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John D. Vandermosten, CFA
312-265-9588 / jvandermosten@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Suite 1600, Chicago, IL 60606

Tiziana Life Sciences PLC (TLSA - NASDAQ)

In A Tizzy about Tiziana

Based on our DCF model and a 15% discount rate, Tiziana is valued at approximately $7.50 per ADR share. Our model applies a 15% probability of ultimate approval and commercialization for the portfolio of assets including foralumab and milciclib. The model includes contributions from the United States and global developed markets.

Current Price (4/9/2021)	$2.67
Valuation	**$7.50**

INITIATION

Tiziana is a research and development company developing three main candidates for a variety of indications in autoimmune disease, cancer and COVID. The lead candidate, foralumab, is a fully human anti-CD3 antibody, being investigated in multiple sclerosis (MS), Crohn's disease (CD) and COVID, administered intranasally and orally via enteric coated capsules. milciclib is the second candidate and is being investigated as a combination product in multiple oncology indications. The third candidate, TZLS-501, is an anti-IL-6R receptor antibody expected to be the subject of an IND submitted in 2021. TZLS-501 is being investigated as a treatment for COVID and other pulmonary diseases such as ARDS.

Ph2 foralumab clinical trials for MS and CD are targeted for 2021 & Ph2 combination trials for milciclib in coming quarters. Tiziana differentiates itself in the use of intranasal, oral and inhaled formulations of mAbs that are able to avoid shortcomings of infused & subcutaneous administration.

Our valuation assumes a 2026 regulatory approval and 2027 commercialization of foralumab for both pMS and CD in conjunction with partners.

SUMMARY DATA

52-Week High	**12.17**
52-Week Low	**1.04**
One-Year Return (%)	**343**
Beta	**0.00**
Average Daily Volume (sh)	**1,011,454**
Shares Outstanding (mil)	**97.3**
Market Capitalization ($mil)	**259**
Short Interest Ratio (days)	**0.1**
Institutional Ownership (%)	**5.2**
Insider Ownership (%)	**39.5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of GBP)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	£0.0 A	£0.0 A	£0.0 A	£0.0 A	£0.0 A
2020	£0.0 A	£0.0 A	£0.0 E	£0.0 E	£0.0 E
2021					£0.0 E
2022					£0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2019	£0.00 A	-£0.03 A	£0.00 A	-£0.03 A	-£0.05 A
2020	£0.00 A	-£0.03 A	£0.00 E	-£0.04 E	-£0.06 E
2021					-£0.11 E
2022					-£0.10 E

INITIATION

We are initiating coverage of Tiziana Life Sciences PLC (NASDAQ: TLSA / LSE: TILS) with a current valuation of $7.50 per American Depository Receipt (ADR) share.[1] This present value is based on our probability adjusted estimates for successful Phase III confirmatory trials in progressive Multiple Sclerosis (pMS) with nasally administered foralumab and Crohn's Disease (CD) with orally administered foralumab which we expect to yield registrational results in 2026. Tiziana is also starting a Phase II study in COVID patients with nasally administered foralumab. Tiziana is developing an anti-IL6 monoclonal antibody as a treatment for inflammatory pulmonary diseases such as acute respiratory distress syndrome (ARDS), COVID and interstitial lung disease (ILD). It is also planning a Phase II study with candidate milciclib in solid tumors. We attach value to the pMS and CD programs and model future revenues.

Tiziana is employing various pathways to address the active indications in its portfolio. Foralumab's anti-CD3 approach tempers the body's immune response by increasing the quantity of T regulatory cells, downregulating T cells and favoring the production of transforming growth factor (TGF)-β via the oral route and interleukin (IL)-10 via nasal administration, which creates a tolerogenic microenvironment. This profile is particularly amenable to targeted indications in pMS, CD and COVID. Milciclib is an inhibitor of multiple cyclin dependent kinases (CDKs) and employs mechanisms that can treat cancer by preventing over proliferation of cancer cells. Tiziana expects to launch a Phase IIb combination trial with milciclib and a tyrosine kinase inhibitor (TKI) in solid tumors and potentially other indications in the near future.

The candidates' mechanism of action in Tiziana's portfolio and their methods of administration bring new approaches to the table which are expected to work upstream of current standard of care, produce fewer side effects, enlist more precise activity and allow for targeted administration to the sites that present the disease. Foralumab is a fully human monoclonal antibody (mAb), evolved from the murine-based anti-CD3 OKT3. The mAb has also been successfully converted to solid form so that it can be administered orally or in a liquid form by the nasal and inhalation routes of administration. This allows for targeted delivery via a route that can avoid major systemic immune response common to infusion.

MS and CD are well-known diseases, each affecting millions of individuals around the globe, although presenting regional differences. Globally, MS is estimated to affect 2.3 million people and over 900,000 in the United States. Prevalence of MS generally increases as populations are measured in equatorial regions to areas further north. Women are also more likely to have MS than men. pMS comprises 10-20% of total MS cases and has limited treatment options. CD is more common in Western Europe and North America and has a prevalence of 100 to 300 per 100,000; the Crohn's Foundation estimates about 780,000 individuals in the United States present the condition. Even numbers of men and women experience the disease and about half will go into remission after treatment. While COVID is highly prevalent today, ARDS, the underlying condition which causes severe lung damage related to COVID and other respiratory diseases normally occurs in about 111,000 individuals in the United States and 338,000 in other middle-class developed economies.

Approved treatment for these diseases presents drawbacks related to efficacy and side effects. Foralumab's activity is promising in improving how the diseases are addressed. It is a fully human monoclonal antibody that is less likely to stimulate a systemic immune response compared with previous generations that contained murine components. Another innovative use of foralumab is administration using a local delivery route (oral for CD, nasal for MS and COVID) thereby avoiding commonly used systemic intravenous infusions. The targeted use of the drug can reduce systemic side effects through the use of lower doses.

After raising $57 million (~£44 million) in August 2020 from a share issuance on NASDAQ, we estimate about £44 million in cash on the balance sheet as of December 31, 2020. The funds will enable Tiziana to launch the anticipated clinical trials in pMS, CD and COVID later this year. Funds on the balance sheet are sufficient for Tiziana to fund operations through mid-2022, at which time we expect an update on progress and additional capital raises. Tiziana carries no debt on the balance sheet and is funded solely with equity issuance. The company has guided towards approximately $30 million in expense over the next couple years.

We anticipate that pivotal data will be available for Tiziana's programs in 2025 and 2026 and first sales will occur in the 2027 and 2028 timeframe for pMS and CD. We will forecast timelines for oncology indications and COVID/ ARDS when further information and funding is available. We anticipate that all candidates will join with partners to

[1] TLSA trades on the NASDAQ as an ADR. One American Depositary Share (ADS) is comprised of two ordinary shares and trades in US Dollars ($). Ordinary shares trade on the London Stock Exchange in Pounds Sterling (£).

participate in registrational studies and be commercialized. There is also a possibility that the alternative administration approach using oral, nasal and inhaled mAbs may be outlicensed to peers commercializing already approved products. This approach can take advantage of the reduced costs, increased ease of use and targeted administration of oral, nasal and inhaled delivery.

Key reasons to own Tiziana shares:

- **Multiple Phase II-ready assets pursuing unmet needs**
  - **Fully human anti-CD3 - foralumab**
    - **Multiple Sclerosis**
    - **Crohn's Disease**
    - **COVID-19 / ARDS**
  - **Pan-CDK Inhibitor - milciclib**
    - **Non-small cell lung carcinoma (NSCLC)**
    - **Hepatocellular carcinoma (HCC)**
  - **Fully human anti-IL-6 receptor – TZLS-501**
    - **ARDS, ILD, COVID-19 and other diseases**
- **Oral, nasal and inhaled administration of antibodies**
  - **Improved ease of use**
  - **No need for hospital-based infusion**
  - **Lower doses required for efficacy**
  - **Reduced systemic exposure and toxicity**
  - **Fewer side effects with reduced systemic exposure and toxicity**
  - **Focused distribution at the target organs in CD and severe lung disorders**
  - **Higher lung drug retention and efficacy while minimising toxicity to other organs**
- **Validation of intranasal foralumab technology in Phase I COVID-19 trial**
  - **Phase II trial announced**

In the following sections we review Tiziana's portfolio including a review of each of the candidates, their technology and clinical development standing. Indications for foralumab are reviewed, including a discussion of the target disease epidemiology, symptoms, risk factors, pathophysiology, treatment and diagnosis for MS and Crohn's. We then discuss competitors, peers and competing therapies to those candidates. Financial and operational results are presented, including an overview of the company's financial position. Management is introduced and risk factors for the company are examined. Finally, we present our valuation methodology which employs a discounted cash flow model to generate our target price of $7.50 per ADR share.[2]

[2] Tiziana trades on the LSE in Pounds Sterling (GBP) and as an American Depositary Share (ADS) on the NASDAQ in US Dollars at a ratio of two ordinary shares to one ADS. Financial reports are presented in GBP. We generate a target price in GBP based on forecasts in GBP and convert it to ADS in US Dollars using the GBP/USD exchange rate.

CANDIDATES, TECHNOLOGY, INDICATIONS & CLINICAL TRIALS

Tiziana Life Sciences is developing three candidates which are actively targeting multiple indications. The company's differentiating characteristic is its delivery technologies that enable administration of monoclonal antibodies as solids in oral, enteric-coated capsules, formulations and in liquid form in nasal and inhaled formulations. These formulations provide several benefits to patients including improved bioavailability, localized targeting of disease, avoidance of systemic distribution, better side effect profile and the ability to administer rapidly in any setting. Improved administration combined with novel biologic proteins in the anti-CD3, anti-cyclin dependent kinase (CDK) and anti-interleukin (IL)-6R classes may provide more effective treatments in a variety of autoimmune, inflammatory and neoplastic conditions.

The company's three candidates include foralumab, a fully human anti-CD3 monoclonal antibody (mAb) that may potentially be efficacious in Crohn's Disease (CD), progressive Multiple Sclerosis (pMS) and other autoimmune diseases. The biologic is also being investigated in moderate to severe COVID-19 infection, with early data suggesting efficacy in addressing not only COVID but many severe respiratory disorders such as acute respiratory distress syndrome (ARDS) by modulating the immune response. The second product in development is milciclib (MIL-chicklib), an orally-dosed inhibitor of multiple CDKs, tropomyosin receptor kinases and Src family kinases. The CDK inhibitor is targeting oncology indications in solid tumors as monotherapy and in combination with other therapies. Tiziana's third offering is TZLS-501, a preclinical candidate intended for inhaled lung and subcutaneous delivery for COVID-19, ILD and ARDS. TZLS-501 is an anti-IL-6R monoclonal antibody which binds to both membrane-bound and soluble forms of the IL-6R, lowering circulating levels of IL-6.

Leading Indications for Tiziana Life Sciences Therapeutics

Tiziana Life Sciences is anticipated to shortly begin clinical trials in three primary indications:

- Crohn's Disease (CD) – enteric coated oral foralumab tablets
- Progressive Multiple Sclerosis (pMS) - intranasal foralumab,
- COVID-19 – intranasal foralumab

Exhibit I – Summary of Tiziana Pipeline[3]

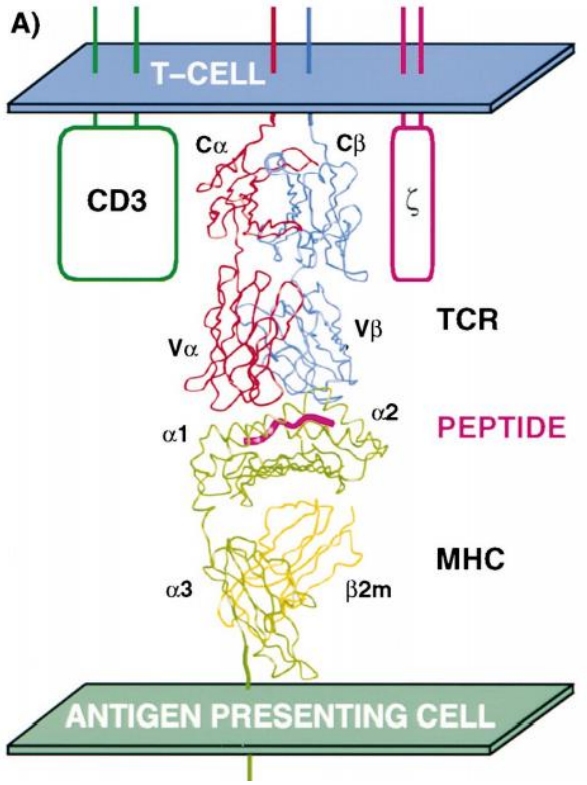
Pipeline Summary	Foralumab	Milciclib	TZLS-501
Active molecule	Fully human anti-CD3 monoclonal Ab	Pan-Cyclin Dependent Kinase inhibitor (human antibody)	Fully human Anti-IL-6 Receptor monoclonal Antibody
Mechanism of Action	Binding and inhibition of the epsilon (ε) chain of the TCR	Prevention of G1 to S transition in cell proliferation by inhibition of several CDKs	Binding membrane bound and soluble IL-6Rs & rapid depletion of circulating IL-6
Route of Administration	Enteric-coated oral capsules, nasal spray	Oral capsules	Nebulizer/ subcutaneous
Potential indications & most promising clinical uses	Crohn's Disease, progressive MS, arthritides, NASH, GvHD, Primary biliary cholangitis, moderate to severe COVID-19	Sorafenib-resistant HCC, other advanced solid malignancies (pancreatic, colon), thymic carcinoma/thymoma, NSCLC	Moderate-severe COVID-19, ARDS
Progress in Research	End of Ph1 for MS (intranasal); end of Ph1 for COVID-19 (intranasal)	End of Ph1 for refractory solid tumors. End of Ph2 in sorafenib resistant HCC. End of Ph1 for HCC in combination with a TKI.	Preclinical for COVID-19 (inhaled)
Major Advantages	Decreased total systemic dose and related side effects when given in oral/ nasal/ inhaler forms. No allergic reactions: fully human mAb	Promising results in early phase studies for single & combination uses for various advanced solid organ tumors.	Direct delivery to the target organ via inhalation route in severe COVID-19 is expected to limit lung damage & provide rapid relief.

[3] Compiled by Zacks Analyst Research

Foralumab

CD3 T-Cell Receptor Activation

Exhibit II –T-cell & APC Interaction (TCR-CD-3 & MHC-II)[4]



The multi-chain T cell receptor/CD3 complex (TCR/CD3) plays a key role in antigen recognition, T cell activation and triggering an antigen-specific immune response. CD3 is a protein complex on T-lymphocytes that serves as a co-receptor together with the TCR complex. It is present on all types of mature T-lymphocytes and is used as an immunohistochemical marker for T cell lineage. T cell receptors (TCRs) cannot bind free antigens on their own. This process requires direct interaction of the TCR receptor with an antigen bound to the major histocompatibility complex (MHC) on antigen-presenting cells (macrophages, B-cells, dendritic cells). MHC can identify one's susceptibility to autoimmune diseases and indicate donor compatibility in transplantation.

