June 20, 2023

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Tiziana Life Sciences PLC (TLSA: NASDAQ)

TLSA: Reduced Microglial Activation in PET Scan

Research Note

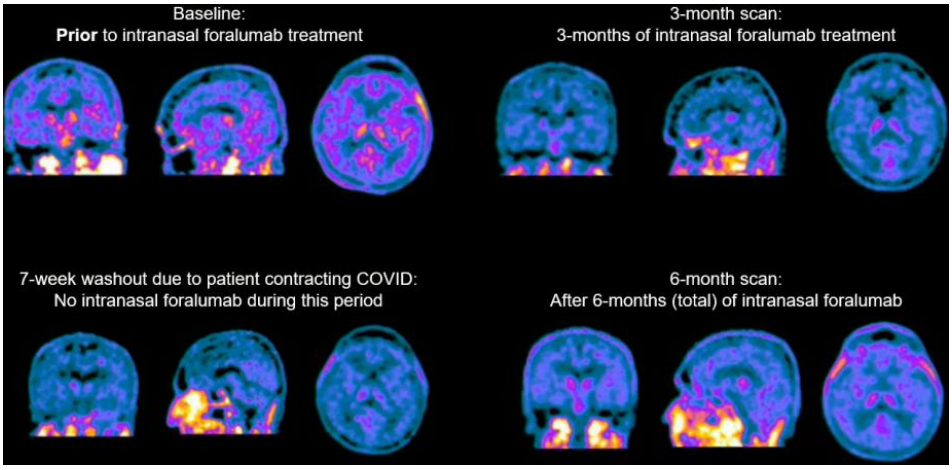
Tiziana Life Sciences PLC (NASDAQ: TLSA) reported new data from its ongoing non-active secondary progressive multiple sclerosis (na-SPMS) expanded access (EA) trial. Details of the new data were provided in a press release and in a webinar made available on June 5th. The call featured Dr. Howard Weiner, M.D., Principal Investigator for the EA trial, acting CEO Gabriele Cerrone and Chief Medical Officer Matthew Davis, M.D.

The agenda for the program began with introductions and a discussion of the development history of intranasal foralumab for treatment of neurodegenerative disease. It continued with an update on the EA trial and observations addressing the six patients enrolled to date. The next segment addressed the upcoming Phase IIa trial, how it will be structured and other details. The last part of the presentation provided an opportunity for analysts and investors to ask questions and receive answers from the management team and Dr. Weiner.

Some of the near-term milestones announced during the event by acting CEO, Gabriele Cerrone, include the receipt of grant funding for ALS, advancement of foralumab in intracerebral hemorrhage and expectation of investigational new drug (IND) application submission for Alzheimer's disease (AD).

Dr. Weiner began his portion of the webinar with a review of microglial cells and how they are regulated by nasal anti-CD3. In many neurodegenerative diseases, the microglial cells in the brain can become inflamed triggered by a number of factors including injury, infection or disease. Nasal anti-CD3 has been administered to both animals and humans, and demonstrated that the microglial inflammation can be reduced. In support of this assertion, Dr. Weiner cited the research provided in a recent Proceedings of the National Academy of Sciences (PNAS) publication. The research examined the effect of the drug in COVID, multiple sclerosis (MS) and healthy subjects.

Exhibit I – Change in Microglial Activation for First EA SPMS Patient[1]



[1] Source: Corporate presentation, KOL Webinar, June 5, 2023.

Tiziana's anti-CD3, nasal foralumab, provides a mechanism of action that supports it use in many other indications besides COVID and MS as demonstrated in animal models. This includes Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Type 1 diabetes and intracerebral hemorrhage among others.

Patient Progress
In the next segment, management reviewed patient progress in the EA group. A slide was presented with PET imaging, capturing microglial activation at baseline and at waypoints during the trial. The first and second patients both showed improvement and a halt to MS progression in their subsequent PET imaging. In all, five of six patients, showed a decrease in microglial activation in PET scans and achieved improvements in disability.

Phase II Trial
A double blind and placebo-controlled Phase II trial is planned for later this year. Two doses will be evaluated, a 50 mcg and 100 mcg dose administered weekly, with a two-on, one-off weekly schedule. 54 patients will be randomized in a 1:1:1 ratio in the 50/100/placebo groups. Endpoints will be measured at three months and include microglial activation as measured through a PET scan, MRI, biomarkers and a clinical evaluation. Depending on the success of the trial, it may be extended, expedited treatment may be pursued or a Phase III may be planned. The magnitude of the unmet need supports the use of Fast Track and Accelerated Approval if the data are supportive.

