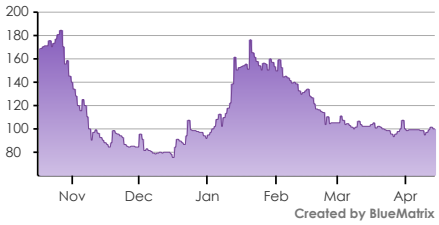
TIZIANA LIFE SCIENCES PLC (LON:TILS)

15 April 2021

Healthcare

52-WEEK HIGH	**300.0p**
52-WEEK LOW	**40.0p**
PRICE	**95.0p**
MARKET CAP (M)	**£185**

Share Price



Major Shareholders

Shares in issue	194,612,289
Avg Three-month trading volume	849,945
Primary Index	LON
Next Key Announcement	News on trial timing Foralumab in CD/MS

Company Information

Address: Tiziana Life Sciences,11/12 St James Square,London SW1Y 4LB
Website: www.tizianalifesciences.com

Analyst Details

Emma Ulker
emma.ulker@proactiveinvestors.com

Tiziana Life Sciences: Advancing the therapeutic pipeline

Tiziana (LON:TILS, NASDAQ:TLSA) is advancing its lead immunotherapy Foralumab, a fully-human anti-CD3 monoclonal antibody (mAb) being developed for oral and nasal routes of administration, providing novel approaches in treating severe inflammatory and autoimmune disease. Top-line data from a recent trial in COVID-19 patients conducted in Brazil demonstrate the exciting potential to reduce lung inflammation, both compared to the control group, and to Foralumab combined with Dexamethasone. These data help validate and de-risk nasal Foralumab, and there is potential read-across for reducing inflammation in the planned phase II study which will pioneer the nasal treatment for multiple sclerosis (MS) patients. TILS is also moving towards a phase II study start in Crohn's disease (CD), the oral version of Foralumab is a pioneering 'take home' oral immunotherapy which can revolutionise treatment for this disease. Other milestones ahead include advancing Milciclib into phase IIb studies for treatment-resistant solid tumours, which can further de-risk the therapeutic pipeline.

TILS reported promising top-line data in a trial of its nasally administered monoclonal antibody (mAb) in mild-to-moderate COVID-19 patients indicating a positive trend in the reduction of lung inflammation. It also reported supportive data indicating a significant reduction in inflammatory markers IL-6 and C-reactive protein, plus anecdotal reports of a rapid improvement in smell and taste sensations that are frequently affected by COVID-19. These trends were seen to improve in the treatment group receiving Foralumab compared to the control as well as in the group receiving a combination of Foralumab and Dexamethasone.

Foralumab data mild-to-moderate COVID19

Cohort (evaluable patients)	Lung CT Scan (% Improvement)	Cytokine IL-6 (% Reduction)	C-Reactive Protein (% Reduction)
Control (n=14)	43	37	40
Foralumab + Dexa (n=12)	75	41	55
Foralumab (n=10)	80	69	85

Source: Tiziana Life Sciences

This evidence supports the rationale for site-targeted administration of mAbs to treat inflammatory disease. It also shows that nasal Foralumab was well tolerated and safe. Nasal Foralumab was targeted at treating lung inflammation rather than the infection suggesting the potential to target the patients infected with the more resistant Brazil or South African variants, or indeed for other types of respiratory inflammation although this needs to be substantiated in further tests. There is also read across to use of nasal Foralumab in MS.

Following on from promising results of the study in COVID-19, TILS is awaiting clearance from FDA to commence a multi-centre, placebo-controlled phase IIb study in up to 60 progressive multiple sclerosis patients across three arms: placebo, 50 ug and 100 ug nasal Foralumab, to be conducted at the lead site at Harvard Brigham and Women's Hospital (BWH), which pioneered the development of nasal Foralumab. The study scope will test safety and tolerability and secondary endpoints of cognitive behaviour, Tregs, microglial suppression and biomarkers.

Chief executive/chief scientific officer: Kunwar Shailubhai was also a co-founder, executive vice-president and CSO of Synergy Pharmaceuticals, the inventor of TRULANCE. He is also a pioneer of GC-C agonist technology. Other former roles include VP of Callisto Pharmaceuticals and Group Leader at Monsanto Co.

Executive chairman: Gabriele Cerrone has a track record of corporate financing having listed nine companies, seven on NASDAQ and two in London. He is the former chairman of Trovagene, Gensignia, Rasna, Contravir and Okyo. He is also the co-founder and director of two NASDAQ-listed companies that brought drugs from the discovery through to US Food & Drug Administration approval: Synergy Pharmaceuticals and Siga Technologies.

TILS has also received FDA permission to start nasal dosing of Foralumab in a single secondary progressing MS (SPMS) patient under an individual patient expanded access, or compassionate use programme. Investigators at the BWH will follow this patient with detailed routine safety, neurological, imaging and PET studies to evaluate microglial imaging. This will test the rationale for activating the mucosal immunity via the cervical lymph nodes signified by modification of immunological and neurodegenerative markers. This will test earlier findings derived from extensive research conducted at the BWH by Dr Howard Weiner. This approach might offer new horizons for treating a disease where until now, approaches have largely been limited to symptom control.

