglial activation as shown in the baseline to six month PET scan.

At Home Dosing

One of the primary difficulties of administering monoclonal antibodies is that they are usually infused, which requires a trip to the hospital or clinic for the drug to be administered. The requirement to go on site also means that patients with severe mobility problems must enter into densely populated areas multiple times per week to receive their therapy. Limited mobility is a common hardship for severe MS patients.

Tiziana overcame the first hurdle related to infusion and was able to develop a nasally administered formulation of foralumab; however, for the clinical trial, it remained necessary for the drug to be administered by a clinic-based provider due to the lack of safety data for the drug. The protocol for the na-SPMS trial required that the drug be administered three times per week at the MS clinic at Mass Brigham, which placed a large burden on patients and caregivers.

In an October 18th press release, Tiziana announced that the FDA will allow a protocol change to allow for at-home dosing now that nasal foralumab is better understood. Some initial training is required for patient administration; however, the shift to at-home treatment is a significant improvement in accessibility and convenience. Previously, those in the EA program were required to visit the hospital three times per week. Under the new protocol, they will only be required to visit the clinic one time every three weeks. At-home administration will also be used for the upcoming Phase IIa study which is expected to start in November.

Start of Phase IIa

Tiziana announced on September 26th that it had initiated its Phase IIa clinical trial evaluating intranasal foralumab for na-SPMS. The company held an investigators' meeting and began work to add six to ten new trial sites in addition to the original site at Brigham and Women's Hospital to recruit patients. Site initiation visits have begun. Proposed endpoints are PET imaging and likely other metrics similar to what was used in the EA program. This included fatigue, disability status, 25-foot walk test and pyramidal scores. For the Phase IIa, the FDA will allow for at-home administration of nasal foralumab, which should dramatically improve the burden of the trial on enrollees.

Addition to the Team

In late August, Tiziana announced that it had appointed William A. Clementi as Chief Development Officer. Dr. Clementi will oversee the company's development strategies and aid in the advancement of the pipeline of therapeutic candidates. His background is as director of marketing at Lorex Pharmaceuticals and he has provided consulting services to drug, biologic, cell-based therapy and other development projects. He has also completed National Institute of Health (NIH) Training Fellowship in drug metabolism and vascular smooth muscle relaxation. Academic credentials include degrees from Boston University and the University of Texas.

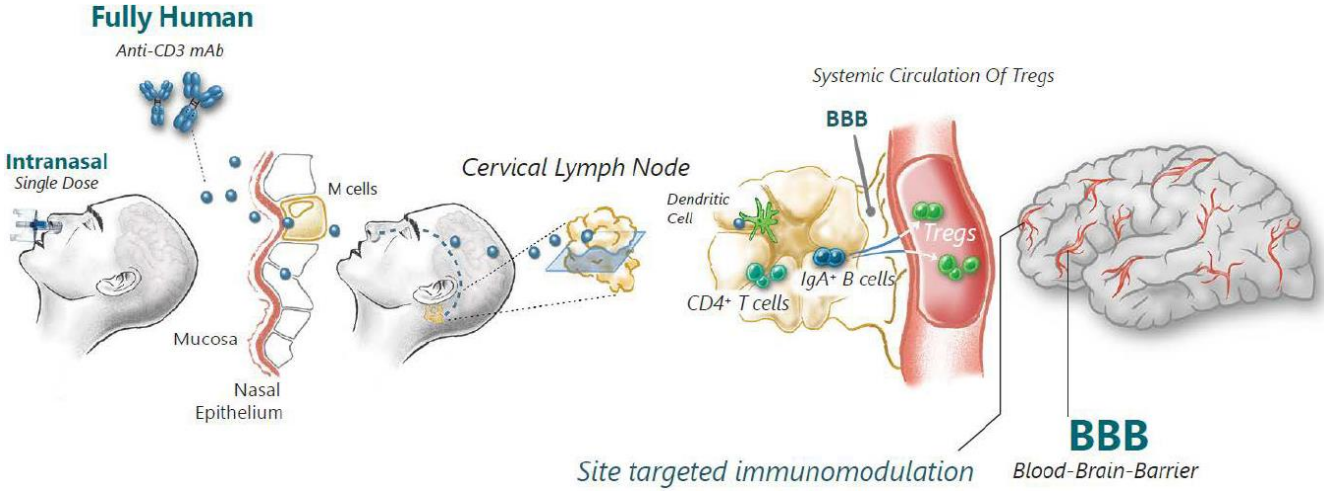
Alzheimer's Disease (AD) Program News

A study validating the mechanism of action of intranasal foralumab in Alzheimer's disease (AD) was published in the journal Proceedings of the National Academy of Sciences (PNAS) in early September 2023. The title of the work is Nasal administration of anti-CD3 monoclonal antibody ameliorates disease in a mouse model of Alzheimer's disease with lead authors Juliana R. Lopes, Xiaoming Zhang, Julia Mayrink, and Tiziana scientific advisor Howard L. Weiner. The article asserts that dysregulation of neuroinflammation, particularly that orchestrated by microglia, plays a significant role in the pathogenesis of AD. It further posits that therapies that target microglia activation constitute a unique approach for treating AD. The study administered nasal foralumab to a mouse model which subse-

quently reduced microglial activation in the animals. Additional testing measured long and short-term memories, which found some improvement in the foralumab-treated mice. While there was a positive impact on microglial activation and memory, no impact on amyloid-β was identified. Findings in the article suggest that nasal anti-CD3 has potential as a novel immunotherapy to treat AD via the targeting of microglial cells.

