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Tiziana Life Sciences PLC (TLSA: NASDAQ)

TLSA: SPMS Phase II to Proceed

Research Note

Tiziana Life Sciences PLC (NASDAQ: TLSA) is preparing to launch a Phase II clinical trial in non-active secondary progressive multiple sclerosis (SPMS) in 3Q:23. Support for the trial comes from the early but promising data that has been generated in the expanded access program. In this note we will review Tiziana's efforts to advance intranasal foralumab in non-active SPMS and other related indications such as Alzheimer's Disease and intracerebral hemorrhage. A series of interviews with Chief Medical Officer Matthew Davis, MD, delves into the details of these upcoming programs. Tiziana reported full year 2022 results and we provide a review of the results in comparison with prior year trends. The company is advancing other programs in COVID and Type 1 diabetes that are at an earlier stage of development but illustrate the wide applicability of anti-CD3 intranasal foralumab in a variety of inflammatory disorders.

Management Interview with Chief Medical Officer Dr. Matthew Davis

Tiziana's Chief Medical Officer, Dr. Matthew Davis participated in a series of interviews which discussed the company's progress in SPMS, clinical improvement in enrolled patients and anticipated Phase II study in the disease. Other topics include future opportunities in Long COVID and Alzheimer's Disease, which will be the subject of an investigational new drug (IND) application to be submitted later this quarter. Other topics of interest include perceptions of the investment environment, M&A activity in life sciences, other trials in multiple sclerosis and new products in the neurodegenerative space among other topics. Scan ahead for links to the interviews:

Exhibit I – Interviews with Dr. Matthew Davis[1]

[1] Source: Screen shot from video interview.

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Summary of Interviews with Chief Medical Officer Matthew Davis, MD

- Tiziana Reports Improvements in Expanded Access SPMS Patients
- Tiziana to Submit IND for Alzheimer's Disease
- Tiziana's Phase II Study in Non-Active, Secondary Progressive Multiple Sclerosis
- SPMS Clinical Improvement with Tiziana's Foralumab
- Tiziana's Phase II SPMS Trial Planned for 3Q:23
- Tiziana's Foralumab a Potential Treatment for Long COVID
- Fireside Chat with Tiziana's Chief Medical Officer

2022 Full Year Results

Tiziana filed its Form 20-F on April 26th, 2023 which provided financial results for the twelve-month period ending December 31st, 2022. In the related press release, Tiziana highlighted anti-CD3 foralumab's progress in SPMS and its advance in other indications including Long COVID, Alzheimer's Disease (AD) and Type 1 Diabetes. Further anti-CD3 work was conducted in an animal model examining intracerebral hemorrhage which was presented at the American Academy of Neurology (AAN) annual meeting.

SPMS in particular has been an area of focus for Tiziana over the last year with an ongoing expanded access program which initially enrolled two patients and has since added another eight. Based on the favorable data generated to date, the company has consulted with the FDA to design a Phase II study in non-active SPMS evaluating intranasal foralumab. The study is expected to begin in the third quarter of 2023.

Multiple Tiziana-oriented publications were promulgated over the prior year, including one examining the mechanism of action for intranasal foralumab in The Proceedings of the National Academy of Sciences (PNAS). We discuss this article in a later section. Another was published in Forbes magazine entitled "New T Cell Antibody Treatment Improves Outcomes for Covid Patients."

In the financial sphere, Tiziana reported no revenues in 2022, reflecting its status as a development company. Research and development expenses totaled $13.0 million, down slightly from 2021's $13.2 million with spending increases in foralumab programs more than offset by declines in Milciclib and TZLS-0501 programs. General and administrative expenditures were $1.6 million, a dramatic fall from the $13.3 million spent in the prior year. Lower option related expenses due to options forfeitures, a decrease in options outstanding during the year, labor cost savings due to a reduced headcount in 2022, a reduction in legal costs due to a one-off reorganization in 2021, insurance savings due to more favorable market conditions for Directors & Officer's insurance, a net gain due to favorable foreign exchange movements and other general savings contributed to the year over year change.

Net loss for the year was ($15.4) million or ($0.15) per share. The cash balance as of December 31, 2022 was $18.1 million, down from $42.2 million at year end 2021. Cash burn was ($19.6) million and cash used in financing was a paltry ($55,000).

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.