The short cytoplasmic tail of the TCR lacks the ability to signal on its own and intracellular signaling is initiated by the CD3 complex. Thus, with antigenic stimulus, when the structurally and functionally interrelated T cell receptor and CD3 complex is activated, the signal is transmitted through the cell membrane to the nucleus.[5] The critical component in intracellular signaling is the CD3-zeta (ζ) chain, which triggers many biochemical events and second messenger activation, leading to transcriptional factor expression and further T cell proliferation, effector function augmentation and cytokine production. Anti-CD3 monoclonal antibodies bind the epsilon (ε) chain of the TCR which plays an essential role in T cell development.[6]

Mucosa Associated Lymphoid Tissue and Oral Tolerance

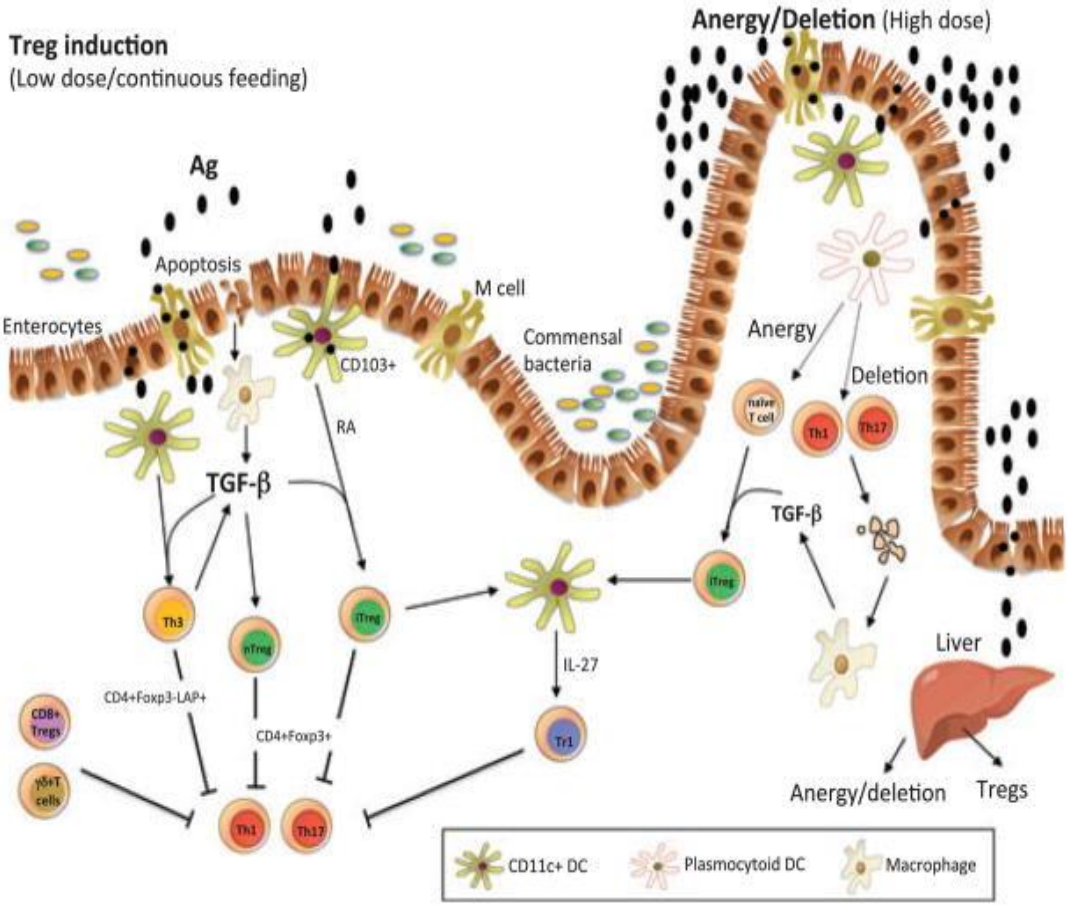
The gut and airway mucosa associated lymphoid tissues constitute the major immune organs in the body which are the primary sites of antigenic exposure. A wide number of immune cells, including dendritic cells and regulatory T cells (Tregs) play a role via their interactions with the intestinal epithelial cells and the gut flora in the modulation of immune reactions (immune-tolerance and immune-induction).

The gut-associated lymphoid tissue (GALT) is the largest immune organ, with an estimated 300 m^2 of surface area in the small bowel and 10^{12} lymphoid cells per m^2 of human small bowel.[7,8] The function of GALT is the ingestion of dietary antigens in a manner that does not result in unwanted immune reactions and protection of the organism from pathogens. Oral tolerance refers to physiologic induction of tolerance that occurs in the GALT and more broadly at other mucosal surfaces such as the respiratory tract.[9,10,11] To induce a gut immune response an antigen must reach the antigen presenting cells by penetrating the mucus layer and the single layered intestinal epithelial cells. Gut epithelium, dendritic cells in the gut wall and mesenteric lymph nodes and various molecules play an integral and interrelated part in the development of oral tolerance.[12,13,14,15] A combination of commensal bacteria in

[4] Hennecke J, Wiley DC. T cell receptor-MHC interactions up close. Cell. 2001 Jan 12;104(1):1-4. doi: 10.1016/s0092-8674(01)00185-4.
[5] https://www.bio-rad-antibodies.com/minireview-cd3-antibody.html
[6] https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=916
[7] Moog F. The lining of the small intestine. Sci Am 1981;245:154–158; 160, 162 et passiom.
[8] Mestecky J, McGhee JR. Immunoglobulin A (IgA): molecular and cellular interactions involved in IgA biosynthesis and immune response. Adv Immunol 1987;40:153–245.
[9] Faria AM, Weiner HL. Oral tolerance. Immunol Rev 2005;206:232–259.
[10] Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. Immunity 2004;21:527–538
[11] Mora JR, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science 2006;314:1157–1160.
[12] Rescigno M, et al. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. Nat Immunol 2001;2:361–367.
[13] Kraus TA, *et al*. Induction of mucosal tolerance in Peyer's patch-deficient, ligated small bowel loops. J Clin Invest 2005;115:2234–2243.
[14] Spahn TW, *et al*. Induction of oral tolerance to cellular immune responses in the absence of Peyer's patches. Eur J Immunol 2001;31:1278–1287.
[15] Spahn TW, et al. Mesenteric lymph nodes are critical for the induction of high-dose oral tolerance in the absence of Peyer's patches. Eur J Immunol 2002;32:1109– 1113.

gut flora, T-cells and dendritic cells set up a tolerogenic microenvironment by the help of interleukin (IL)-10, retinoic acid and TGF-β.[16]

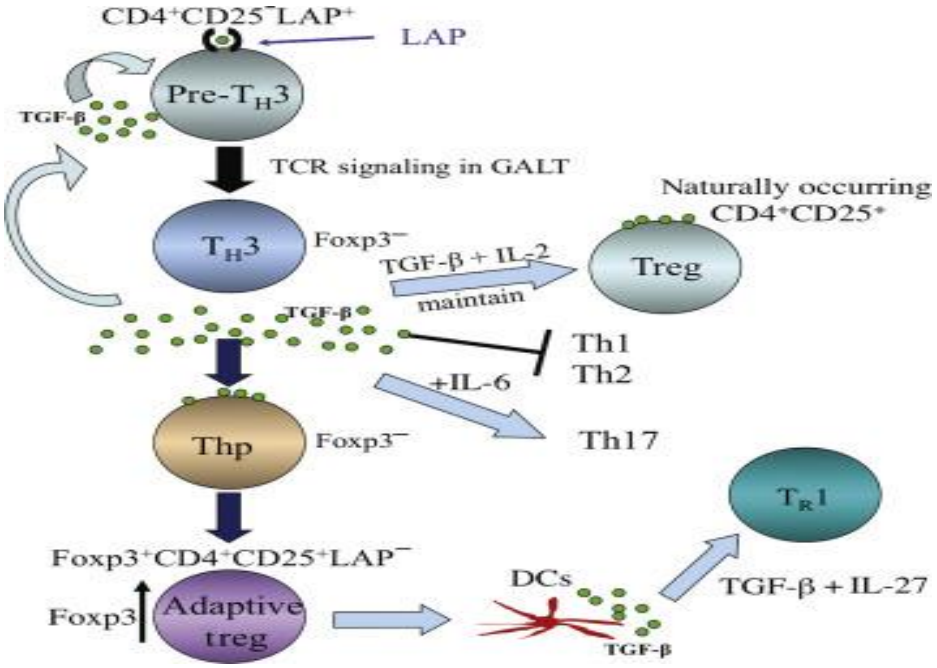
Exhibit III - Event Cascade for Oral Tolerance Induction[17]



Tregs are the gatekeepers of immune tolerance. They suppress activation, proliferation and effector responses of both innate and adaptive immune cells. Most, if not all autoimmune diseases have been associated with alterations of frequency and/or function of Tregs. There is a dose-dependent mechanism of oral tolerance where low doses of a fed antigen favor the induction of Tregs, whereas higher doses favor the induction of anergy or deletion. These complex mechanisms utilize various immune cells and cytokines, the most prominent of which are various types of Tregs and other T cell subsets, gut dendritic cells, retinoic acid (vitamin A), IL-10 and TGF-β. Anti-CD3 monoclonal antibody (mAb) therapy is associated with an increased number and function of several Treg cell populations and regulatory cytokines. Thus Tregs are very appealing for immunotherapy against autoimmune disorders, where Tiziana's foralumab is a promising candidate. There is substantial evidence in the literature that the gut-activated Th3 cell is able to suppress systemic autoimmune and inflammatory responses, via a complex cascade of cellular and paracrine interactions.

[16] Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. Immunol. Rev. 241(1), 241–259 (2011)
[17] Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. Immunol. Rev. 241(1), 241–259 (2011)

Exhibit IV - Regulatory T-cell Cascade Following Induction of Th3 Type Tregs by Oral Antigen or Oral Anti-CD3.[18]



Oral Anti-CD3 vs. Intravenous Anti-CD3 Mechanism of Action

While the tolerogenic effects of intravenously administered anti-CD3 monoclonal antibodies have been thoroughly investigated since the 1990s, the discovery that their oral use can induce tolerance, particularly in lower doses, dates back to 2006.[19] Anti-CD3 antibodies delete T cells when given intravenously. Monoclonal antibodies were initially not given orally because of the assumption that they would be degraded in the digestive tract before they could perform their desired biological activity. Since the study by Ochi *et al*., it is recognized that oral use of anti-CD3 mAbs can lead to desired immune tolerance and induction of Treg cells, suppressing both the clinical and pathological autoimmune disease features in mice models.[20]

When anti-CD3 is given intravenously it modulates CD3 from the cell surface and lyses CD3+ T cells. Oral anti-CD3, on the other hand, does not enter the blood stream or modulate CD3 from the cell surface but acts locally in the gut to induce Th3 type CD4+ CD25- LAP+ Tregs in the mesenteric lymph nodes, thus avoiding the development of cytokine release syndrome, an unwanted complication of intravenous anti-CD3 therapies.[21] Intravenous anti-CD3 has been reported to induce Tregs that act in a TGF-β-dependent fashion, but only after lysis of T cells.[22]

Anti-CD3 mAb Oral/Nasal Administration Clinical Trials

Animal models have shown that oral and nasal administration of antigens ameliorate autoimmune and inflammatory disorders by activating the regulatory T-cells. Autoimmune disease models demonstrating promising results with the use of oral or nasal anti-CD3 antibodies include:

- Experimental autoimmune encephalitis
- Streptozocin-induced autoimmune diabetes[23]
- Autoimmune diabetes in the non-obese diabetic mouse

[18] Pabst, O. *et al.* Mechanisms of Oral Tolerance to Soluble Protein Antigens. Mucosal Immunology (Fourth Edition), 2015. LAP: latency associated peptide
[19] Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. Immunol. Rev. 241(1), 241–259 (2011)
[20] Ochi H, et al. Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing CD4+ CD25-LAP+ T cells. Nat Med 2006;12:627–635.
[21] Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56. Published 2018 Jun 15. doi:10.1186/s40425-018-0343-9
[22] Belghith M, Bluestone JA, Barriot S, Megret J, Bach JF, Chatenoud L. TGF-beta-dependent mechanisms mediate restoration of self-tolerance induced by antibodies to CD3 in overt autoimmune diabetes. Nat Med 2003;9:1202–1208.
[23] Ishikawa H, Ochi H, Chen ML, Frenkel D, Maron R, Weiner HL. Inhibition of autoimmune diabetes by oral administration of anti-CD3 monoclonal antibody. Diabetes 2007;56:2103–2109.

- Collagen-induced arthritis[24]
- Type II diabetes[25]
- Lupus[26]
- CD4+CD45RB high T cell transfer model of inflammatory bowel disease (IBD)[27]
- Atherosclerosis[28]

These animal studies have shown that the anti-CD3 monoclonal antibodies, when administered orally or nasally, are able to yield favorable results with treatment of experimental autoimmune disorders. Orally administered anti-CD3 antibodies retain their biological activity in the gut and are taken up by gut epithelium.[29]

The successful translation of preclinical data into clinical practice will require determining the appropriate patient populations, validating the biomarkers to measure the drug effects, determining their potency and side effects in combination therapies with other immunomodulatory treatments. So far there is substantial evidence suggesting that the effects of oral anti-CD3 is more advantageous to induce antigen-specific versus antigen non-specific Tregs for the treatment of autoimmune and inflammatory diseases. It is assumed that the induction of antigen-specific Tregs is preferable, as it leads to specific immune modulation with fewer potential side effects.

Similar to the gut, the respiratory system, which is the second most challenged site for continuous antigenic encounter, has been tested by nasal and inhaler routes of anti-CD3 monoclonal antibody administrations and results have shown promising findings in animal models for lupus and collagen induced arthritis.

Studies suggest that nasal tolerance induction by anti-CD3 mAb depends mostly on IL-10, while oral tolerance induction is mainly dependent on TGF-β.[30] Nasal administration of anti-CD3 mAbs remains to be further explored as well as the oral administration but both routes seem to be equally safe and promising therapeutic approaches which are physiological and potentially less toxic in tackling autoimmune disorders.

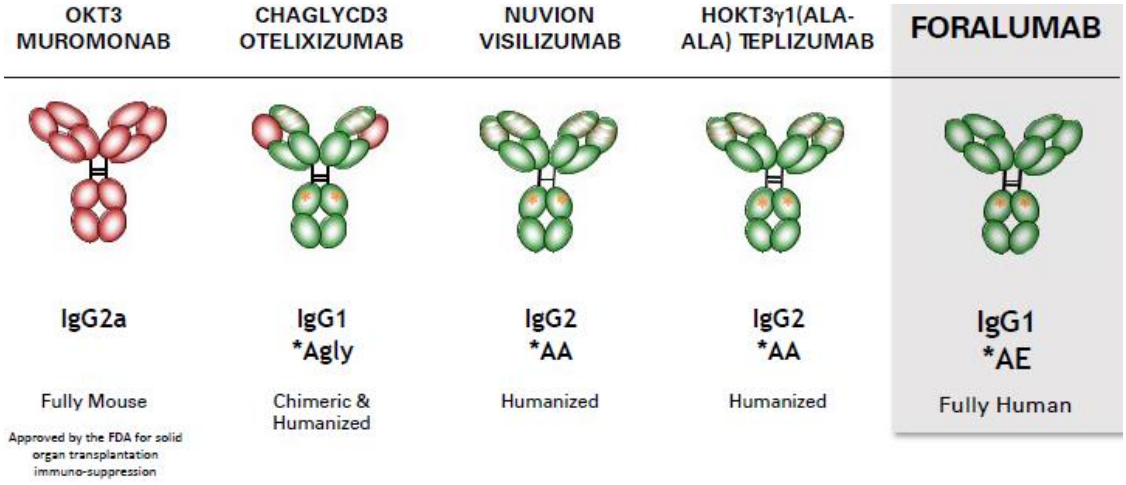
To date, there are four clinically available anti-CD3 mAbs:

- Teplizumab (hOKT3γ1, Ala-Ala and MGA031) is a humanized IgG1 antibody that was developed by grafting the complementarity determining region of OKT3 into a human IgG1 backbone. This antibody has been clinically developed by MacroGenics and Eli Lilly.
- Otelixizumab (ChAglyCD3, TRX4, GSK2136525) is a humanized IgG1 type antibody derived from the rat antibody YTH12.5. TolerX and GSK were involved in its clinical development.
- Visilizumab (Nuvion, HuM291) is a humanized IgG2 antibody. It is being clinically developed by PDL BioPharma.
- Foralumab (28F11-AE; NI-0401) is the only entirely human IgG1 type anti-CD3 mAb. The completely human origin of this agent further decreases side effects that have been previously noted with other humanized anti-CD3 mAbs.21 It is being clinically developed by Tiziana Life Sciences.

While otelixizumab and teplizumab were predominantly tested in patients with type 1 diabetes, visilizumab and foralumab were mostly studied in inflammatory bowel disease (IBD). Teplizumab is the subject of a Biologics License Application (BLA) that has been submitted to the FDA for Type 1 Diabetes by Provention Bio with a target action goal date of July 2, 2021.

