Tiziana Life Sciences Plc (TLSA – $1.05*)
Buy; $3.00 PT; $101.2M Market Cap
Breaking News
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FDA Allows Add'l MS Patients' Enrollment; Crohn's Study Progression Makes for a Data-Rich 2H22; Reit. Buy, $3 PT

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Summary and Recommendation

On 4/5, TLSA reported that collaborators at the Brigham and Women's Hospital (BWH) in Boston, MA, have received a "Study May Proceed" letter from the FDA permitting the ongoing Expanded Access IND program for intranasal foralumab to enroll up to eight additional secondary progressive multiple sclerosis (SPMS) patients; this is a noteworthy MS study protocol amendment, particularly since it now allows for a significantly increased enrollment as well as extended treatment period. Recall, TLSA had previously enrolled two patients, with the FDA requiring the first patient to demonstrate a clean safety profile following 3 months of treatment, then allowing treatment to continue to 6 months, at which point a second patient was also allowed to enroll. Being a fully humanized anti-CD3 antibody, foralumab cannot cross-react with CD3 from other species and hence has had limitations to the scope of preclinical toxicology studies to evaluate longer-term exposure that allows for chronic dosing. Having already reported a clean safety and favorable tolerability profile at 3- and 6-months for SPMS patient #1, TLSA also noted impressive whole-brain foralumab treatment effects, i.e., standardized uptake value ratio (SUVR) data, i.e., -23% and -38%, respectively, when compared to a pseudo reference region that showed minimal change in PET SUV across time points, implying an unprecedented effect on microglial activation not previously seen by even strong anti-inflammatory drugs such as Tysabri (link). TLSA guided for 3-month data from SPMS patient #2 to be released in May.

Additionally, for oral foralumab formulation, TLSA also recently announced the initiation of Ph. Ib trial in mild-to-moderate Crohn's disease patients to evaluate a multiple dose regimen, with encouragingly a broader patient population and a shorter dosing period aimed at expediting patient enrollment, which TLSA anticipates completing in 4Q with data release shortly thereafter. We are encouraged by notable recent pipeline progression translating to reinvigorated investor interest, with TLSA equity up ~98% off 2/25 52-week low, but still trading at over-sold levels amid macro sector headwinds for small-cap biotechs, with an EV of <$50M and off ~70% from 52-week high.

Key Points

- **Expanded MS study protocol will deploy the same foralumab dosing regimen**, i.e., 50 mg three times a week (MWF), with a provision to be increased to 100 mg three times a week (MWF) if needed to improve clinical benefit. TLSA anticipates submission of treatment plan to the BWH's Institutional Review Board (IRB) prior to initiation of patient enrollment, which is anticipated to be initiated in July 2022. While the primary objectives for the study remain evaluation of safety and tolerability, TLSA anticipates evaluating (1) immune responses, e.g., IFN-g, IL-18, IL-1β and IL-6, and (2) clinical responses notably PET to assess inhibition of microglial activation which in turn holds the key to demonstrating transformative treatment effects on MRI scans and disability progression, e.g., EDSS, Timed 25-Foot Walk Test (T25FW), 9-Hole Peg Test (9HPT), Symbol Digit Modality Test (SDMT). The oral foralumab IND amendment request would specifically allow for the molecule's investigation in a broader patient population as well as a shorter dosing period; *(continued on pg. 2)*

specifically, the amended protocol is now designed to focus on mild-to-moderate Crohn's Disease patients dosed up to 5 mg once daily for five consecutive days, with safety monitored throughout the treatment period in the hospital or clinical research unit (CRU). Recall, TLSA had previously submitted an IND to conduct a Ph. 1b study in moderate-to-severe active Crohn's Disease patients to evaluate safety of enteric-coated foralumab capsules administered orally once daily for 14 days as an inpatient study in the hospital or CRU with safety monitoring, for which the FDA issued a 'Study May Proceed letter'; however, initial feasibility findings indicated that enrollment of patients in this initial safety study, requiring 14-day hospitalization, was highly challenging due to the COVID-19 pandemic. Notably, data from an earlier Phase 1a, single-ascending dose (SAD) study with orally administered foralumab in healthy volunteers determined that the treatment was well-tolerated up to 5 mg, which was the highest dose tested. The Ph. Ib study will also evaluate the PD effects on modulation of immunobiomarkers, including calprotectin, a widely used biomarker for gut inflammation, in stools, as a secondary endpoint.

Valuation

We base our Buy rating and 12-month price target of $3 per share on a discounted cash flow (DCF) analysis of revenue and cash flow projection through 2030. Our projections of free cash flow to the firm from sales of oral foralumab for moderate to severe Crohn's disease and nasal foralumab for non-active SPMS are adjusted and weighted based on historical regulatory approval rates of similar treatments at similar stages of development. Our DCF analysis applies a WACC-calculated 14.5% discount rate and a 2% terminal growth rate, in line with other clinical-stage biotech companies, yielding an implied enterprise value of $78M. For 2030, the final projected year of our model, we forecast $500M in total risk-adjusted revenue, which assumes a 35% probability of clinical and regulatory success for oral foralumab and 25% for nasal foralumab. Of note, nasal foralumab could potentially pursue approval via orphan drug designation, in our opinion, intended for rare diseases or conditions that affect less than 200,000 individuals in the U.S. Through this regulatory pathway, TLSA will be able to have the agency involved in the early stages regarding the trial design and endpoint selection and likely facilitate expedited approval, given the unmet need. We currently do not ascribe any value in our model to TZLS-501 and milciclib, as we await additional clinical data and subsequent guidance on the regulatory path to market.

Risks

Clinical risks. It is uncertain whether the clinical benefit observed in the clinical studies for foralumab and future registrational trials will be sufficient to support regulatory approval in the U.S., Europe, and other countries. Negative safety and/or efficacy findings in these trials could lead to downward revisions to our price target.

Regulatory risks. The regulatory pathway for all of TLSA's programs in the U.S. is uncertain, and it is unclear whether positive data will be sufficient for a New Drug Application (NDA) submission for each program in the U.S. Additionally, there is no certainty that any of TLSA's drugs will be approved or reimbursed. If the regulatory path for TLSA's candidates is more complex and/or time-consuming than anticipated, there could be a materially negative impact to our estimates and price target, even with success in achieving clinical endpoints.

IP risks. The patent protection related to foralumab and other candidates may expire in the near term and be subject to litigations from competitors. For example, the methods of use patent, pertaining to autoimmune or Inflammatory disease and disorder, for foralumab is expected to expire in 2025.

Commercialization risks. The market potential of TLSA's therapies may not be as significant as projected. In addition, TLSA will need to establish a sales and medical affairs infrastructure in the U.S., Europe, and other geographies for foralumab and other pipeline candidates.

Financing risk. With approximately $66M in cash and cash equivalents, TLSA will likely need to raise additional capital for continued clinical and preclinical candidate development, perhaps via additional equity financing, before reaching profitability, likely resulting in equity share dilution.

Stock price volatility. Share price volatility is common for developmental biopharma firms like Tiziana Life Sciences.

*Closing price of last trading day immediately prior to the date of this publication unless otherwise indicated.

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