Dr. Howard Weiner, the chairman of Tiziana's scientific advisory board, presented research at the International Conference on Alzheimer's and Parkinson's Disease and Related Neurological Disorders (ADPD) Conference on April 1, 2023. ADPD was held in Gothenburg, Sweden. Dr. Weiner is a close collaborator with Tiziana on anti-CD3 therapies, a Co-Director of the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital and a founding member of Mass General Brigham. The title of Dr. Weiner's lecture was Immunotherapy of Alzheimer's Disease by Modulation of Innate Immunity.

Exhibit III – Intranasally-Administered Foralumab for Neurodegenerative Diseases[3]



The data presented, which is related to the effect of anti-CD3 in a rodent model, demonstrated the reduction of microglia activation and behavior improvement in rodent models of AD. Dr. Weiner hypothesized that the modulation of innate immunity via targeting microglia will play a synergistic role with approved anti-amyloid Alzheimer's treatments, which include lecanemab and aducanumab. Research has shown that intranasal rodent anti-CD3 mAb and intranasal fully human anti-CD3 mAb (foralumab) will decrease microglia activation in rodents and humans. Foralumab's mechanism of action, which reduces inflammation, appears to be complementary to the beta-amyloid sequestration mechanism of the approved biologics in animal models.

Tiziana is applying for and expects to receive $3 million of non-dilutive funding from an undisclosed Alzheimer's foundation. The funds will support the recently cleared Phase IIa trial. The application for the grant was targeted for 2Q:23. The study will evaluate the outcomes related to microglial activation for three months of intranasal foralumab administration. Endpoints will determine whether or not Tiziana's candidate can reduce neuroinflammation triggered by beta-amyloid plaque and return activated microglia to a baseline homeostatic state.

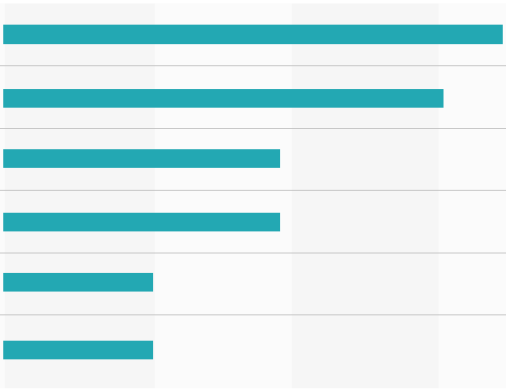
Milestones

- Filing of IND for foralumab in AD – 3Q:23
- AD IND clearance – August 2023
- Begin Alzheimer's Phase II trial – 4Q:23
- Results from initial AD clinical study – 2H:24

[3] Source: Tiziana Corporate Presentation, January 2023

Exhibit III – Tiziana Development Pipeline[4]

	THERAPEUTIC AREA	PRECLINICAL	IND	PHASE 1	PHASE 2	PHASE 3	COMMENTS
FORALUMAB: NASAL (fully human anti-CD3 mAb)	Non-active SPMS*						Phase 2a expected to begin 3Q 2023
	Alzheimer's						IND clearance received 3Q 2023
	Long COVID						IND planned 4Q 2023
	Early Onset Type 1 DM						
	ALS**						
	Intracerebral Hemorrhage (ICH).						



Summary

Attention has shifted back to na-SPMS as six-month readouts from the EA trial were presented. Tiziana also announces the start of its Phase IIa multiple sclerosis trial and obtains permission to administer nasal foralumab at home for both EA and upcoming Phase IIa subjects in na-SPMS. Company executives are also sharing the news with stakeholders at investor events and scientific conferences. High intensity work levels have led to the appointment of Dr. William Clementi as Chief Development Officer who will oversee Tiziana's development strategies.

Tiziana has been advancing foralumab in both its SPMS and AD programs with recent IND clearance for the latter. Results from preclinical work on AD was published in PNAS showing benefits in a mouse model and reduction in inflammation. Now that the IND has been cleared for Alzheimer's disease, preparations to start the trial will begin with the first enrollee expected in early 2024. We expect to see several new clinical trial related milestones in the next months.

[4] Source: Corporate presentation, October, 2023.

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