[24] Wu HY, Maron R, Tukpah AM, Weiner HL. Mucosal anti-CD3 monoclonal antibody attenuates collagen-induced arthritis that is associated with induction of LAP+ regulatory T cells and is enhanced by administration of an emulsome-based Th2-skewing adjuvant. J Immunol 2010;185:3401– 3407.
[25] Ilan Y, et al. Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice. Proc Natl Acad Sci USA 2010;107:9765–9770.
[26] Wu HY, Center EM, Tsokos GC, Weiner HL. Suppression of murine SLE by oral anti-CD3: inducible CD4+CD25-LAP+ regulatory T cells control the expansion of IL-17+follicular helper T cells. Lupus 2009;18:586–596.
[27] Forster K, Goethel A, Chan CWT, Zanello G, Streutker C, Croitoru K. An oral CD3-Specific antibody suppresses T-cell-induced colitis and alters cytokine responses to T-cell activation in mice. Gastroenterology 143(5), 1298–1307 (2012).
[28] Sasaki N, et al. Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice. Circulation 2009;120:1996–2005.
[29] Ishikawa H, Ochi H, Chen ML, Frenkel D, Maron R, Weiner HL. Inhibition of Autoimmune Diabetes by Oral Administration of Anti-CD3 Monoclonal Antibody. Diabetes 56(8), 2103–2109 (2007).
[30] Kuhn C, Weiner HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. Immunotherapy 2016; 8:889-906.

Exhibit V – Evolution of Anti-CD3 mAbs[31]



A first Phase I trial, assessing safety and efficacy of visilizumab in patients with severe corticosteroid-refractory ulcerative colitis yielded promising results especially with a reduced dose of 10 µg/kg/day yielding an acceptable safety profile (reduced lymphopenia). 84% of patients showed a clinical response, with 41% entering clinical remission and 44% endoscopic remission.[32] A follow-up, randomized, double-blind, placebo-controlled trial was conducted to confirm the efficacy of visilizumab for the treatment of IBD, but was used at only half of the original dose level. The study was terminated prematurely because of safety and efficacy concerns.[33] As a consequence, the clinical development of visilizumab was halted by PDL Pharma.

Foralumab

Foralumab is an anti-CD3 monoclonal antibody that reduces T cell activation and cytokine release, via enhancing the production of IL-10, TGF-β and partial exhaustion of T cells. It specifically acts on the epsilon (ε) chain of the CD3-TCR complex. Foralumab immunogenicity is negligible as it is a fully human antibody, unlike its earlier counterparts with rodent elements. Due to its unique structure, it stimulates only minor cytokine release *in vivo* while maintaining CD3/TCR modulation and T-cell depletion, further contributing to its overall safety in intravenous use.[34]

Foralumab Clinical Trials

Foralumab and its precursors have been the subject of Phase I and Phase II trials for a number of autoimmune disorders such as non-alcoholic steatohepatitis (NASH), lupus, arthritis and type 1 diabetes among others. In a Phase IIa study, oral OKT3, the precursor to foralumab, has been tested on biopsy-proven NASH patients and results were consistent with favorable patient tolerance and safety, with positive biological outcomes for several hepatic function tests, metabolic and immunologic parameters.[35]

A Phase I trial of the oral, enteric capsule formulation of foralumab in healthy subjects was initiated in December 2019 and its results were reported in January 2020. The proprietary oral formulation, comprising the lyophilized and stabilized free-flowing powder of formulated foralumab encapsulated in an enteric-coated capsule, was well-tolerated at all doses tested and there were no drug-related safety issues even at the highest dose of 5 mg in this trial. Based on the positive outcome of the Phase I trial, a Phase II trial in Crohn's Disease patients is expected to begin in 2021.

The gut immune system is the primary target of Crohn's Disease (CD) and is also one of the leading objectives for Tiziana's foralumab. The drug was assessed in a Phase I/II clinical trial in patients with moderate to severe active CD.[36] Intravenous administration of up to 1 mg for 5 days was considered safe with manageable side effects. Even

[31] Source: Tiziana Life Sciences Corporate Presentation, January 2021.
[32] Plevy S, Salzberg B, Van Assche G et al. A Phase I Study of Visilizumab, a Humanized Anti-CD3 Monoclonal Antibody, in Severe Steroid-Refractory Ulcerative Colitis. Gastroenterology 133(5), 1414–1422 (2007).
[33] Sandborn WJ, Colombel JF, Frankel M et al. Anti-CD3 antibody visilizumab is not effective in patients with intravenous corticosteroid-refractory ulcerative colitis. Gut 59(11), 1485–1492 (2010).
[34] Dean Y, Dépis F, Kosco-Vilbois M. Combination therapies in the context of anti-CD3 antibodies for the treatment of autoimmune diseases. Swiss Med. Wkly 142, w13711 (2012).
[35] Lalazar G. Mizrahi M, Turgeman İ. Et al. Oral administration of OKT3MAb to Patients with NASH, Promotes Regulatory T-cell Induction, and Alleviated Insulin Resistance: Results of a Phase IIa Blinded Placebo – Controlled Trial. J. Clin. Immunol 2015;35:399-407.
[36] Van der Woude CJ, *et al*. Phase I, double-blind, randomized, placebo-controlled, dose-escalation study of NI-0401 (a fully human anti-CD3 monoclonal antibody) in patients with moderate to severe active Crohn's disease. Inflamm. Bowel Dis. 16(10),1708–1716 (2010).

though the power of this study was not sufficient to assess clinical efficacy, the dose of 1 mg appeared to improve the endoscopic index score but not exacerbate clinical symptoms as assessed by the CD activity index. Oral formulations of foralumab in animal models have shown favorable results in skin xenograft rejection in humanized mice.[37] Intravenous foralumab has been studied in one Phase I and two Phase II clinical trials (Crohn's disease and Acute Renal Allograft Rejection) conducted by previous license holder Novimmune.

For MS, nasal administration of foralumab was tested in a Phase I clinical trial on healthy volunteers at a single center, single arm, ascending dose study in which low doses (10, 50 and 250 µg/dose) of foralumab and placebo were nasally administered for 5 consecutive days. All nasal doses were well tolerated. On March 30 2021, Tiziana announced that the FDA had granted expanded access in secondary progressive multiple sclerosis (SPMS). Although this work is not intended to support the ultimate approval of foralumab for use in SPMS, it will inform stakeholders about the potential benefits of the drug. The Expanded Access program is not intended to provide information about the safety or effectiveness of foralumab, but will bring the product to the attention of regulatory authorities and investors. For more information please see our recent article here.

Nasally-administered foralumab has now been tried in Phase I in patients with mild to moderate COVID symptoms. Topline data for this study was reported on February 2, 2021. The trial, held in Brazil, was the first of its kind to feature a nasally administered formulation of a monoclonal antibody. The study was a 39-subject, exploratory trial comparing the use of foralumab in COVID patients with mild to moderate symptoms who are not yet hospitalized. The objectives of the trial were to assess safety and to assess if the treatment may be able to delay the progression of the disease to reduce hospitalization. The three cohorts include a control arm, a foralumab arm and a foralumab + dexamethasone arm. The drug was dosed once per day over 10 days of treatment. For more information on the study, please see our recent article here. Based on the favorable results, on March 30, Tiziana reported plans to launch a Phase II study in moderate to severe hospitalized COVID patients. The effort will examine the benefits of nasally administered foralumab in these individuals along with standard of care treatment. If successful, this effort will demonstrate the safety and efficacy of a potent immunomodulator used against a serious respiratory illness.

Crohn's Disease

Crohn's Disease (CD) is an inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract. Causes for CD are unknown, but contributing and common factors appear to be related to the environment, genetic makeup and immune system. Many researchers believe that abnormal immune system activation from viral or bacterial infection might be the leading cause of CD by chronic inflammation and ulceration of the GI tract.[38]

Symptoms

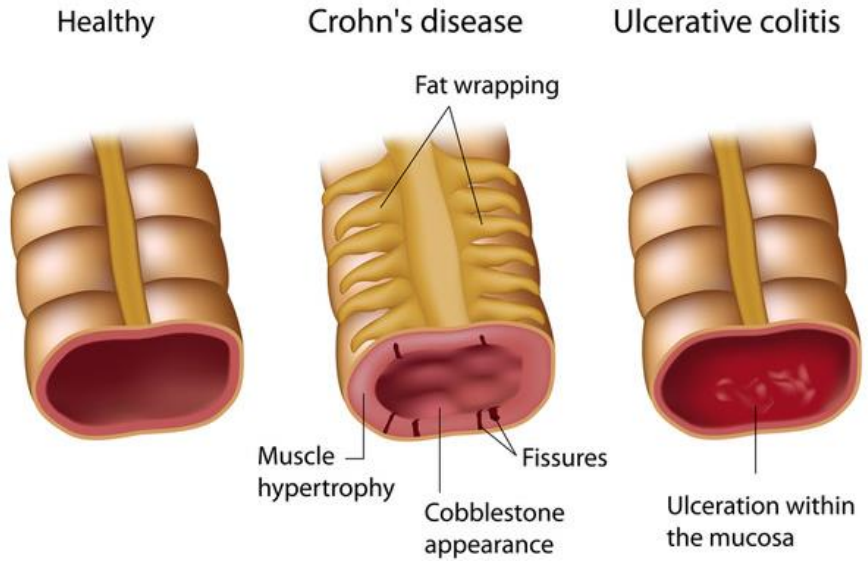
Similar to other IBD's, the severity of CD symptoms can range from mild to extreme, often including abdominal pain and cramping, diarrhea, fever, constipation, weight loss, rectal bleeding, fistulas and more.[39] CD can occur at any age and affects both sexes equally, but most people experience symptoms for many years before being diagnosed around age 30.[40,41]

Prevalence

The number of adults with CD is estimated to be approximately 780,000 – 1.6 million in the US.[42] Other sources find that CD has a prevalence of 100 to 300 per 100,000 in Europe and North America. European descent is more likely to predict the disease compared with other backgrounds.[43] Other sources identify from 1.6 to 3.1 million Americans with IBD, of which ~40% are estimated to suffer from Crohn's.[44,45] A study by Kappelman *et al.* examined prevalence by age and found a prevalence of 20 per 100,000 in individuals younger than 20 and a prevalence of 201 per 100,000 in those above 20.[46]

[37] Ogura M, Deng. S, Preston-Hurlburt P. Et al. Oral treatment with foralumab, a fully human anti-CD3 monoclonal antibody, prevents skin xenograft rejection in humanized mice. Clinical Immunology 2017;183:240-246
[38] https://www.crohnscolitisfoundation.org/what-is-crohns-disease/causes
[39] https://www.mayoclinic.org/diseases-conditions/crohns-disease/symptoms-causes/syc-20353304
[40] https://www.healthgrades.com/right-care/crohns-disease/crohns-disease
[41] https://www.medicinenet.com/crohns_disease/article.htm
[42] Crohn's & Colitis Foundation of America, IBD Factbook 2019.
[43] MedlinePlus, U.S. National Library of Medicine. Crohn disease. Accessed March 2021.
[44] Shivashankar R, Tremaine WJ, Harmsen WS, and Loftus EV Jr. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clinical Gastroenterology and Hepatology 2017;15:857–863.
[45] Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years — United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1166–1169.
[46] Kappelman, M.D., *et al.* The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007 Dec;5(12):1424-9. doi: 10.1016/j.cgh.2007.07.012. Epub 2007 Sep 29.

Exhibit VI – Inflammatory Bowel Disease[47]



Diagnosis

Since there are no known causes or triggers for CD, its diagnosis is wide ranging and usually requires a battery of tests to confirm. Common tests used for diagnosis of CD are lab blood and stool tests, barium X-ray, colonoscopy, endoscopy, CT/Magnetic Resonance Imaging scans and/or biopsy.[48] Depending on the test results, location and stage of the disease, treatment options will vary.

Treatment

There are a number of treatment options for CD, but the goal is to provide long-term remission and manage symptoms or flare-ups as there is no definitive cure. Treatment options are unique to each patient and include dietary/ lifestyle changes, bowel rest, anti-diarrheal, anti-inflammatory, antibiotic, immunomodulators and biologic therapies. Complicated cases may require surgical intervention. The primary goal is to manage the severity and frequency of the symptoms, all subsequent medications treatment options are to reduce GI inflammation, maintain remission, reduce side effects and maintain quality of life for patients.[49] Common anti-inflammatory drugs used are aminosalicylates (balsalazide, mesalamine, olsalazine, sulfasalazine) and corticosteroids (budesonide, hydrocortisone, methylprednisolone, and prednisone).[7] Generally, aminosalicylates are prescribed to newly diagnosed or patients with mild symptoms while corticosteroids are used for more severe cases. Immunomodulators are available if anti-inflammatory drugs are not effective. They work to suppress the body's inflammation response but may also weaken the immune system. Immunomodulators are slower to act but are helpful for those going into remission by modifying the immune system so that it can minimize inflammation. Common immunomodulators are: 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate.[50] Ciprofloxacin and metronidazole are two antibiotics commonly prescribed to treat secondary infections, intestinal bacteria, fistulas, and abscesses.[51] The most promising type of treatment options are biologics.[52] There are three classes of biologics used, anti-tumor necrosis factor (TNF) agents, integrin receptor antagonists and interleukin-12 and -23 antagonists. All three classes target different receptors to block proteins that are thought to promote inflammation in the GI tract.[53]

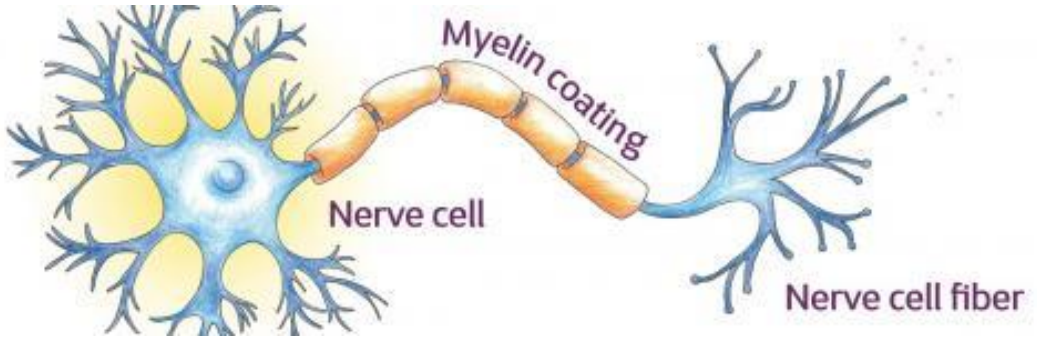
Multiple Sclerosis and Its Subtypes

Multiple sclerosis (MS) is a neurological condition that affects the central nervous system (CNS), specifically white matter. The immune system mistakenly inflames and damages myelin, the insulating layer that wraps and protects axonal processes of nerves in the brain and spinal cord. Damage to the myelin sheaths of neurons prevents communication throughout the CNS and blocks effective transmission of electrical signals leading to various neurologi-

[47] Source: Shutterstock.com
[48] https://www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease/diagnosis
[49] https://www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease/treatment
[50] http://ibdmedicationguide.org/browse
[51] http://ibdmedicationguide.org/browse#antibiotics
[52] https://pubmed.ncbi.nlm.nih.gov/28132526/
[53] http://ibdmedicationguide.org//browse#biologics

cal findings. This autoimmune, inflammatory disease typically presents itself in the third or fourth decade of life. The causes of MS are unknown. Researchers have speculated that it may be related to virus and bacteria exposure, geographic location, genetics or immunological malfunctions.

Exhibit VII – Myelin Sheath[54]



MS is clinically classified into four types: relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), primary-progressive multiple sclerosis (PPMS) and progressive-relapsing multiple sclerosis (PRMS).

- RRMS is the most common disease course, patients have symptoms and respond well to treatments, leading to long episodes of remission. Patients experience defined attacks of new or increasing neurologic symptoms which are followed by periods of remission. During remission, where some or all of the symptoms may disappear, there is no apparent disease progression.
- SPMS occurs when symptoms arise during a stage in remission and are not resolving with treatments, in contrast to PPMS which occurs when there are no periods of remission and the disease progresses.
- PRMS occurs when symptoms are worsening over time but there are episodes of remission.[55]
- PPMS differs from RRMS in that there is a steady deterioration of neurologic function after the onset of symptoms.
    - Neurologic functions for PPMS become steadily worse in the early stages.
    - PPMS lacks flare ups of symptoms, also known as relapses or attacks and there is no remission.
    - While there may be periods of temporary improvement, overall neurologic progression is consistently declining.
    - Progressive MS (pMS) builds up over time and is characterized by worsening neurologic function from first symptoms, without early relapses or remissions. This is the worst clinical type of MS and the target of Tiziana's foralumab.