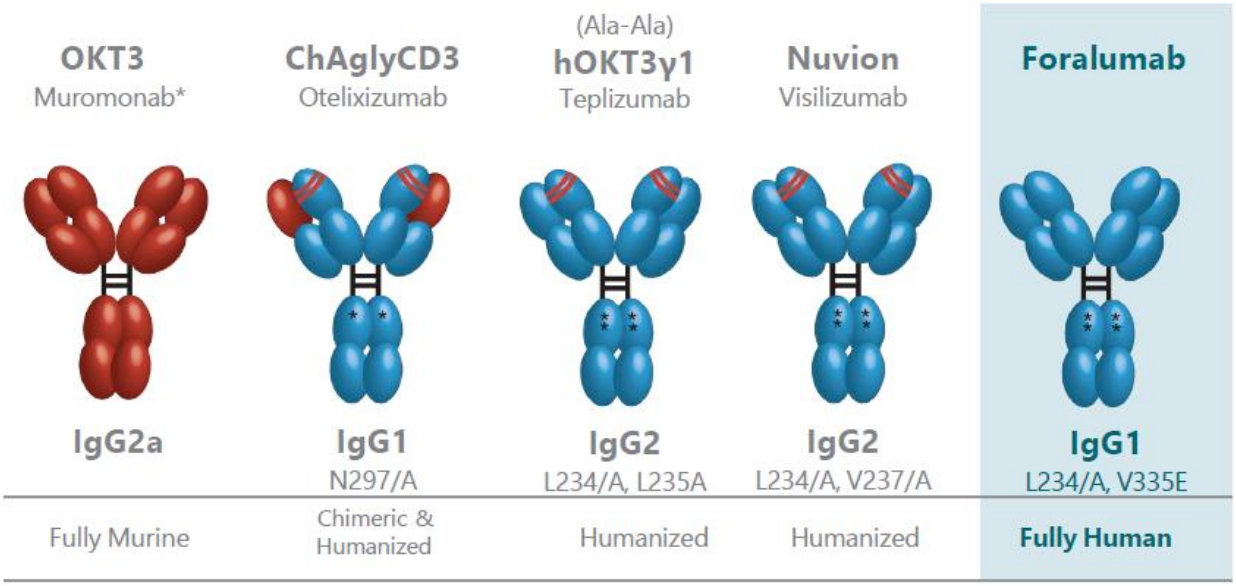
An abstract was put forward at the American Academy of Neurology annual meeting by Dr. Saef Izzy *et al*. The research demonstrated that the intranasally administered anti-CD3 reduced microglial activation and lesion volume after intracerebral hemorrhage. Further observations found that treatment improved 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).

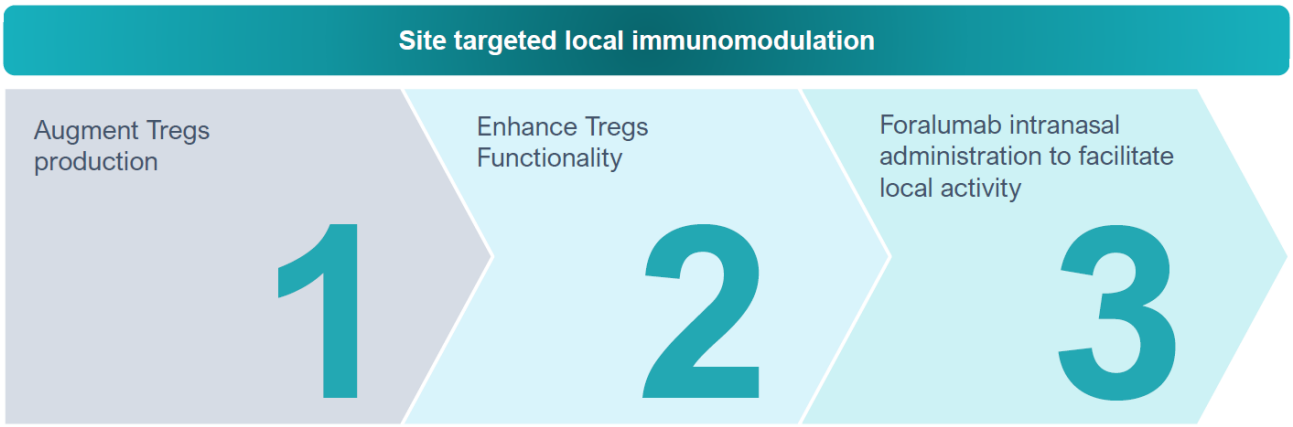
Role of Various T Cells
T cells play a critical role in the immune response to inflammation. When there is an increase in inflammation, T cells are activated and mobilized to the site of inflammation to help control the immune response. Inflammation is a normal response of the immune system to infection, injury or other types of stress. When inflammation occurs, immune cells release pro-inflammatory cytokines, which can attract T cells to the site of inflammation. Upon arrival, they can regulate the immune response by releasing cytokines that either promote or suppress inflammation.