Analyst Questions
Analyst and investor questions were wide ranging and addressed speed of action, dosing objectives, partnership seeking efforts and pipeline priority. One important transaction that was highlighted by Tiziana was the Provention Bio acquisition for $2.9 billion. Sanofi bought the company for its TZIELD anti-CD3 asset for Type 1 Diabetes. Management also highlighted some expected milestones including a near term submission of the AD IND and start of a trial this year and results from both the Phase II in na-SPMS and AD in 2024.

Follow up Press Release
The KOL event was followed by a press release on June 15th reiterating the findings presented in the webinar. The much-heralded Phase II trial remains on track to begin in 3Q:23. Non-active SPMS (na-SPMS) is a result of microglial activation and inflammation, conditions which destroy the myelin, the protective sheath covering of nerve fibers. The disease also contributes to the formation of MS lesions. The absence of approved treatment for na-SPMS supports the advancement of intranasal foralumab for these patients. The reduction in microglial activation in five of six expanded access patients is another column of support for the proof-of-concept trial. Other anticipated clinical work revolves around the Alzheimer's disease (AD) investigational new drug application (IND). The submission of the IND is expected in the very near term, and if cleared will support the start of the AD program. The Long COVID program is the subject of an IND planned for 4Q:23.

Dr. Matthew Davis Assumes Additional Responsibility

Tiziana's Chief Medical Officer, Dr. Matthew Davis added a new title to his name with the addition of Chief Operating Officer (COO) as described in a June 13th press release. Dr. Davis' new responsibilities will include overseeing Tiziana's daily operations, including R&D, manufacturing, clinical trials and commercialization efforts.

Intracerebral Hemorrhage

Building on its work in other indications for its anti-CD3 franchise, Tiziana has conducted preclinical work that supports further clinical efforts in hemorrhagic stroke. The monoclonal antibody has shown promise in mice, improving motor and cognitive outcomes after a month of treatment. The mechanism of action for the nasally administered anti-CD3 induces FoxP3+ T regs and interleukin (IL)-10 producing FoxP3+ T regs in the brain.

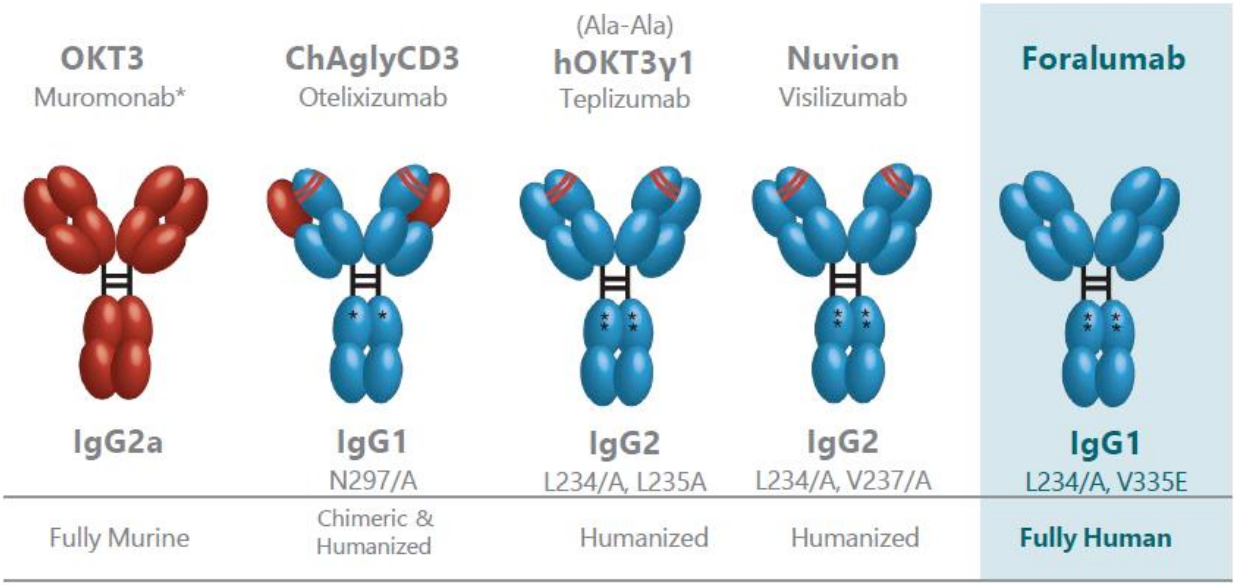
An abstract was put forward at the American Academy of Neurology annual meeting by Dr. Saef Izzy *et al*. The research demonstrated that the intranasally administered anti-CD3 reduced microglial activation and lesion volume after intracerebral hemorrhage. Further observations found that treatment improved behavioral outcomes, including motor, spatial learning and hippocampal-dependent working memory functions.