Symptoms

The signs, symptoms and severity of MS are unique to each individual and often present depending on the disease progression and particular location of affected nerves.[56] Many symptoms are common and most affect movement such as ocular muscle movement causing vision problems (such as double or blurry vision), blindness (with optic nerve involvement), balance and coordination problems, headaches, itching, burning sensations, limb numbness and others.[57] There are other complications and symptoms that are seen when MS progresses, such as mobility issues, memory and cognition problem, fatigue, loss of bladder and bowel control, leg and arm spasticity among others.[58]

[54] MS Society Webpage. https://www.mssociety.org.uk/research/explore-our-research/emerging-research-and-treatments/myelin-repair. Accessed March 2021.
[55] https://www.nationalmssociety.org/What-is-MS/Types-of-MS
[56] https://www.hopkinsmedicine.org/health/conditions-and-diseases/multiple-sclerosis-ms
[57] https://www.medicinenet.com/multiple_sclerosis_ms_early_signs_and_types/article.htm
[58] https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms

Diagnosis

MS diagnosis is not straightforward and may require numerous medical tests including physical examination, blood test and MRIs. For individuals with progressive disease or those presenting less common symptoms, a proper diagnosis may require spinal taps to sample cerebrospinal fluid and an evoked potential test which measures electrical signals in the brain.[59]

Treatment

Treatment options vary and are unique to each patient with the goal of mediating symptoms, slowing disease progression, prolonging remission and increasing recovery from flare ups. Some patients in early stages of the disease may have minor symptoms that require no treatment[21] while others are treated based on how their disease develops. Flare ups are addressed with corticosteroids or plasma exchanges which help in early stages or with milder cases of inflammation and when other treatments have not been effective. Disease-modifying therapies (DMTs)[60] are various medications prescribed with the intent to slow the progression of the disease or decrease the frequency of relapsing symptoms.[61] Depending on each patient, oral, injectable or infused medications may be appropriate. Some injectable treatments are interferon-β medications and glatiramer acetate. Oral treatments are also available and include fingolimod, dimethyl fumarate, diroximel fumarate, teriflunomide, siponimod and cladribine. Infusion treatment options with monoclonal antibodies include ocrelizumab, natalizumab and alemtuzumab.[21] Each medication is prescribed for different stages of MS and has the potential for serious side effects. There are other therapies that may be prescribed to treat secondary or tertiary symptoms which include physical therapy to build/maintain strength and mobility, muscle relaxers, antidepressants.

Ocrelizumab, a recombinant anti-CD20 humanized mAb, is the only FDA approved treatment for relapsing or primary progressive forms of MS (PPMS).

Prevalence

Large efforts have been undertaken to identify the number of patients suffering from MS, but the effort is challenging since many of them fail to recognize early symptoms and are not diagnosed until later stages. The Atlas of MS estimates that 2.8 million people worldwide suffer from the disease, with over 900,000 of the total residing in the United States.[62] Data from the US shows a fluctuating rate depending upon region, sex, and race, with white females living in northern geographies affected more than any other group. A comprehensive survey reviewing data from around the globe found prevalence rates from 30 to 50 per 100,000 in middle European latitudes and from 100 to 200 per 100,000 in northern climes in Canada and areas adjacent to the North Sea.[63] Women are more at risk than men and four times as many women as men have the disease.[64] Exact reasons as to why rates are higher in white women living in northern climates remain unknown, but some theories suggest that the geographic region itself might play a role. As one moves further from the equator he or she is less likely to receive sunlight, which reduces the body's ability to produce vitamin D, a risk factor for MS. Reasons for differences in prevalence rates based on race and sex are still unknown.

Approximately 10-20% of individuals with multiple sclerosis present PPMS and 65% of those with initial relapsing MS suffer from SPMS. 85% of patients are initially diagnosed with RRMS and the remainder unknown or unclassified.[65,66,67]

[59] https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/diagnosis-treatment/drc-20350274
[60] https://my.clevelandclinic.org/health/diseases/17248-multiple-sclerosis#management-and-treatment
[61] https://www.multiplesclerosis.com/us/treatment.php#a3
[62] Atlas of MS 3rd Edition. Mapping multiple sclerosis around the world, key epidemiology findings. MS International Federation, September 2020.
[63] Rosati, G., The prevalence of multiple sclerosis in the world: an update. Neurological Science (2001) 22:117-139.
[64] Johns Hopkins Medicine website. Multiple Sclerosis: Why are Women More At Risk? Accessed March 2021.
[65] National MS Society. MS Types Overview. Accessed online March 2021. https://www.nationalmssociety.org/What-is-MS/Types-of-MS
[66] Khurana, V. *et al.* Estimated prevalence of secondary progressive multiple sclerosis in the USA and Europe: results from a systematic literature search. Neurology. April 23, 2018.
[67] Bazell, C. *et al.* A Claims-Based Analysis of Secondary Progressive Multiple Sclerosis (SPMS): Prevalence, Demographics and Costs. Novartis Pharmaceuticals Corporation. April 2019.

COVID-19

Epidemiology

The majority of COVID-19 cases are asymptomatic or mild. The CDC estimates over 30 million cases in the US, and global estimates approach 129 million cumulative cases and 2.8 million deaths.[68] Vaccines are now becoming increasingly available to the public and this may have an effect on COVID-19 incidence. Progression of severe symptoms of COVID-19 appears to depend on the individual patient and their immune response. A subset of COVID-19 patients appear to be prone to cytokine release syndrome (CRS), also known as cytokine storm.[69]

Symptoms

Symptoms of COVID-19 include fever, dry cough and fatigue. Less commonly, patients experience aches, sore throat, headache, diarrhea, conjunctivitis, and loss of smell and taste.[70] In severe COVID-19, patients experience extreme difficulty breathing and shortness of breath. The resulting hypoxia produces symptoms of confusion, sweating, dizziness, hypotension and elevated heart rate as well as discoloration at the extremities due to lack of adequate tissue oxygenation.

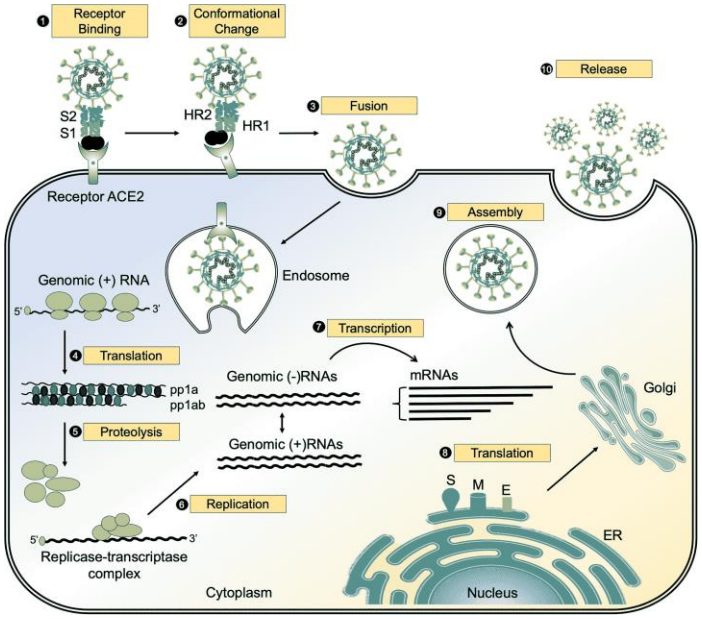
Risk factors

The CDC cites general COVID-19 risk factors as age, race/ethnicity, gender, certain medical conditions and medication use, poverty/crowding, certain occupations and pregnancy.[71] Regarding mortality, American Indian or Native Americans and Hispanic or Latino Americans are 2.4 and 2.3 times more likely to die from COVID-19 than white, non-Hispanic persons. Risk for death increases with age, with those aged 85 and older 7,900 times more likely to die than the reference population of 5-17 years of age.[72]

Pathophysiology

COVID-19 results from an infection by the SARS-CoV-2 virus. Via the ACE2 receptor, SARS-CoV-2 infects the epithelial cells lining the respiratory tract using its spike proteins. ACE2 receptors are expressed on a variety of cells, including cells of the alveoli, and even the digestive tract. Upon binding, the virus is endocytosed and translocated into endosomes, or fuses with the envelope of the host cell membrane. Upon entering, viral RNA is released into the cytoplasm of the host cell. A replication transcription complex is formed, driving production of copied viral RNA. Transcription of the replicated viral RNA produces mRNA. From this mRNA, the host cell facilitates the translation to create new viral proteins, which are then released into the surrounding cellular environment to infect other cells.

Exhibit VIII - Mechanism of SARS-CoV-2 Infection[73]



Standard of Care

There is no cure for COVID, only treatments to address certain aspects of the disease to either speed recovery, or to prolong survival. The FDA has approved remdesivir, an intravenous viral replication inhibitor (antiviral), for treatment of COVID. Results for the ACTT-1 trial of remdesivir in COVID patients were published in the *New England Journal of Medicine* and showed clinical benefit

[68] World Covid-19 tracker: Latest cases and deaths by country (cnn.com)
[69] Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical rheumatology, 39(7), 2085–2094. https://doi.org/10.1007/s10067-020-05190-5
[70] Coronavirus (who.int)
[71] Assessing Risk Factors for Severe COVID-19 Illness | CDC
[72] Risk for COVID-19 Infection, Hospitalization, and Death By Age Group | CDC
[73] Li, S., Li, S., Disoma, C., Zheng, R., Zhou, M., Razzaq, A., Liu, P., Zhou, Y., Dong, Z., Du, A., Peng, J., Hu, L., Huang, J., Feng, P., Jiang, T. and Xia, Z. (2021), SARS-CoV-2: Mechanism of infection and emerging technologies for future prospects. Rev Med Virol, 31: e2168. https://doi.org/10.1002/rmv.2168

in recovery, and in mortality of patients receiving supplemental oxygen at 4% versus 13% on placebo.[74] However, the antiviral does not directly address the inflammation that is deadly in some patients.

Because COVID-19 has only recently emerged, many of the therapies available are in early stages of development, including foralumab. As inflammation is central to the pathology, many anti-inflammatory agents have been considered to combat advanced COVID-19, including chloroquine, hydroxychloroquine, JAK inhibitors, IL-6 inhibitors, IL-1 inhibitors, anti-TNF-alpha agents, corticosteroids, intravenous immunoglobulin, and colchicine.

In addition to drugs, patients are typically administered supplemental oxygen and a mechanical ventilator to assist with breathing. Patients may lay in a prone position, facing downward, to facilitate breathing. Diuretics may also help to reduce the fluid buildup in the lungs.

Diagnosis

Any number of COVID-19 tests can be implemented to detect viral infection. Primarily, tests to detect the presence of the virus include RT-PCR, serology and antigen immune-assays. Reverse transcription polymerase chain reaction (RT-PCR) testing detects viral RNA using fluorogenic primers/probes, using thermal cycling and polymerase enzymes to amplify the RNA to a level where the fluorescent indicator can work.[75] Lateral flow immuno-assays flow sample across a membrane that is embedded with various antibodies that are specific to certain antigens. Sample blood is collected and if anti-SARS-CoV-2 antibodies are present, they will bind to the flow-assay's reagent which can then be easily detected.

[74] Final report confirms remdesivir benefits for COVID-19 | National Institutes of Health (NIH)
[75] Shyu, D., Dorroh, J., Holtmeyer, C., Ritter, D., Upendran, A., Kannan, R., Dandachi, D., Rojas-Moreno, C., Whitt, S. P., & Regunath, H. (2020). Laboratory Tests for COVID-19: A Review of Peer-Reviewed Publications and Implications for Clinical Use. *Missouri medicine*, *117*(3), 184–195.

Milciclib

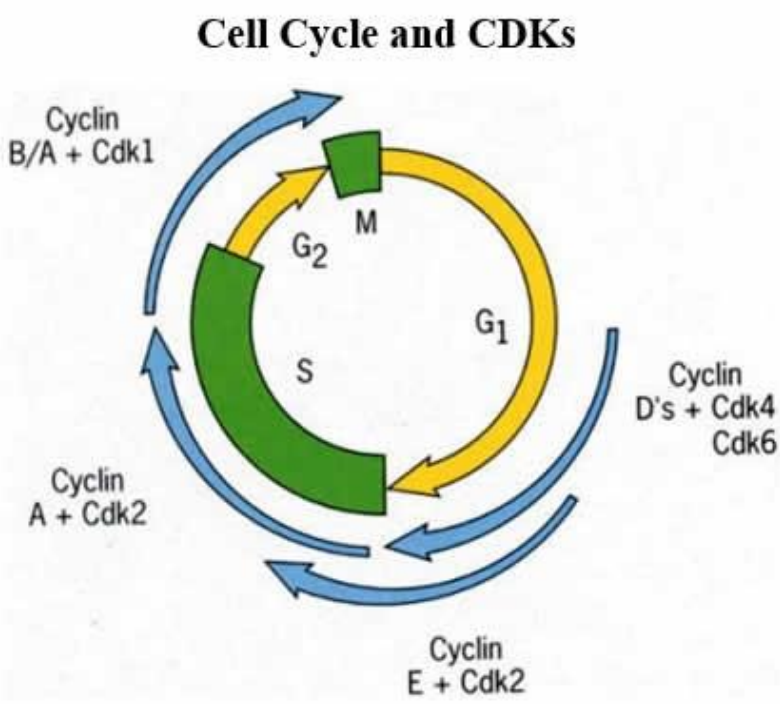
Kinases and Cancer

Protein kinases are involved in cellular function related to metabolism, cell cycle regulation, survival and differentiation.[76] Phosphorylation systems are tightly regulated, and dysregulation of certain kinases has been associated with specific cancers. Kinase dysregulation can manifest as over-expression, relocation, fusion, point mutations or dysregulation of upstream signaling. Due to the relevance of kinases in cancer, and the diversity of kinases and their dysfunction, targeted, individualized approach is now being considered. Kinase inhibitors have been developed over decades, although some types, such as cyclin-dependent kinases have been met with challenges in clinical evaluation.

Cyclin-dependent Kinases (CDK)

Cyclin-dependent kinases (CDK) are of particular interest in oncology as they regulate the eukaryotic cell cycle. As the name suggests, these kinases interact and form complexes with cellular cyclins. When cells divide, they undergo a phased cycle known as mitosis. Mitosis is a complex and tightly regulated process that has been highly conserved over the course of evolution.[77] Because tumorigenesis is characteristically dependent on cell division, CDKs have been the target of cancer research. CDKs drive all cell cycle transitions. Regulation begins with the G1 phase of the cell cycle, during which D-type cyclins can form complexes with either CDK4 or CDK6 leading to phosphorylation and inactivation of the retinoblastoma (RB) protein, allowing the cell cycle to progress.[78] When retinoblastoma protein is phosphorylated, the cell cycle is allowed to progress from G1 to synthesis (S) phase. Subsequent progression from the S phase to the G2/M phase is regulated by CDK1/2. Inversely, natural inhibition of CDK and associated complexes acts to regulate inappropriate cell proliferation.

Exhibit IX - Cell Cycle and CDKs[79]



The CDK4/6-RB axis is subverted in a vast majority of cancers. Therapies that address dysfunction in CDK should counter cancer proliferation although clinical trials have struggled to confirm this. Drugs that modulate CDK activity have been investigated in clinical trials over the past two decades.