One type of T cell, called a cytotoxic T cell, can directly kill infected or damaged cells to prevent the spread of infection or tissue damage. Other types, such as helper T cells, can release cytokines that activate other immune cells, such as macrophages, to help clear pathogens or damaged tissue.

[2] Source: Tiziana Corporate Presentation, January 2023

Tregs play a critical role in regulating inflammation. They are a type of T cell that can suppress or dampen immune responses, including inflammation. During an immune response, Tregs are activated and can migrate to the site of inflammation. Once there, they can release anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which can inhibit the activity of other immune cells and suppress the inflammatory response. Tregs can also directly interact with other immune cells, such as dendritic cells, macrophages, and T helper cells, to suppress their activity and reduce inflammation. Additionally, Tregs can help to prevent the development of autoimmune diseases by suppressing the activity of self-reactive immune cells that could potentially attack healthy tissues in the body.

Exhibit III – Foralumab Improves Treg Production and Enhances Functionality[3]



Methods Used in Study
In healthy volunteers, subjects were treated with 100 µg of nasal foralumab given daily for 10 consecutive days. Blood was collected two days prior to the start of dosing and collected again 10 days after dosing began. Analysis of the T cells, B cells and monocytes in the blood showed downregulation of inflammatory pathways such as hypercytokinemia[4] and interferon signaling pathway in both groups. The investigators also identified a coronavirus pathogenesis pathway that was downregulated in the foralumab group but not in untreated controls. Immunomodulatory effects were most pronounced in CD3+ T cells and additional evidence found changes indirectly affecting both monocytes and B cells.

Findings
Investigators identified several common mechanisms in this review of healthy, COVID and MS afflicted subjects. The comparison found that GIMAP7 and TGFB1 gene expression were upregulated, while NKG7 gene expression was downregulated in all three cohorts. The results were backed up by similar findings in a mouse animal model. Testing in healthy human subjects allowed the team identify common changes in those treated with foralumab.

Investigators under Tiziana's umbrella have performed additional work using the anti-CD3 foralumab in Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS) and an undisclosed rare pediatric disease where there are no other treatments showing that there may be a benefit to patients. Others have performed studies showing that anti-CD3 may mitigate the severity of diabetes, arthritis, inflammatory bowel disease and lupus.

Alzheimer's Disease (AD)

Dr. Howard Weiner, who is 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

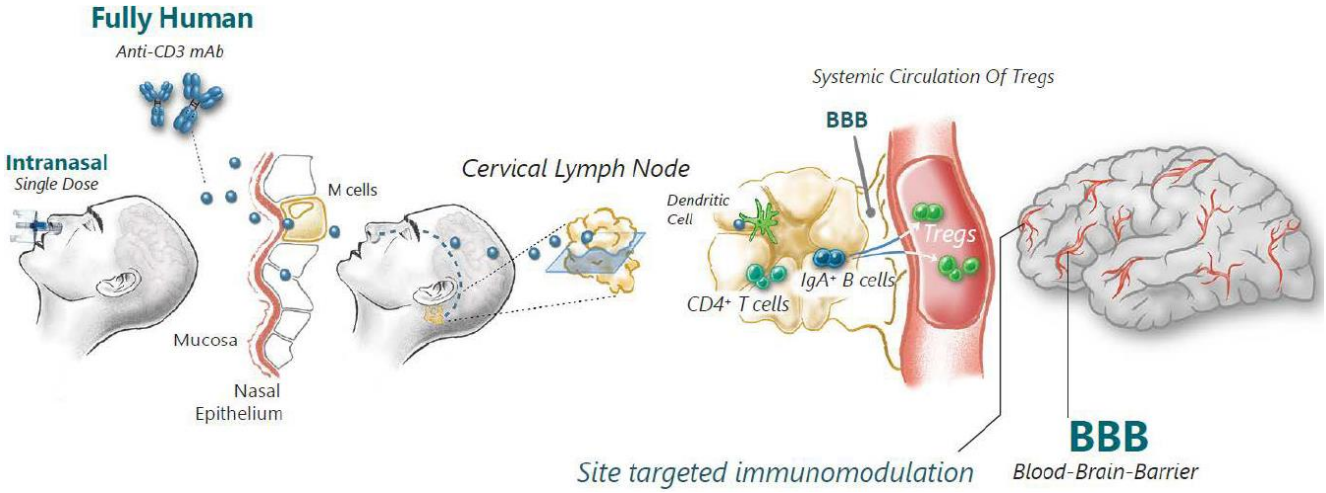
[3] Source: Tiziana Corporate Presentation, January 2023
[4] Hypercytokinemia is a condition characterized by an excessive production of cytokines, which are proteins produced by the immune system to regulate inflammation and the immune response. In hypercytokinemia, the immune system produces an excessive amount of cytokines, leading to a state of systemic inflammation that can cause tissue damage and organ dysfunction.