Intranasal Foralumab in COVID

In March, Tiziana published a series of press releases describing findings related to foralumab in an article entitled "Nasal administration of anti-CD3 mAb (Foralumab) downregulates NKG7 and increases TGFB1 and GIMAP7 expression in T cells in subjects with COVID-19." The study was published in The Proceedings of the National Academy of Sciences (PNAS), a peer reviewed journal of the National Academy of Sciences (NAS). Foralumab is a fully human anti-CD3 monoclonal antibody that is administered intranasally that is being investigated in multiple domains. This includes COVID, secondary progressive multiple sclerosis (SPMS) and other neurodegenerative and autoimmune disorders. The study was conducted to investigate T cell function in patients taking foralumab and identified a complex mechanism that re-regulates the immune system.

The study employed serum proteomics and RNA-sequencing to evaluate subjects evaluated in multiple trials. The investigators observed a downregulation in several inflammatory markers and an increase in effector function, following the nasal administration of foralumab. Chronic inflammation is associated with health problems including tissue damage, impaired healing, autoimmune disorders and a variety of other conditions. Dysregulation of effector function can result in chronic inflammation, autoimmunity or other immune-related diseases. Tiziana's anti-CD3 nasally administered foralumab dampened NKG7 and GIMAP7 expression while increasing TGFB1 mRNA expression. Investigators propose that foralumab induces a quiescence program in T cells through the modulation of these genes.

Exhibit II – The Evolution of Foralumab[2]



COVID Patients
Activated T cells appear in greater quantities for patients with moderate COVID and do not return to normal levels during the recovery phase, leading to respiratory distress and organ damage. Anti-CD3 has been shown to modulate the immune system and bring it back into balance. Anti-CD3 tempers the immune response by stimulating the release of T regulatory cells (Tregs).

Alzheimer's Disease (AD)

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.

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 treat-

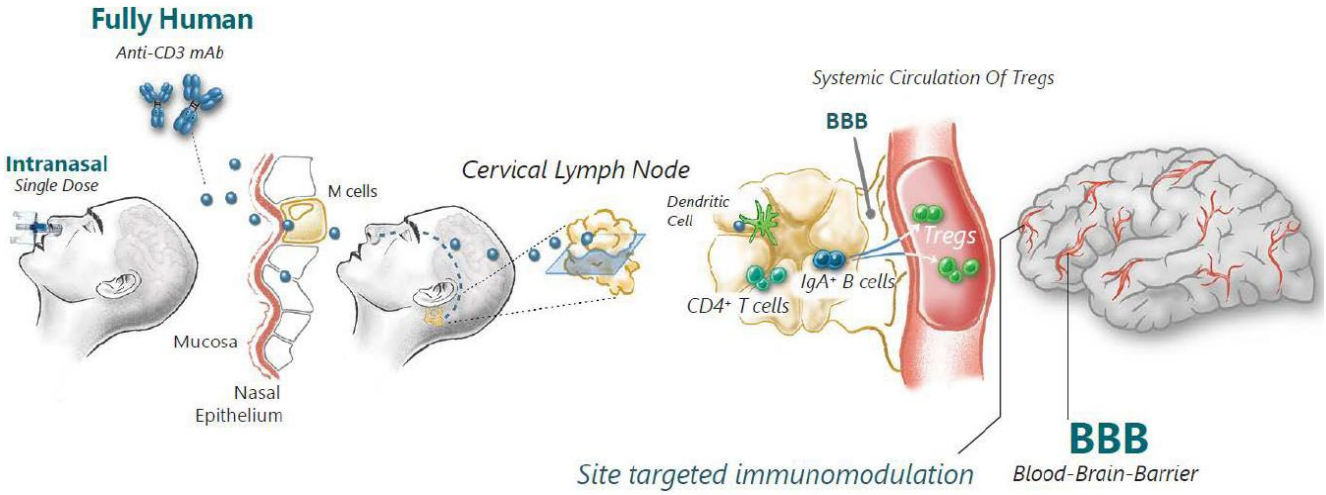
[2] Source: Tiziana Corporate Presentation, January 2023

ments, 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.

Successful preclinical development has led to the assembly of an investigational new drug (IND) application for AD. Earlier in the year, Tiziana held a Type B meeting with the FDA which produced comments that guided the formulation of the IND. The IND is expected to be submitted for regulatory review in 2Q:23. If the FDA has no questions or holds regarding the application, then Tiziana may begin its clinical trial 30 days after the submission date.

Tiziana is applying for and expects to receive $3 million of non-dilutive funding from an as yet undisclosed Alzheimer's foundation. The funds will support the Phase IIa trial. The application for the grant will be in 2Q:23 with a response expected in 3Q: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.