[76] Kannaiyan, R., & Mahadevan, D. (2018). A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert review of anticancer therapy*, *18*(12), 1249–1270. https://doi.org/10.1080/14737140.2018.1527688
[77] Asghar, U., Witkiewicz, A. K., Turner, N. C., & Knudsen, E. S. (2015). The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nature reviews. Drug discovery*, *14*(2), 130–146. https://doi.org/10.1038/nrd4504
[78] Kannaiyan, R., & Mahadevan, D. (2018). A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert review of anticancer therapy*, *18*(12), 1249–1270. https://doi.org/10.1080/14737140.2018.1527688
[79] Tiziana Life Sciences

CDK Inhibitors

CDK inhibitors have been developed and tested in several tumor types over the past 20 years. First generation agents were nonspecific, dubbed pan-CDK inhibitors. One such example was Flavopiridol (alvocidib), developed by Sanofi-Aventis. Flavopiridol was shown to inhibit CDK1, 2, 4, 6, 7 and 9. The pan-CDK inhibitor showed results *in vitro* although *in vivo* results showed less activity in targeted indications. Phase II studies fell short of expectations in malignant melanoma and colorectal cancer . Over the span of 2001-2012, Flavopiridol has been investigated in gastric carcinoma, stage IV non-small cell lung cancer, advanced colorectal cancer, endometrial carcinoma, advanced renal cell carcinoma, relapsed chronic lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and refractory metastatic pancreatic cancer.[80] Unfortunately, no Phase III studies resulted from the attempts. Flavopiridol did see partial response in 41% of patients in a chronic lymphocytic leukemia trial. Roscovitine, another early CDK inhibitor also experienced challenges in demonstrating significant patient benefit.

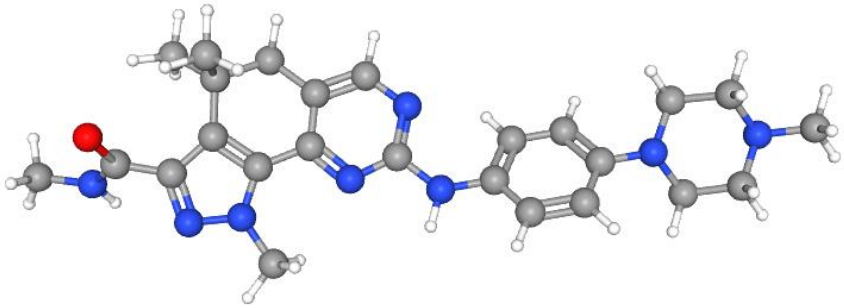
With advancing knowledge of the cellular role of CDK, second generation CDK inhibitors aimed to tailor pharmacology for better CDK selectivity, to tune which and to what extent CDK types were inhibited. Of second generation CDK inhibitors, Merck's dinaciclib has been most studied. It was engineered for potent inhibition of CDK1, 2, 5, and 9. Despite preclinical work that demonstrated superior suppression of RB phosphorylation and efficacy in a broad range of cancer cell lines, clinical results were less impressive. Dinaciclib had, at best, no discernible response in advanced breast cancer, previously treated non-small cell lung cancer, and advanced acute myeloid leukemia.[81] In relapsed multiple myeloma, 2 of 27 patients achieved partial response, and like Flavopiridol, dinaciclib was also evaluated in chronic lymphocytic leukemia, the result of which supported a randomized Phase III study. The study was constructed as a head-to-head comparison with ofatumumab that completed December 2014, where dinaciclib had superior progression-free and median survival and overall response, but more adverse events.[82]

According to ClinicalTrials.gov, there are several active Phase I or II trials of dinaciclib in various stages of recruitment. Other second generation CDK inhibitors have also been developed, each with a specific pharmacological profile. CDK inhibitors that specifically target either CDK4 or CDK6 to isolate the effect of specific inhibition have also been developed, although, murine knockout models have added further confusion as tissue development persisted despite absence of CDK4 and/or CDK6 and in the absence of D-type cyclins. The failures of tried CDK inhibitors have been attributed to the need for further research, challenges in patient selection, and treatment timing. There remains an unmet need in cancer and CDK-based therapeutics continue to be explored and investigated.

Milciclib

Tiziana's milciclib is a pan-CDK inhibitor with affinity for CDK1, 2, 4, 5, 7 and Src family kinases as well. Its chemical structure is $C_{25}H_{32}N_8O$. Milciclib's development was first publicized in 2009 and included the identification of a parent molecule with good CDK inhibition, specifically targeted at the ATP binding site of CDK2/cyclin A. The synthesis of analogues further tailored the compound's selectivity and desired solubility characteristics.[83]

Exhibit X – Chemical Structure of Milciclib[84]



[80] Asghar, U., Witkiewicz, A. K., Turner, N. C., & Knudsen, E. S. (2015). The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nature reviews. Drug discovery*, *14*(2), 130–146. https://doi.org/10.1038/nrd4504

[81] Asghar, U., Witkiewicz, A. K., Turner, N. C., & Knudsen, E. S. (2015). The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nature reviews. Drug discovery*, *14*(2), 130–146. https://doi.org/10.1038/nrd4504

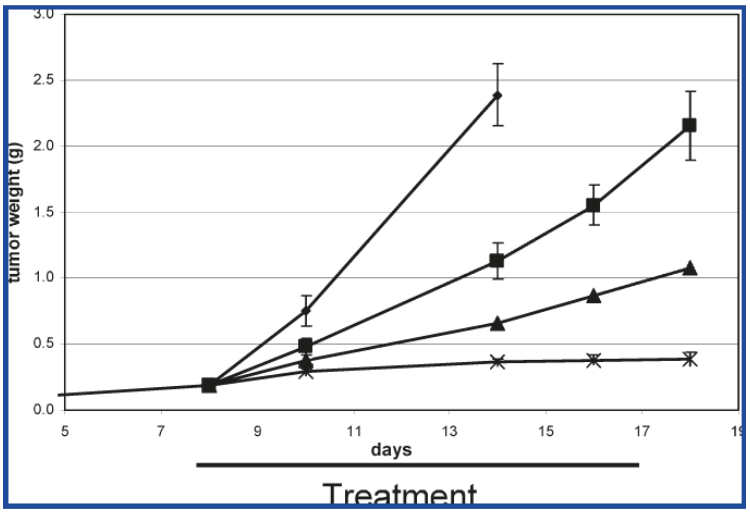
[82] Paolo Ghia, Lydia Scarfo, Kumudu Pathiraja, Martha Derosier, Karen Small, Nigel Patton; A Phase 3 Study to Evaluate the Efficacy and Safety of Dinaciclib Compared to Ofatumumab in Patients with Refractory Chronic Lymphocytic Leukemia. *Blood* 2015; 126 (23): 4171.

[83] Brasca, M. G., Amboldi, N., Ballinari, D., Cameron, A., Casale, E., Cervi, G., ... & Ciomei, M. (2009). Identification of N, 1, 4, 4-Tetramethyl-8-{[4-(4-methylpiperazin-1-yl) phenyl] amino}-4, 5-dihydro-1 H-pyrazolo [4, 3-h] quinazoline-3-carboxamide (PHA-848125), a Potent, Orally Available Cyclin Dependent Kinase Inhibitor. *Journal of medicinal chemistry*, *52*(16), 5152-5163.

[84] National Library of Medicine. PubChem. Milciclib compound summary. pubchem.ncbi.nlm.nih.gov/compound/Milciclib Accessed March 2021.

As milciclib emerged from a pool of candidates, its cellular potency and physicochemical properties supported evaluation as an orally active CDK inhibitor. Milciclib was screened against a panel of 43 other kinases where it was revealed to be a potent inhibitor of CDK1, 2, 4, 5 and 7. Milciclib also inhibited TRKA, which is associated with aggressive solid tumors. Milciclib's effect on cell cycle progression and DNA synthesis was evaluated in ovarian carcinoma cells where it showed clear reduction of S-phase population of cancer cells and DNA synthesis at 1 µM over 24 hours. In other work evaluating retinoblastoma (RB) phosphorylation, cells treated with milciclib 1 µM and 3 µM displayed a clear reduction in hyperphosphorylated RB and its accumulation. Based on the results, milciclib escalated to a human ovarian xenograft murine model. Ascending doses of milciclib were administered twice-daily for 10 days, concurrent with pharmacokinetic monitoring of the compound. Results showed dose-dependent inhibition of tumor growth up to 91%.

Exhibit XI - Tumor Mass vs Time in Milciclib-Treated Murine Model[85]



Preclinical research continued as milciclib was evaluated for its effect in a K-RAS^{G12D} lung adenocarcinoma transgenic mouse model.[86] The evaluation further included a panel of tumoral cell lines and in various human xenografts and carcinogen-induced tumors as well as disseminated primary leukemia[87] in cellular and animal glioma models.[88] Together, the preclinical results supported milciclib's entry into the clinic. Results from recent experimentation in hepatocellular carcinoma murine model, in combination with sorafenib, was published in 2020,[89] which built on work done in 2012 implicating microRNA-221's in liver cancer and supported milciclib in the indication.[90]

Milciclib Clinical Studies

In a Phase I study,[91] 16 patients with refractory solid tumors of varying types were enrolled and treated with once-daily milciclib at 45, 60 and 80 mg/m^2/day, seven days on seven days off in 4-week cycle, in combination with a fixed dose of gemcitabine at 1000 mg/m^2/day, infused on days 1, 8 and 15 in a 4-week cycle. The purpose of the trial was to determine safety and toxicity. Dose limiting toxicities occurred in only one out of nine patients in the 80 mg arm, the highest dose. The patient experienced grade 4 thrombocytopenia, grade three ataxia and grade 2 tremors. Among 14 evaluable patients, one NSCLC patient showed partial response and four patients, each with a different cancer, showed long-term disease stabilization.

[85] Brasca, M. G., Amboldi, N., Ballinari, D., Cameron, A., Casale, E., Cervi, G. & Ciomei, M. (2009). Identification of N, 1, 4, 4-Tetramethyl-8-{[4-(4-methylpiperazin-1-yl) phenyl] amino}-4, 5-dihydro-1 H-pyrazolo [4, 3-h] quinazoline-3-carboxamide (PHA-848125), a Potent, Orally Available Cyclin Dependent Kinase Inhibitor. *Journal of medicinal chemistry*, *52*(16), 5152-5163.

[86] Degrassi, A., Russo, M., Nanni, C., Patton, V., Alzani, R., Giusti, A. M. & Texido, G. (2010). Efficacy of PHA-848125, a cyclin-dependent kinase inhibitor, on the K-RasG12DLA2 lung adenocarcinoma transgenic mouse model: evaluation by multimodality imaging. Molecular cancer therapeutics, 9(3), 673-681.

[87] Albanese, C., Alzani, R., Amboldi, N., Avanzi, N., Ballinari, D., Brasca, M. G. & Ciomei, M. (2010). Dual targeting of CDK and tropomyosin receptor kinase families by the oral inhibitor PHA-848125, an agent with broad-spectrum antitumor efficacy. Molecular cancer therapeutics, 9(8), 2243-2254.

[88] Albanese, C., Alzani, R., Amboldi, N., Degrassi, A., Festuccia, C., Fiorentini, F. & Ciomei, M. (2013). Anti-tumour efficacy on glioma models of PHA-848125, a multi-kinase inhibitor able to cross the blood–brain barrier. British journal of pharmacology, 169(1), 156-166.

[89] Aastha Jindal, Vaseem A Palejwala, Marina Ciomei, Anna Degrassi, Gemma Texido, et al. (2020) Milciclib and sorafenib synergistically down-regulate c-Myc to suppress tumor growth in an orthotopic murine model of human hepatocellular carcinoma 7: DOI: 10.15761/JTS.1000416.

[90] Callegari, E., Elamin, B. K., Giannone, F., Milazzo, M., Altavilla, G., Fornari, F. & Negrini, M. (2012). Liver tumorigenicity promoted by microRNA-221 in a mouse transgenic model. Hepatology, 56(3), 1025-1033.

[91] Aspeslagh, S., Shailubhai, K., Bahleda, R., Gazzah, A., Varga, A., Hollebecque, A. & Soria, J. C. (2017). Phase I dose-escalation study of milciclib in combination with gemcitabine in patients with refractory solid tumors. Cancer chemotherapy and pharmacology, 79(6), 1257-1265.

Three Phase II studies have been conducted. Two of the studies were separate, multi-centered trials, CDKO-125A-006 (NCT01011439) with 72 patients previously treated with one chemotherapy and CDKO-125A-007 with 30 patients, previously treated with multiple chemotherapies. These trials were conducted in the US, France and Italy. In trial 006, 27.8% of patients had B3 thymoma (B3T) and 72.2% had thymic carcinoma (TC). In 007, 56.7% and 43.3% had B3T and TC, respectively. Milciclib was administered orally, 150 mg daily for multiple cycles, with one cycle consisting of seven days on and seven days off. Primary endpoint of progression-free survival and secondary endpoint of overall survival were met in both trials. In terms of safety, half of patients in both studies experienced at least one adverse event. Common Grade 3-4 toxicities were neutropenia, increases in creatinine, amylase and lipase, nausea and asthenia. Finally, partial and complete responses were observed in some patients.

Exhibit XII - Trial Results From CDKO-125A-006 and CDKO-125A-007[92]

Treatment Efficacy	CDKO-125a-006				CDKO-125a-007			
	Primary endpoint: PFS-3>17% evaluable patients				Primary endpoint: PFS-3>40% evaluable patients			
	Evaluable		Treated		Evaluable		Treated	
	(N=54)		(N=72)		(N=24)		(N=30)	
	TC (n=39)	B3T (n=15)	TC (n=52)	B3T (n=20)	TC (n=11)	B3T (n=13)	TC (n=13)	B3T (n=17)
PFS-3 (%)	35.9	66.7	34.6	60.0	63.6	46.2	53.8	41.2
Median PFS (mos)	4.47	14.46	4.47	8.97	9.76	5.65	9.76	5.65
Median OS (mos)	22.34	36.57	23.79	36.57	not reached	not reached	17.94	21.03
DOR (mos)	8.41	not reached	8.41	5.49	2.76	not reached	2.76	not reached
Stable Disease (SD)(%)	66.7	86.7	65.4	75.0	72.7	84.6	61.5	70.6
DCR (CR+PR+SD)(%)	71.8	86.7	69.2	80.0	81.8	84.6	69.2	70.6
ORR (%)	5.1	n/a	3.8	5.0	9.1	n/a	7.7	n/a
PR%	5.1	n/a	3.8	5.0	9.1	n/a	7.7	n/a
PD%	28.2	13.3	25.0	15.0	18.2	15.4	23.1	11.8

In a Phase IIa study[93] (NCT03109886), safety and tolerability of milciclib in sorafenib refractory or intolerant patients with hepatocellular carcinoma (HCC) were evaluated. The single-arm, multi-center study in advanced hepatocellular carcinoma took place in Italy, Greece and Israel. 31 patients were enrolled and 28 were evaluable for efficacy. 14 out of 28 completed six months of treatment. Milciclib was well tolerated with manageable toxicity. 18 of 31 treated patients had drug related adverse events with the most frequent being diarrhea, nausea, asthenia, fatigue, retinal hemorrhage, rash and myalgia. 9 of 14 patients continued treatment under Compassionate Use after study conclusion. The study met primary and secondary endpoints of progression-free survival and time to progression of 5.9 months and clinical benefit rate of 61%.

Milciclib was also evaluated for safety and clinical activity in combination with regorafenib in a single-arm Phase I.[94] The trial enrolled liver transplant patients with hepatocellular carcinoma recurrence where recurrence affects ~40% of patients. Seven patients were enrolled. Regorafenib was administered at 8 mg daily for three weeks on and one week off. Milciclib was administered 100 mg daily on a four day on, three day off cycle. The combination of milciclib and regorafenib was well tolerated, with a majority of patients showing disease stabilization and reduction in alpha fetoprotein (AFP) levels within the first month.

In summary, Tiziana has evaluated milciclib, its pan-CDK inhibitor with gemcitabine in refractory solid tumors in Phase I, as a monotherapy in thymic carcinoma and thymoma patients in two Phase II studies, as a monotherapy in sorafenib-resistant hepatocellular carcinoma patients in Phase IIa, and in Phase I in recurrent hepatocellular carcinoma in transplant patients. Together, these studies form a foundation to pursue advanced clinical studies. Management has guided toward Phase II studies that are expected to begin in the next few quarters. We will update our report and analysis when details are provided.