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.

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 IV – Intranasally-Administered Foralumab for Neurodegenerative Diseases[5]

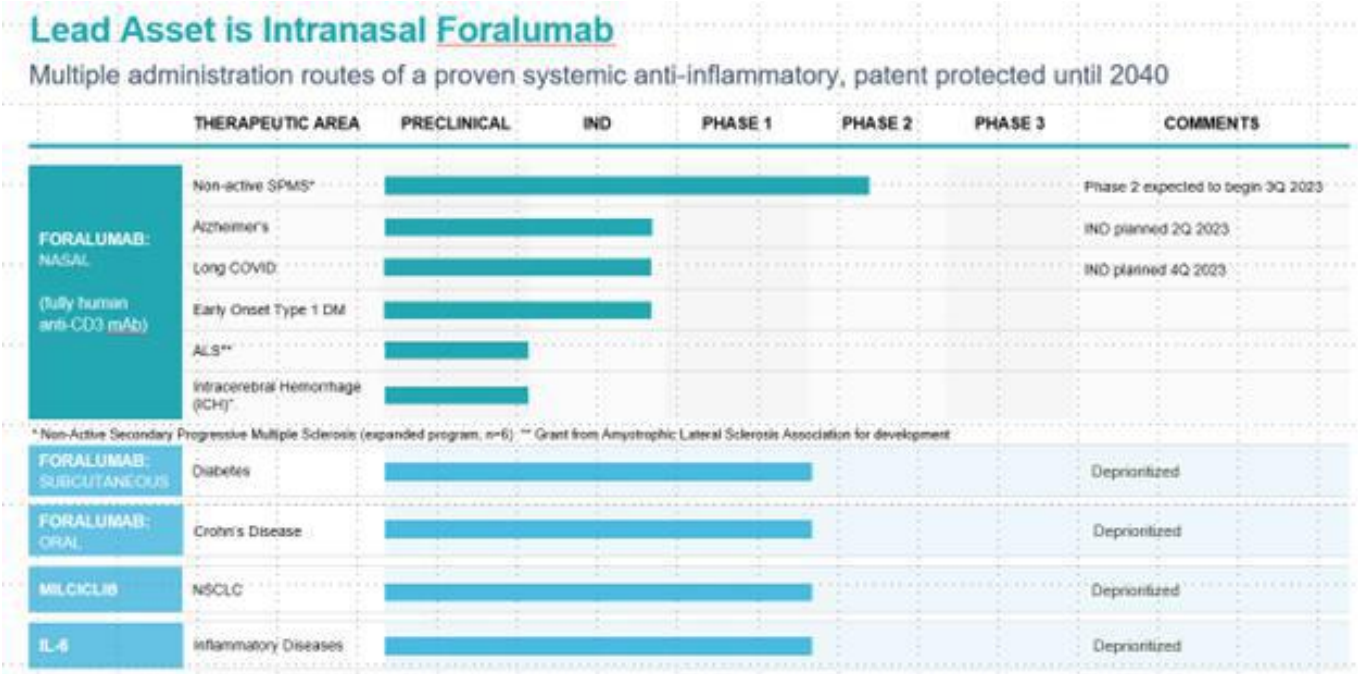


Milestones

- 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 – 2Q:23
- 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

[5] Source: Tiziana Corporate Presentation, January 2023

Exhibit V – Tiziana Development Pipeline[6]



Summary

Tiziana has been busy with its efforts to advance intranasal foralumab and is making clinical progress in SPMS and preclinical progress for Alzheimer's Disease, Type 1 Diabetes, intracerebral hemorrhage, COVID and other inflammatory disorders. To provide additional color to Tiziana's activities, Chief Medical Officer Matthew Davis, MD, participated in a series of interviews discussing these programs. 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.

Tiziana is now conducting expanded access (EA) studies on secondary progressive multiple sclerosis (SPMS) patients and is preparing to launch a Phase II study in non-active SPMS which is expected to begin in 3Q:23. The strong results shown to date support further advancement of foralumab in this population. An active timeline is expected over the next few months as the first two four-person cohorts are evaluated, FDA meetings take place and preparations for a Phase II begin. If all goes to plan, a few months after beginning the Phase II, a futility analysis will be conducted to evaluate the success of foralumab in a larger population. Additional efforts in other neurodegenerative diseases including AD and ALS are expected to be financially supported by partners. We expect to hear further updates on the SMPS enrollment progress and advancements in other programs as we progress through 2023.

[6] Source: 2022 Annual Report, SEC Form 20-F

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