MS is a devastating, chronic inflammatory disease of the CNS, affecting approximately 2.3mln people worldwide and up to 1mln people in the US, according to a study conducted by the National MS Society. Generally, MS is divided into its most prevalent relapsing and remitting type (RRMS), and primary and secondary progressive forms (SPMS/PPMS). There are a fairly limited number of other late stage clinical programmes for progressive MS. So, if the alternative modality and mechanism of nasal Foralumab are safe and efficacious, it could be an important supplementation to other treatment options. This is a particularly interesting approach given the severe side effect profile of first-line treatments such as Ocrevus, which includes infections and infusion reactions, and the acute unmet need.

TILS is also preparing to commence a phase Ib/II study of the oral form of Foralumab in Crohn's disease. Oral administration of anti-CD3 mAbs has already been clinically validated in patients with inflammatory bowel disease. The clinical trial is a pioneering approach as it will be the first-ever study of 'take home' oral immunotherapy capsules to our knowledge. The protocol is for dosing once a day for six months with an open-label adaptive design at (0.5, 1.25. 2.5 and 5.0 mg) for 14 days to test the safety of the highest dose. It then progresses to three arms at (0.5, 2.5 and 5 mg). The study's primary endpoints are safety and tolerability and will also include secondary endpoints to test the localised efficacy, clinical response and mechanism of action of Foralumab. These include mucosal healing, pharmacokinetics, drug-specific antibodies and biomarkers.

Clearly, the implications are significant since the advanced CD therapy market is dominated by mAbs including Humira. AbbVie's anti-TNF alpha mAb and IL-12/IL-23 targeting Stelara features along with Humira among the top ten selling treatments worldwide. Analysts peg the prospective value of the CD market at over US$20bn in the next decade. While the landscape is dominated by big pharma, Foralumab's potential in CD could lie in treating populations that are failing on first-line therapies, or for patients suffering from serious side effects of long-term treatment. For Humira, these include serious infections. In addition, its competitive advantage could be as an attractive dosing alternative to the generally intravenous (IV) or subcutaneously administered standard therapies. This could also be easier and less expensive to administer than IV mAbs.

The company is also evaluating the next steps for multi-kinase inhibitor Milciclib. This would test its efficacy seen in advanced cancers in liver cancer for priority in Asia where the disease is most prevalent in patients resistant to standard treatment with Sorafenib. It also sees potential to treat unmet need in KRAS mutated non-small cell lung cancer (NSCLC) based on positive anti-cancer activity seen *in vivo*. The KRAS mutation is a key driver of aggressive and treatment-resistant solid tumours and accounts for around 25% of all cases of NSCLC which has an overall survival rate of around 20 months.

Milciclib is an oral therapy targeting the interruption of cell cycle growth of solid cancers by inhibiting a range of proteins known as cyclin-dependent kinases (CDKs), tropomycin receptor kinases (TRKs) and Src kinases. Milciclib has been tested in eight phase I and II clinical studies in 316 patients. They have shown it to be a promising treatment for controlling abnormal cell growth and prolonging

patient survival in advanced and metastatic cancers as well as confirming its positive safety profile.

The preclinical toxicology studies of nasally administered formulation of TILS' anti-IL6R mAb, TZLS-501 have been successfully completed, and an investigational new drug (IND) submission is anticipated imminently, to test the safety of the nasally-administered formulation. This can address respiratory disease treatment including potentially COVID-19 inflammation and acute respiratory distress Syndrome (ARDs). In our view, however, TILS is likely to prioritise Foralumab for treating COVID-19.

Conclusions: TILS' market valuation has fallen back in the last six months by around 50%, despite announcing positive clinical data for nasal Foralumab supporting its anti-inflammatory effect. The current cash position of c US$50mln (c £37mln) provides an approximate enterprise value for Tiziana of just £147mln whereas it has three phase II programmes. The Accustem spin-out has been executed so the sole focus is on the therapeutic pipeline.

The key value drivers include, in our view, are further progress with Foralumab in MS and Crohn's. So, further advances such as trial starts and evidence to support the early promise of anti-inflammatory mechanisms, and corroboration of the site targeted approaches can help de-risk the pipeline further. This in turn should be a positive catalyst for the current market value of TILS. Taken in context, peers such as Provention Bio (PRVB) has a market cap of US$500mln. Its lead programme is anti-CD3 humanised mAb Teplizumab (phase III) being developed for type-one diabetes.

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London
+44 207 989 0813
The Business Centre
6 Wool House
74 Back Church Lane
London E1 1AF

New York
+1 347 449 0879
767 Third Avenue
Floor 17
New York
NY 10017

Vancouver
+1 604-688-8158
Suite 965
1055 West Georgia Street
Vancouver, B.C. Canada
V6E 3P3

Sydney
+61 (0) 2 9280 0700
Suite 102
55 Mountain Street
Ultimo, NSW 2007