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

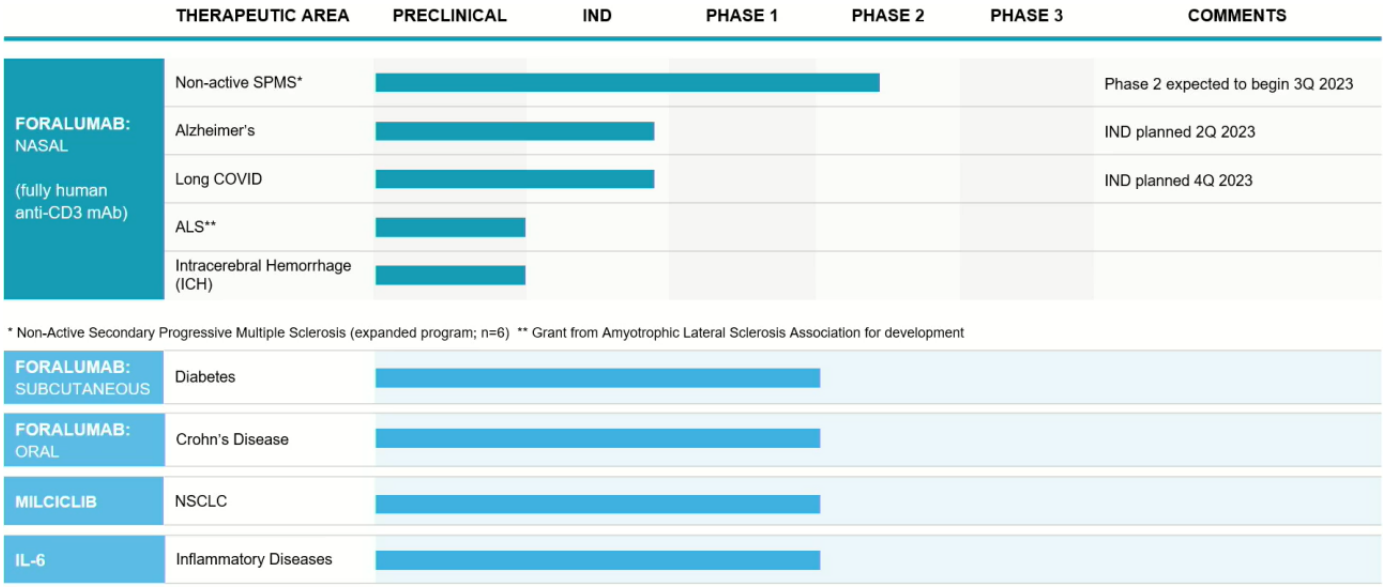


Milestones

- First cohort of expanded program patients (EA3-EA6) receives first dose – January 2023
- Type C meeting for Phase II in SPMS requested from FDA – January 2023
- Six- and nine-month PET scan results for first two expanded access patients (EA1 & EA2) - 1Q:23
- Three-month PET scans on first four-patient SPMS cohort (EA3-EA6) – 2Q:23
- Second cohort of patients of expanded program (EA7-EA10) to be enrolled – 2Q:23
- FDA Type C meeting feedback on SPMS program – 1Q:23
- FDA submission of Phase II protocol for SPMS – April 2023
- Results from first four-patient SPMS cohort – June 2023
- Start of Phase II SPMS study – 3Q:23
- Filing of IND for foralumab in Alzheimer's disease – 3Q:23
- Phase II SPMS enrollment start – 3Q:23
- Begin Alzheimer's Phase I trial – 4Q:23
- File foralumab IND for Type 1 Diabetes – 2023
- Results from initial AD clinical study - 2024
- Phase II na-SPMS readout – 4Q:24

[3] Source: Tiziana Corporate Presentation, January 2023

Exhibit IV – Tiziana Development Pipeline[4]



Summary

Tiziana reported continued good news for its SPMS program with five of six subjects in the expanded access trial demonstrating a reduction in microglial activation. The EA program will continue and a Phase II trial in na-SPMS will begin in the third quarter. Depending on the strength of the data, results from the Phase II trial could be strong enough to support expedited treatment from the FDA. Tiziana has other assets it its quiver that are also making advances. Alzheimer's disease and Long COVID are two other programs that are expected to be the subject of INDs in 2023. The company announced the receipt of grant funding for ALS and will conduct work for this indication as well.

Efforts in COVID yielded a study published in PNAS, which identified the impact of nasally administered foralumab on a variety of subjects with viral disease, autoimmune disorder and with good health. The article reviewed the use of the monoclonal antibody in multiple diseases and in animal models which showed upregulation and downregulation of a variety of genes associated with immune response. We expect to hear further updates on the pipeline of programs as we progress through 2023.

[4] Source: Corporate presentation, KOL Webinar, June 5, 2023.

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