[92] Besse *et al.* Milciclib (PHA-848125AC), a Pan-Ciclin D-Dependent Kinase Inhibitor, Demonstrated Efficacy in Two Phase II Studies with Thymic Carcinoma (TC) and B3 Thymoma (B3T) patients. ASCO 2018
[93] DOI: 10.1200/JCO.2020.38.15_suppl.e16711 Journal of Clinical Oncology - published online before print May 25, 2020
[94] DOI: 10.1200/JCO.2020.38.15_suppl.e16634 Journal of Clinical Oncology - published online before print May 25, 2020

TZLS-501

TZLS-501 is an anti-interleukin-6 receptor (IL-6R) monoclonal antibody (mAb) that aims to address inflammation that drives COVID related Acute Respiratory Distress Syndrome (ARDS). Tiziana holds a worldwide exclusive license for TZLS-501 (NI-1201) from Bristol Myers Squibb (BMY) which is a fully human mAb that binds to both the membrane-bound and soluble forms of IL-6R and diminishing IL-6 in the blood circulation[95] Excessive IL-6 is considered as the key element in cytokine release syndrome (CRS) and chronic inflammation in the lungs of patients with COVID and severe acute respiratory illness such as ARDS. By administering the biologic via inhalation route, Tiziana is pursuing a novel approach in direct delivery of TZLS-501 to the target organ, the lungs.

IL-6 and IL-6R in COVID-19 ARDS

Interleukin (IL) 6 is a pro-inflammatory cytokine and an anti-inflammatory myokine encoded by the IL-6 gene. IL-6R is a receptor that interacts with IL-6. COVID-19 is often associated with respiratory distress, especially in severe and fatal cases. The infection and respiratory distress lead to an immune and inflammatory reaction that can drive ARDS and be fatal in COVID-19 patients. Inflammatory response in the body is driven by cytokines such as IL-6.

TZLS-501

Anti-IL-6R mAb have been recommended for use by some national health agencies such as China's National Health Commission for treatment of inflammation and elevated cytokine levels in COVID-19 patients. Tiziana's proprietary aerosolization technology for TZLS-501 allows complex and delicate biologics to be delivered directly to the lungs, the primary site of the infection in COVID-19. Direct application of the mAbs to the lungs avoids systemic toxicity and delivers the therapy where needed. Tiziana aims to complete development of the inhalation technology, via handheld inhaler or nebulizer, needed to deliver TZLS-501 in 2021. Manufacturing for clinical studies is expected to complete in early 2021, concurrent with IND submission.

ARDS (COVID-19 Associated)

ARDS, or acute respiratory distress syndrome refers to a specific type of lung damage that can result from a variety of causes, including COVID-19.[96] ARDS is characterized by injury to the lungs accompanied by fluid accumulation that diminish the organ's ability to supply oxygen to the body and symptoms can develop within a few hours of lung trauma. ARDS in COVID-19 patients is driven by SARS-CoV-2 infection.

Epidemiology

In the US, researchers estimate there are 111,000 to 190,000[97] diagnosed with ARDS each year. However, COVID ARDS prevalence is unique and is not included in this figure. The majority of COVID cases are asymptomatic or mild. However, COVID is now a leading cause of death in the US, with approximately 560,000 deaths since the pandemic began.[98]

The mechanism associated with COVID mortality is cytokine storm, the inflammatory condition that TZLS-501 aims to address as an IL-6R targeting mAb. Inflammatory excess drives COVID ARDS; respiratory failure is a leading cause of death in COVID patients.

Symptoms

Symptoms of ARDS include extreme difficulty breathing and shortness of breath. The patient can only take rapid and shallow breaths. The resulting hypoxia produces symptoms of confusion, sweating, dizziness, hypotension and elevated heart rate as well as discoloration at the extremities. COVID sufferers often require ventilators.

[95] Lacroix, M. et al., Novel Insights into Interleukin 6 (IL-6) Cis- and Trans-signaling Pathways by Differentially Manipulating the Assembly of the IL-6 signaling Complex. J Biol Chem. 2015 Nov 6; 290 (45): 26943-26953
[96] Acute Respiratory Distress Syndrome (ARDS) > Fact Sheets > Yale Medicine
[97] Acute Respiratory Distress Syndrome (ARDS) > Fact Sheets > Yale Medicine
[98] Source: Centers for Disease Control and Prevention. Accessed April 11, 2021.

Risk factors

The CDC cites severe COVID infection risk factors as age, race/ethnicity, gender, certain medical conditions and medication use, poverty/crowding, certain occupations and pregnancy.[99] Regarding mortality, American Indian or Native Americans and Hispanic or Latino Americans are 2.4 and 2.3 times more likely to die from COVID than white, non-Hispanic persons. Risk for death increases with age, with those aged 85 and older 7,900 times more likely to die than the reference population of 5-17 years of age.[100]

Risk of COVID-related ARDS arises not only from the coronavirus. Trends have been identified among subgroups of patients who are prone to severe COVID and ARDS. These patients tend to have very high levels of serum ferritin and D-dimer, hepatic dysfunction, thrombotic tendency and disseminated intravascular coagulation (DIC).[101] Risk of morbid COVID may be linked to a patient's intrinsic genetic ability to clear the virus.[102] Lower interferon levels, increased neutrophil extracellular traps and increased pyroptosis are among theories of COVID susceptibility.

Pathophysiology

ARDS results from injury to the lungs. The lungs achieve gas exchange by their internal surface area created by alveoli, or microscopic air sacs, and surrounding capillaries.[103] The damage to the alveoli and surrounding capillaries results in edema that further obstructs gas exchange at the alveolar surface. This can be directly caused by viral infection, such as by SARS-CoV-2, pneumonia, aspiration, toxic inhalation, chest trauma, near-drowning, and fat embolism. However, not only is ARDS characterized by hypoxia, but by an accompanying inflammatory response. The inflammatory response can worsen the condition by triggering inflammation in remote parts of the body that are already hypoxic. Because COVID-related ARDS has an additional infection component, the inflammatory aspect of the combination is highly significant. COVID is caused by SARS-CoV-2 infection of lung tissue. Infection of the lower respiratory tract leads to pneumonia and can lead to ARDS. The infection can incite a feed-forward cycle in the immune system leading to what is known as CRS and is also known as cytokine storm, where the body's immune reaction overreacts, severely damaging the infected tissue, the lungs. By targeting reduction of IL-6, an inflammatory cytokine, via the IL-6 receptor, Tiziana's TZLS-501 aims specifically to address the inflammatory component of COVID-related ARDS and minimize damage to the lung tissue.

Standard of Care

There is no cure for ARDS or COVID, but treatments can help to address certain aspects of the disease. The FDA has approved remdesivir, an intravenous viral replication inhibitor (antiviral), for treatment of COVID-19. However, the antiviral does not directly address the inflammation that is deadly in some patients.

Because of the recency of COVID-19, many of the therapies available are novel ones in early stages of development, including TZLS-501. IL-6R inhibitors have been considered in the fight against COVID-19. Tocilizumab is one IL-6R-inhibitor humanized mAb that demonstrated resolution of fever and hypoxemia and improvement in serum C-reactive protein (CRP), and pulmonary CT.[104] However, disadvantages of tocilizumab therapy include susceptibility to infection, hepatotoxicity, hypertriglyceridemia and diverticulitis. Because tocilizumab is administered intravenously, and TZLS-501 is administered nasally, directly to the affected area of the lungs, TZLS-501 may avoid the systemic toxicity associated with intravenous use, which may allow higher doses or lower side effects.

Diagnosis

ARDS itself cannot be diagnosed using a single test. As the name suggests, it is a syndrome, or a symptomatic composite, meaning it describes a cluster of symptoms with varying manifestations. With COVID-19 ARDS, COVID-19 tests can be implemented to detect viral infection. To evaluate ARDS symptoms in COVID-19 patients, a physician will monitor lung and cardiovascular function, as well as look for symptoms of hypoxia, together indicative of ARDS. Pulse oximeters can be used to evaluate the oxygen saturation in the blood. Imaging techniques such as x-rays and CT scans allow insight into the patient's lung condition and presence of fluid.

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[99] Assessing Risk Factors for Severe COVID-19 Illness | CDC
[100] Risk for COVID-19 Infection, Hospitalization, and Death By Age Group | CDC
[101] Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical rheumatology, 39(7), 2085–2094. https://doi.org/10.1007/s10067-020-05190-5
[102] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020 Jul;39(7):2085-2094. doi: 10.1007/s10067-020-05190-5. Epub 2020 May 30. PMID: 32474885; PMCID: PMC7260446.
[103] Acute Respiratory Distress Syndrome (ARDS) > Fact Sheets > Yale Medicine
[104] Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical rheumatology*, *39*(7), 2085–2094. https://doi.org/10.1007/s10067-020-05190-5

COMPETITORS, PEERS & COMPETING THERAPIES

Tiziana is advancing three compounds in its portfolio comprising assets in the anti-CD3, cyclin-dependent kinase (CDK) inhibitor and anti-interleukin (IL)-6R spaces. There are a number of predecessors, peers and competitors in these areas from a variety of biopharmaceutical companies that have contributed to the drug classes and indications.

We start with the anti-CD3 monoclonal antibody, which has been around for decades beginning with Orthoclone OKT3, marketed by Janssen in the 1980s. The mouse antibody was approved to prevent rejection of transplanted organs; however, it is no longer available. As a successor, a chimeric and humanized anti-CD3 designated Otelixizumab was under development in the 2000s, but failed to show efficacy in a Phase III trial for Type 1 diabetes. A further evolution of the mAb led to the development of the humanized visilizumab by PDL Pharma which was later abandoned. A similar anti-CD3 candidate to visilizumab called teplizumab was submitted to the FDA in a BLA by Provention Bio in Type 1 diabetes in 2020. The FDA has set a target action date for this application on July 2, 2021. It is anticipated that foralumab will have an improved side effect profile as it is fully human in contrast to its predecessors which included murine elements.

Tiziana is targeting foralumab for Crohn's Disease, progressive Multiple Sclerosis and COVID. In CD, there are several classes of drugs that are used to address the disease. In the biologics space, natalizumab, vedolizumab, infliximab, adalimumab, certolizumab pegol and ustekinumab are used, with a variety of action mechanisms. Biogen, Takeda, Johnson & Johnson (Janssen), AbbVie and UCB are responsible for developing and commercializing this portfolio of products. Many therapies exist for MS; however, they address MS attacks or relapses rather than the progressive form. Treatments include corticosteroids, interferon beta medication, glatiramer acetate, fingolimod, dimethyl fumarate, diroximel fumarate, teriflunomide, siponimod and cladribine among others. Merck, Pfizer, Novartis, Biogen, Alkermes, Bristol Myers and others have developed and commercialized these products. Ocrelizumab is the only treatment approved for primary progressive MS. It is a humanized antibody targeting CD20+ B lymphocytes, which contribute to nerve damage in MS. The drug was developed and commercialized by Roche's subsidiary Genentech and currently enjoys patent protection. Efforts to develop a treatment for COVID have been broad with remdesivir and dexamethasone both used in patients with serious symptoms. There are other products in development to address the virus' symptoms too numerous to discuss here.

The anti-CDK space has been busy and there are several approved products in this class including palbociclib, ribociclib, abemaciclib and trilaciclib all approved in cancer indications, especially HR+ HER2- breast cancer. Development work and commercialization has been undertaken by competitors Pfizer, Novartis, Astex, Eli Lilly and G1 Therapeutics. Other candidates in this class, including dinaciclib, flavopiridol and roscovitine all entered clinical trials but were abandoned due to poor efficacy or adverse effects.

Exhibit XIII – Peers and Competitors[105]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
ABBV	AbbVie	$107.54	$189,789	$258,864	Bruton's TKI, cancer; Humira, Skyrizi for CD
ALKS	Alkermes	$19.02	$3,029	$2,666	Vumerity development for relapsing MS
ALPN	Alpine Immune Sci	$11.33	$271	$173	Inflammatory disease, IO; Lupus & advanced malignancies
ARDS	Aridis Pharma	$5.60	$63	$55	Antibacterial inhaled mAbs, COVID (AR-711 & AR-713)
BAYRY	Bayer	$15.91	$62,439	$97,450	Regorafenib: GBM; Sorafenib: HCC, RCC
BMY	Bristol Myers	$62.61	$139,866	$172,371	Cabozantinib for RCC with Opdivo
ESALY	Eisai	$67.14	$19,912	$18,210	Lenvima (multiple kinase inhibitor (VEGFR 1/2/3) in HCC)
EXEL	Exelixis	$23.12	$7,213	$6,007	TK inhibitor cabozantinib for RCC
GILD	Gilead	$65.11	$81,977	$108,342	Cayston, monobactam antibiotic for inhalation
GSK	GlaxoSmithKline	$36.65	$98,684	$120,387	Otelixizumab, anti-CD3 diabetes, autimmune
GTHX	G1 Tx	$25.57	$1,073	$885	Ph3 trilaciclib (IV CDK4/6i) for colorectal cancer
IMAB	I-MAB	$51.65	$3,716	$2,950	TJ202, CD38 mAb: MM, autoimmune
JNJ	Johnson^2	$161.25	$424,524	$431,974	Remicade, Stelara: CD;
LLY	Eli Lilly	$184.49	$176,924	$189,830	Teplizumab, anti-CD3 diabetes, autimmune
MRK	Merck	$76.31	$193,094	$210,392	Keytruda; dinaciclib CDK inhibit
NVS	Novartis	$87.55	$200,376	$215,072	Kisqali,HR+/HER2- BC,CDK4; Kesimpta, Mayzent, MS
PRVB	Provention Bio	$8.00	$507	$385	Anti-CD3 mAb for T1D, teplizumab
RHHBY	Roche	$41.93	$287,157	$284,902	Ocrevus for MS, mosunetuzumab bispecific CD20/CD3
TAK	Takeda	$17.25	$54,385	$90,983	Entyvio for CD
VTRS	Viatris (Mylan)	$13.40	$16,169	$40,237	OBI Podhaler, inhaled tobramycin antibiotic
pvt	Abcuro				Autoimmune and cancer; inclusion body myositis, MM
pvt	Altheia Science				Autoimmune & cancer; T1D, MS
pvt	Astex				Kisqali (ribociclib) (HR+/HER2- breast cancer, targets CDK4)
pvt	CisThera				Autoimmune & cancer; candidates: CT140 & CT400
pvt	Kanaph Tx				Autoimmune & cancer; bispecifics, IO
pvt	Ventus				Immunology, oncology
TLSA	Tiziana Life Sci	$2.67	$259	$215	Foralumab (anti-CD3), Milciclib (anti-CDK) & TZLS-501 (anti-IL6R)

[105] Price and market capitalization data is as of April 9, 2021. Source: Zacks Research System.

INTELLECTUAL PROPERTY

Tiziana has been granted numerous patents worldwide and has other patents pending for its portfolio of candidates. The company's global patents primarily revolve around foralumab, milciclib and TZLS-501. Novimmune (now assumed by Bristol Myers) granted use of the patents for anti-CD3 and anti-IL-6R antibodies to Tiziana. The company has rights to Milciclib under license from Nerviano, which includes five US patents and two others in Europe and Eurasia. There are also patents pending related to milciclib throughout the world. A second patent family related to milciclib relates to salts and crystal forms of the drug and their methods of use. The patent is valid in the US, and various jurisdictions in Asia and Europe.

Tiziana entered into an exclusive agreement with the Brigham and Women's Hospital to sublicense foralumab for use via a nasal route. The agreement was executed in April 2018 to develop a novel formulation of the mAb dosed in a medical device for nasal administration. The Brigham license required an upfront fee and ongoing patent maintenance and prosecution costs. The arrangement requires the payment of milestones, low-single digit royalties on annual net sales and a 12% royalty on non-royalty sub-license revenues. Foralumab is also the subject of a license agreement between Tiziana and Novimmune executed in December 2014. The license provides for worldwide exclusive rights from Novimmune and rights to certain patent licenses related to a sublicense from Bristol-Myers for CD3 receptor mAbs and their use in development and commercialization of related products. Upfront and ongoing milestone payments are required as is a low-single digit percentage of net sales of licensed products and services along with amounts owed to Bristol-Myers under the requirements of the sub-license.

Foralumab also has patent protection for its oral formulation which was granted in 2020 and is expected to last until at least 2040. The patent for use of a nasal formulation has not yet been granted. If successfully secured, this patent could also last into the 2040s.

Milciclib is sublicensed from Nerviano Medical Sciences in a worldwide, exclusive license to commercialize products and services that include the compound. The agreement, which was consummated in 2015 allows Tiziana to grant sublicenses and use third party manufacturers and distributors to support commercialization of products that incorporate milciclib as an active ingredient. Milciclib is protected under numerous patents with expirations that range from 2024 to 2030, excluding any patent term adjustments or extensions. The longer dated patents cover methods of using milciclib for the treatment of multiple indications and combination treatments including the use of cytotoxic agents. The patent entitled "Milciclib & therapeutic combination formulations for use in cancer treatment" will extend protection until 2038.

TZLS-501 is the subject of the IL-6R agreement between Tiziana and Novimmune. The arrangement requires the payment of an upfront fee of $100,000 and a low-single-digit royalty on net sales of licensed products and a low-double digit royalty on revenues from sub-license agreements. Other amounts related to a sublicense from Bristol-Myers are also required.

We summarize the patent families relevant to Tiziana for its three pipeline candidates, foralumab, milciclib and TZLS-501 in the following exhibit. We also include the appropriate regions and select US patent numbers where appropriate.

Exhibit XIV – Key Tiziana Patents[106]

Compound	Title	Patent #	Region
Foralumab	Methods of use, autoimmune or inflammatory diseases and disorders	Various	Broad
Foralumab	Composition & methods of use	Various	Broad
Foralumab	Formulations & dosing regimen	Various	N.Am, EU, China, other
Foralumab	Methods of Use (CNS disorders)	Various	National
Foralumab	Methods of use (gastrointestinal, autoimmune, inflammatory)	Various	PCT
Foralumab	Anti-CD3 antibody formulations	10,688,186	US
Foralumab	Anti-CD3 antibodies and methods of use thereof	9,850,304	US
Foralumab	Anti-CD3 antibodies and methods of use thereof	7,728,114	US
Foralumab	Anti-CD3 antibodies and methods of use thereof	8,551,478	US
Milciclib	Composition of matter, methods of use, process of manufacturing	Various	Broad
Milciclib	Methods of use, multiple indications	Various	US,EU,Asia
Milciclib	Methods of use, combination therapies with cytotoxics	Various	US,EU,Asia
Milciclib	Compositions of related entities, formulations & methods of treatment	Various	US,EU,Asia
Milciclib	Methods of use-combination therapies with therapeutic antibodies	Various	US,EU,Asia
Milciclib	Milciclib & therapeutic combination formulations for use in cancer treatment	Various	US, PCT
Milciclib	Use of Milciclib with TKIs,	10,758,541	US
TZLS-501	Composition of matter & methods of use	Various	Broad
TZLS-501	Anti-IL-6/IL-6R antibodies and methods of use thereof	10,759,862	US

[106] Source: United States Patent Office (uspto.gov) and Zacks analyst work.

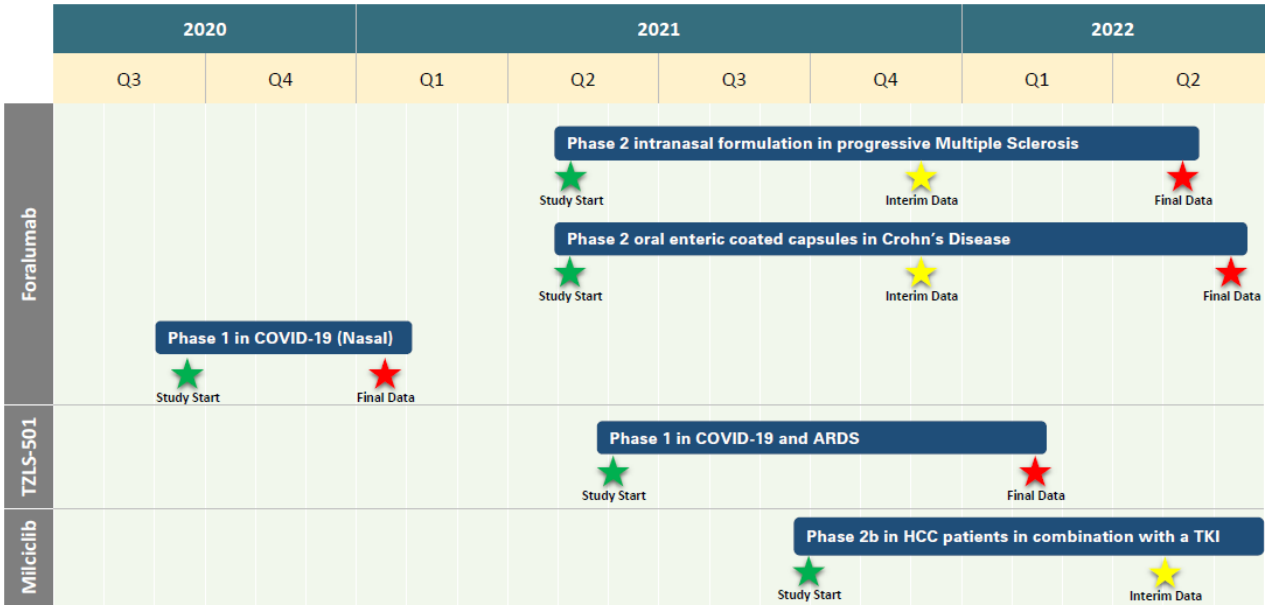
FINANCIAL & OPERATIONAL RESULTS

Corporate Milestones

Tiziana is planning to conduct multiple clinical trials in multiple indications. Below we list key recent and future milestones.

- US$10 million raise - March 2020
- FY19 report - June 2020
- First-ever patent granted for oral anti-CD3 mAb - June 2020
- US$57.3 million raise – August 2020
- Half-year report - September 2020
- Demerger with StemPrintER - October 2020
- Initiation of foralumab in COVID trial - November 2020
- Announcement of Phase Ib/II with Parexel in CD - November 2020
- Completion of foralumab COVID trial - January 2021
- AIM Delisting - January 2021
- Main Market LSE Uplisting - January 2021
- Positive readout from foralumab in COVID-19 trial - February 2021
- Appointment of Thomas Adams, Ph.D. as Head of Drug Development - February 2021
- Foralumab launch of Phase II in COVID – March 2021
- TZLS-501 primate toxicology completion – 1Q:21
- Foralumab launch of Phase II intranasal in pMS - 2Q:21
- Foralumab in single SPMS patient, Expanded Access Program – 2Q:21
- Foralumab launch of Phase II oral enteric in CD - 2Q:21
- TZLS-501 IND submission – 2Q:21

Exhibit XV – Upcoming Milestones[107]



[107] Source: Tiziana Corporate Presentation, February 2021.

Tiziana began 2020 with positive results from its Phase I clinical trial investigating the safety of oral foralumab in healthy volunteers. The trial evaluated 1.25 mg, 2.5 mg and 5.0 mg dose foralumab in enteric-coated capsules resulting in no drug-related safety issues even at the highest dose. On March 16, 2020, the company announced and closed an issue of 3,333,333 ADS at US$3.00 per ADS raising approximately US$10 million. The issue included an underwriter option to purchase up to an additional 499,999 ADS with ThinkEquity acting as sole book-running manager for the offer. In April 2020, Tiziana both acquired a nanoparticle-based formulation technology for controlled delivery of Actinomycin D from Rasna Therapeutics, and filed a patent for combination of nanoparticle-Actinomycin D with anti-IL-6 receptor mAb for treatment of myelodysplastic syndrome, acute myeloid leukemia and coronaviruses. In return for the asset, Tiziana paid US$120,000 in upfronts and will continue with milestone payments of up to an additional US$630,000 in total.

Tiziana reported final results for FY19 in June of 2020. Other June events included the issuance of 2,343,445 ordinary shares and 468,689 ADS through an at-the-market (ATM) sales agreement totaling gross proceeds of US$2,785,003. Tiziana also entered into an agreement with STC Biologics for manufacturing of anti-IL-6 receptor mAb, acquired from Bristol Myers Squibb, to support clinical development, namely evaluation in COVID-19 patients that began the following November. Tiziana was also granted the first ever patent on oral-administration of lyophilized and stabilized anti-CD3 mAb (foralumab). Scientific Advisory Board member Dr. Howard Weiner received a grant to investigate nasal anti-CD3 mAb in Alzheimer's Disease. Gregor MacRae stepped down from his role on Tiziana's Board after being appointed to the Board in January of the same year.

In July 2020, Tiziana notified its intent to uplist from the AIM to the LSE main market. Tiziana held its annual general meeting where all resolutions were duly passed. Tiziana submitted a patent application for use of anti-CD3 fully human mAb (foralumab) in COVID, in combination with other anti-viral agents and another application for the same to enhance CAR-T[108] therapy. John Brancaccio, retired CPA with extensive international pharmaceutical and biotech experience, was appointed to Tiziana's Board as a non-executive director.

The month of August began with the closing of a US$57.25 million raise. The raise issued 11.0 million ADR shares (NASDAQ: TLSA) representing 22.0 million new common shares (LSE: TILS) at a price of US$5.20 per ADS. Each ADS represents two common (ordinary) Tiziana shares. ThinkEquity, a division of Fordham Financial Management Inc., acted as sole placement agent. Proceeds are intended to support clinical development of foralumab, expedite development of TZLS-501 in COVID-19, and provide working capital. Tiziana also announced that it had signed agreements with four CROs to expedite development of TZLS-501, anti-IL-6R mAb for COVID. The CROs included FHI Clinical, STC Biologics, Sciarra Labs, and ITR Laboratories Canada. In the same month, Tiziana was also granted a patent for the use of anti-IL-6/IL-6 receptor mAb for prophylactic and therapeutic intervention of COVID and other pulmonary diseases, another for use of milciclib in combination with tyrosine kinase inhibitors in hepatocellular carcinoma and other cancers, and yet another for use of anti-CD3 mAb in treatment of Crohn's Disease. Tiziana also announced that it retained Scientific Advisory Board member Dr. Napoleone Ferrara, notable for his discovery of Avastin and Lucentis, for an additional three-year term.

Tiziana issued its semi-annual report on September 30, 2020. The report highlighted Tiziana's candidates and technology, including foralumab, TZLS-501 and StemPrintER. It also recounted the acquisition of nanoparticle formulation of Actinomycin D intellectual property from Rasna Therapeutics, the granting of a key US patent enabling oral formulation of foralumab, and three US patent applications. Following the reporting period, Tiziana also was issued three US patents and two US patent applications were filed. The report also described the demerging of Tiziana's StemPrintER asset into a separate and independent entity, Accustem Sciences Limited. In the financial sphere, Tiziana reported that for the six months ended June 30, 2020, losses amounted to £3.91 million. Tiziana had £7.2 million in cash on its balance sheet. During the reported period, Tiziana had raised £12.9 million, £8.1 million of which was raised through a public offering on the NASDAQ Global Market, £2.8 million through an ATM sales agreement, and £2.0m through the exercise of warrants and options. R&D costs were (£760,000), down ~50% from the restated prior year period of (£1.5 million). Operating expenses for the six months totaled approximately (£3.2 million), increased ~48% from six months ended 2019 of (£2.1 million).

Tiziana's most recent general meeting was held on October 2, 2020. The result of the meeting was the passing of two resolutions regarding the demerger between Tiziana and Accustem. The intent to demerge was announced in September 2020 and the demerger took place the following month. On November 20, 2020, Tiziana announced that it had entered into a collaboration with Parexel Biotech, a division of the CRO Parexel International, to conduct a global Phase Ib/II trial of enteric coated capsule formulation of foralumab. The trial will target enrollment of 60 patients in the US and Europe.

[108] Chimeric Antigen Receptor T cell

Tiziana's first announcement for 2021 came on January 13, introducing Neil Graham MBBS, MD, MPH as Chief Medical Officer. Dr. Graham brought his experience and expertise in infectious diseases, Phase I-IV clinical development including regulatory filings, and global biotech and pharma R&D.

On February 2, 2021, Tiziana reported positive data for its clinical trial of nasal foralumab in COVID patients, which had been completed the previous month, and initiated in November 2020. Foralumab is an anti-CD3 monoclonal antibody that has anti-inflammatory effect through modulation of the immune system, making it potentially agnostic of coronavirus variant. Patients were dosed with either foralumab alone or in combination with oral dexamethasone. The study was a collaboration with teams at Harvard Medical School and INTRIALS, a CRO based in Brazil. The trial was intended to assess safety and be exploratory, without the power to draw statistical conclusions. Trial results showed that all treatments were well tolerated, without grade 3 or 4 severe adverse events in any cohort. CT scans showed approximately double the improvement in patients treated with foralumab compared to control. Data on pharmacokinetics, immunological biomarkers, stimulation of Tregs and immunological response had not been reported; however, a more in-depth follow-up report is expected shortly.

At the end of March, Tiziana announced two new important initiatives which we discuss in a note available here. The first is FDA clearance of an IND to treat one secondary progressive multiple sclerosis (SPMS) patient under the expanded access program. Success with this patient could provide additional support for moving ahead with clinical trials in pMS and give stakeholders additional confidence in foralumab's efficacy in this condition. The second announcement provided details on Tiziana's intention to launch a Phase II foralumab trial in COVID patients with moderate to severe symptoms. Supported by the positive results in the recently completed Phase I trial, the new study will be designed as a randomized, placebo-controlled trial in patients receiving standard of care background therapy.

MANAGEMENT PROFILES

Kunwar Shailubhai, Ph.D., MBA, Chief Executive Officer, Chief Scientific Officer, Executive Director

Kunwar Shailubhai, Ph.D., MBA, joined Tiziana as its Chief Executive Officer and Chief Scientific Officer in May 2017. Dr. Shailubhai brings more than 25 years of experience within the life science industry, combined with a distinguished track record of success in translating drugs from concept through commercialization to market.

Dr. Shailubhai has also served as the Executive Director of Tiziana's Board since 2015. He actively played key roles in development of growth strategies through several key licensing of technologies and drug candidates. Dr. Shailubhai steered the company through prioritization of projects to focus on novel drug candidates for treatment of autoimmune and inflammatory diseases and cancer. He has also served as a member of Okyo Pharma's Board since June 2017.

From 2017 to 2020, Dr. Shailubhai served as CEO of Rasna Therapeutics, Inc., a developer of therapeutics to address the high unmet need that exists for AML and other forms of leukemia. Before that, he co-founded Synergy Pharmaceuticals, Inc. (NASDAQ: SGYP) in 2000, and served as its EVP and CSO for almost 17 years, where he led the non-clinical, CMC and clinical development of Trulance from inception to approval by the FDA. He co-invented and pioneered Synergy's platform technology for functional GI disorders, inflammatory bowel disease, GI cancer and other human diseases. Dr. Shailubhai directed all aspects of Synergy's IP estate. From 2003 until 2008, Dr. Shailubhai served as Senior Vice President of Discovery Research at Callisto Pharmaceuticals. Dr. Shailubhai has also held positions at Monsanto Company, serving as Group Leader, Cancer Prevention and at the National Institutes of Health.

Dr. Shailubhai received his Ph.D. in microbiology from the University of Baroda, India, and his MBA from the University of Missouri, St. Louis. He has more than 20 issued patents and over 50 peer-reviewed publications.

Neil Graham, MBBS, MD, MPH, Chief Medical Officer

Dr. Graham was appointed CMO of Tiziana, recently, in January 2021. Over the course of his career, Dr. Graham has developed expertise in Biotech and Pharma R&D with therapeutics and diagnostics. His development expertise spans virology, respiratory, dermatology, allergy and rheumatology and has contributed to the advancement of multiple IND, NDA and BLA filings.

From 2010 to 2020, Dr. Graham was VP of Strategic Program Direction, Immunology and Inflammation at Regeneron Pharmaceuticals, Inc., where he managed and oversaw a large portion of the Regeneron pipeline portfolio including leading the immunology and inflammation antibody products across all stages of development from preclinical to post-launch. He was instrumental in the development of DUPIXENT (dupilumab), from Phase I through its initial launch for atopic dermatitis, as well as expanding its development into asthma, sinusitis, and eight other indications. Dr. Graham also led the product development for KEVZARA (sarilumab), and REGN3500, an anti-IL-33 antibody for asthma and COPD.

Prior to Regeneron, Dr. Graham served as Senior Vice President, Program and Portfolio Management at Vertex, where he oversaw the team of program leaders and managers across the portfolio from Phase 1 through launch. Before that he held roles as CMO at both Trimeris Inc. and XTL Biopharmaceuticals, and worked as Director, HIV Medical Affairs at GlaxoWellcome. Earlier in his career, Dr. Graham was an Associate Professor of Medicine and Epidemiology at John Hopkins University, School of Hygiene and Public Health.

He is the author of five chapters and books and more than 140 peer-reviewed journal articles. Dr. Graham earned an MD, MBBS and MPH from the University of Adelaide in Australia.

Jules Jacob, Senior Director of Chemistry, Manufacturing, Controls & Non-Clinical Development

Mr. Jacob joined Tiziana in July 2017, bringing 30 years of drug development experience. He was previously Senior Director, Product Development at Aprecia Pharmaceuticals, where he headed development of Spritam and other 505(b)(2) products. Prior to that, Mr. Jacob was Director of Formulation Development at Panacos Pharmaceuticals, developing first-in-class maturation inhibitors for treatment of HIV. Mr. Jacob served as Director of Research and Development and Director of Technology Development at Spherics Pharmaceuticals, developing bioadhesive dosage forms for treatment of CNS disorders, following the 505(b)(2) regulatory pathway.

Mr. Jacob holds over 30 issued patents (US and international) and 38 US patent applications in the fields of drug delivery (proteins, peptides, DNA), nanoencapsulation, microencapsulation, solid oral dosage formulation, polymer compositions, gene therapy, tumor immunotherapy, protein micronization and formulation, imaging and bioadhesion. He has authored more than 30 scientific articles and book chapters and was Grand Award winner of the 2005 Eurand-CRS sponsored "Novel Approaches in Industrial Oral Drug Delivery Award." Mr. Jacob completed his undergraduate degree and graduate education in biological and medical sciences at Brown University and has an active visiting faculty appointment in the Department of Molecular Pharmacology, Physiology and Biotechnology at Brown.

Vaseem A Palejwala, Ph.D., Director, Clinical Operations

Dr. Palejwala joined Tiziana in January 2017 as Director, Discovery and Preclinical Research, later serving as Director, Clinical Operations. Dr. Palejwala brings 18 years of experience in drug discovery and development.

Since 2012, Dr. Palejwala has served as Director of Discovery and Preclinical Research at Synergy Pharmaceuticals Inc. (NASDAQ: SGYP) where he actively contributed to establishing preclinical animal models for testing therapeutic efficacy and mechanism of action of plecanatide (Trulance) and dolcanatide in the gastrointestinal tract. He also prepared the preclinical pharmacology section of NDA for Trulance.

From 2001 - 2012, Dr. Palejwala held multiple roles at Sanofi Pharmaceuticals, contributing to advancing small molecule and biologic programs in immunology, inflammation, oncology, CNS and metabolic disorders. He contributed to establishing and managing high throughput gene expression profiling platform capabilities at Sanofi and collaborated/contributed in cross-cultural/cross-functional team settings.

Dr. Palejwala received his masters and doctorate in microbiology from the Maharaja Sayajirao University of Baroda in India and post-doctoral training in Molecular Genetics at the University of Medicine and Dentistry in New Jersey.

Keeren Shah, Finance Director

Keeren Shah has served as the Finance Director (non-statutory) of Tiziana since August 2020. Ms. Shah previously served as the Group Financial Controller for both Tiziana and Accustem from June 2016 to July 2020. Prior to joining Tiziana, Ms. Shah spent 10 years at Visa, Inc. as a Senior Leader in its finance team where she was responsible for key financial controller activities, financial planning and analysis, and core processes as well as leading and participating in key transformation programmes and Visa, Inc.'s initial public offering. Before joining Visa, Ms. Shah has also held a variety of finance positions at other leading companies including Arthur Andersen and BBC Worldwide. She holds a Bachelor of Arts with honours in Economics from the University of Manchester.

RISKS

All investments contain an element of risk which reflects business uncertainty and opportunity. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical power-houses that have dozens of established products, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large and small firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products. The typical risks faced by companies operating in the biotechnology space include risks related to liquidity, financing & trading, clinical trials, regulatory, personnel, intellectual property, marketing, and geopolitics.

Pandemic Risk

Pandemic risk has emerged as one of the leading concerns over the last year. The pandemic has disrupted economic and other activity in the United States and around the globe. It has also caused significant volatility in financial markets. Economic activity worldwide has contracted and may take many quarters to improve. While the financial markets have not declined in tandem with economic growth, risk perception may increase and financial markets may begin to reflect a lower level of economic activity and decreased availability of capital. Early stage clinical firms lacking revenues rely on capital markets to sustain development efforts and may be sensitive to changes in risk perception and trading dynamics.

Tiziana is at a clinical stage of development with programs in varying stages of completion. Tiziana bears risk of the pandemic limiting clinical bandwidth for Tiziana's programs to progress in a timely manner, as fewer patients visit the clinic, and more clinical resources are devoted to addressing the immediate threat of COVID. Tiziana also bears risk related to the availability of financing and capital to support its programs as the pandemic may disrupt capital markets in an economic downturn. Tiziana is advancing a program in COVID; however, if the virus is suppressed, efforts and resources committed to the COVID program may not produce value.

Liquidity, Financing & Trading

Access to financing comes and goes in cycles. During periods of improving confidence and plentiful liquidity, capital may be easy to obtain; however, during a crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they depend on the financial markets to fund their work. Pre-revenue biotech firms rely primarily on equity issuance to fund their operations. The duration of drug development is considerable, and can last as long as 12 to 15 years before product revenues come in the door. Funds can be sourced through debt or grants and tax credits; however, these sources may reduce the flexibility of the company and can create difficulties if debt is unable to be repaid.

If capital is not readily available when needed, a company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route forward or force a company to accept onerous terms.

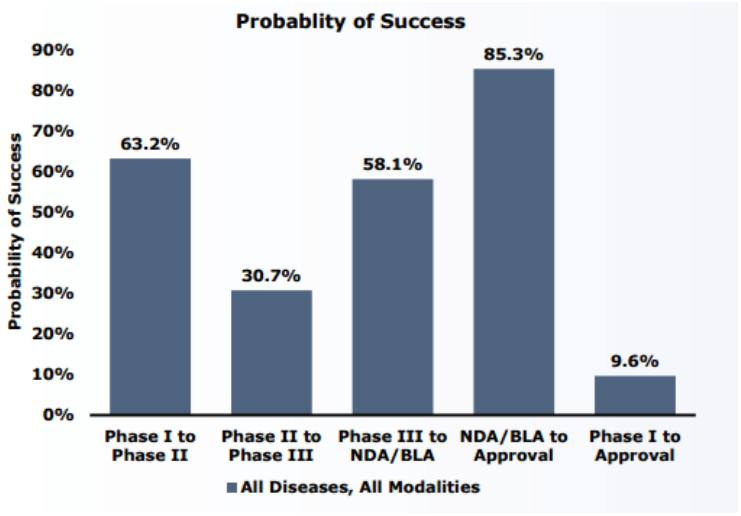
Trading volumes are lower for smaller biotech firms, creating liquidity risk for the investor and large transactions may have a material impact on share price. In periods of crisis or heightened risk perception, share price may be volatile. Companies with smaller capitalizations are typically considered riskier and changes in sentiment may adversely affect their trading prices and volumes. Smaller firms may also have less visibility, compete for investor dollars in a shallow market and be excluded from market indices.

Tiziana has not generated revenues since inception and is not expected to produce sales until a candidate is approved. The company has multiple programs in varying stages of development and consumed capital at an annual rate of ~£10 million per year in 1H:20, with ~£7.2 million in cash and equivalents as of June 30, 2020. In 2021 and subsequent years, the company may consume up to £30 million per year as new clinical trials are launched. Tiziana completed a US$57.25 million capital raise in August 2020, providing the resources to meet near-term operational objectives.

Clinical Development, Regulatory and Commercialization

For smaller early-stage companies, investing in drug development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing a drug frequently takes from 12 to 15 years depending on market and company-specific conditions. On average, only one in a thousand compounds in discovery is eventually approved, creating a high hurdle for success.

Exhibit XVI – Success of Phased Trials and Regulatory Approval[109]



The future of a drug development company is largely dependent on the data produced from clinical trials. Due to the cost, magnitude and complexity typical of this work, partners are often sought to share risk. Partners may have competing demands which can adversely affect the work they are managing on behalf of the firm. Contract research organizations (CROs) first must be identified and an agreement met. Subcontractors must abide by strict execution and trial parameters that if violated can jeopardize trial success. They supervise and execute research, biometric and pharmacovigilance, which are complex tasks. Any financial instability of the CRO itself will be a risk as well. Patient recruitment and retention may be difficult. Clinical sites need to be established. Each clinical site bears its own risks including risks based on geography. Clinical investigational centers need sufficient capacity and the candidate drug needs to be manufactured according to current Good Manufacturing Practices (cGMP) and be available to administer. Finally, clinical endpoints need to reach statistical significance to justify regulatory approval.

Regulatory risk centers on a sponsor's interactions with regulatory authorities such as the FDA and EMA related to clinical trial requirements, marketing approval of the candidate, expedited pathways and the associated oversight. Previous success with the FDA or other regulatory agencies is another attractive attribute for a sponsor. Success is uncertain and may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Some accelerated pathways to approval are available such as those outlined in the Orphan Drug Act and the Breakthrough Therapy designation; however, changes in sentiment or perceived safety of drugs approved through these routes could influence the regulatory environment to demand a more rigorous process and the duration of the approval process may be extended or additional requirements may be put in place.

Successful marketing of approved drug candidates relies on adoption by patients and providers. The approved drug must have convincing clinical trial data and maintain a favorable reputation among prescribers. Marketing is expensive and requires an experienced sales force and a presence in the marketing area. Marketed products remain under surveillance and any unexpected adverse effects damage the product's reputation. Furthermore, the risk of a competing or superior therapy is a continuous threat. Insurance coverage is also important. Rapidly obtaining a preferred position on health plan and payor formularies is critical to achieving target penetration rates. If health plans and payors cannot agree on appropriate pricing for the drug and the compound fails to offer a significant benefit above standard of care, the product may not be available on formularies.

Tiziana has multiple programs. While this may diversify risk to some extent, management of multiple candidates and trials may prove costly in not only time and capital, but even in management resources. Should financial resources ever become a constraint, management may be forced to choose to delay or even abandon candidates.

[109] Thomas, D.W. *et al.* Clinical Development Success Rates 2006-2015. Bio, Biomedtracker, Amplion. June 2016.

Should any of Tiziana's candidates be approved, the challenge will then be to market the candidate battling for share in competition with other products.

Tiziana will seek approval from the EMA, FDA and other regulatory bodies and requirements for these agencies differ. Seeking marketing approval from multiple agencies will incur additional fees and hurdles. Tiziana's milciclib was granted Orphan Drug Designation in the US and EU. While Orphan Designation is accompanied by marketing exclusivity, the designation itself implies a limited market size. Recruitment for trials can be challenging in smaller patient populations. Likewise, recovery of development costs is spread amongst a smaller population, resulting often in heightened treatment pricing, a burden for patients. Reimbursement from payors can play a key role.

Personnel

Biotechnology companies rely on the expertise and leadership of their executives to make both technical and strategic decisions and investments. Due to the highly competitive nature of the industry, many talented personnel are sought after and firms with the best resources are in the strongest position to attract talented leaders. Leadership turnover can be high in small biotech firms. Change in management is disruptive and can dramatically change the course of a firm. Personnel turnover can place a small company at a disadvantage when compared to larger firms with more specialized employees and executives. Furthermore, there can be risks and challenges associated with adding talent as the firm grows in size, especially with capital constraints. The size of the firm, volatility of stock price and a large component of compensation made up of equity-based compensation can deter certain talent from joining the firm or make it difficult to retain.

As a small firm, Tiziana has a limited number of personnel, all of whom play an important role. The loss of Dr. Kunwar Shailubhai, CEO, Dr. Neil Graham, CMO, Jules Jacob, Senior Director of Chemistry, Manufacturing, Controls & Non-Clinical Development, or Dr. Vaseem Palejwala, Director, Clinical Operations, would severely impact the firm.

Intellectual Property

Intellectual property is the backbone of biotechnology development. Even with government regulation, patent protection is not guaranteed. The patent application process requires time, capital and the disclosure of substantial detail on the company's technology which is eventually made public. Despite submission of an application, patents may not be granted. Patent protection requires legal resources that a startup biotech firm may not have. Furthermore, countries differ in the degree and type of intellectual property protection. Some firms may in- or out-license intellectual property, which exposes parties holding the patent to risk of adherence and litigation regarding the parameters of the licensing. Finally, patent protection is temporary and there is no guarantee that the firm will benefit from the patent protection before it expires. Tiziana has patents granted worldwide, with expiration ranging from 2024 to 2040.

Geopolitical

Recent trade tensions between the US and China threaten the world economy and have been exacerbated during the ongoing pandemic. There has been a cross-pollination of capital and drug development between China and North America in recent years which may slow as a result of the trade and political disputes between the countries. This conflict may reduce the availability of capital, partnerships and future development deals between companies in the two nations. The UK seceded from the European Union in 2020, potentially creating new difficulties for companies seeking access across the EU-UK border. Tiziana is headquartered in the UK. The country's new status as independent from the EU may create difficulties sourcing inputs and allowing for travel of corporate executives. There may also be additional hurdles required to overcome to obtain marketing approval in the island nation. Previously, a drug approved under the centralized procedure in the European Union would be approved in all member states. However, with the withdrawal of the UK, additional efforts and expense may be required to obtain marketing approval in this large European market. The role of the EMA in the UK remains unclear.

VALUATION

Tiziana's portfolio of assets offers multiple candidates pursuing various indications primed to enter Phase I, II and III clinical trials. Our valuation targets the pursuit of progressive Multiple Sclerosis (pMS) and Crohn's Disease (CD) in the US and in developed markets. Other indications that we expect to go forward as additional supportive data and funding come along include solid tumors and acute respiratory distress syndrome (ARDS). We will add a valuation component for these endeavors upon further clarity regarding the pathway forward.

There is only one drug approved for pMS called ocrelizumab by Genentech, providing limited benefit to pMS patients. With only one other competitor and remaining unmet need, an approved foralumab indication in pMS would hold a favorable position in the market. We model a prevalence of approximately 100,000 cases of pMS in the United States and about 180,000 in the rest of the developed world. Phase II trials are slated to begin in 2021 and Phase III studies are anticipated in 2023. If successful, we anticipate a BLA will be filed with the FDA and other regulatory authorities for foralumab in 2026 for use in pMS. Assuming approval, first US sales are expected in 2027 and in other regions, 2028.

pMS is a smaller population with only one other disease modifying therapy; therefore we assume initial penetration of 5% and a steady ramp up to 15% penetration by the fourth year of sales in both the US and ex-US markets. Pricing for foralumab in the pMS indication is modeled at $50,000 per year of treatment in the US and $25,000 elsewhere, with prices inflating at 3% per year.

Effectiveness for current therapies for CD is insufficient and there is demand for new therapies that can provide improved effectiveness. Based on our literature review we see a prevalence of about 1 million cases for CD in the United States and 3 million in the rest of the developed world. Phase II trials are anticipated to begin in 2021, followed by our estimate of Phase III trials in 2023. Data supportive of a BLA is expected by 2026 at which time the BLA will be submitted to the FDA and other regulatory authorities in 2026. Assuming a favorable response, commercialization of foralumab for CD will begin in 2027 in the United States and 2028 in the rest of the world.

Given the large number of competing therapies in the Crohn's Disease indication,[110] our model assumes a modest penetration of 0.5% in the first year of commercialization rising to 1.5% by year four. Pricing for foralumab treatment in MS is expected to be $50,000 annually, growing at 3% inflation.[111]

Tiziana owes a low single digit royalty on sales to Nerviano for net sales of a foralumab product. For nasal formulations of foralumab, the company additionally owes a low single digit royalty to Brigham and Women's Hospital. We anticipate that Tiziana will work with partners to complete late stage development and commercialize approved products taking advantage of an existing large global sales force. Common licensing arrangements include upfront payments, milestones and royalties based on sales. To simplify our approach we assume royalties on sales will represent the entirety of the financial benefit from partners. We model a net 27% royalty for oral CD sales and a 24% royalty for nasal pMS sales recognizing the stage of development where a partner was added and the royalties that are owed to ultimate license holders.

Our valuation approach employs a discounted cash flow model. Assumptions include a discount rate of 15% and a terminal growth rate of -10%. To our net present value (NPV), we attach a 15% probability of FDA approval and ultimate commercialization based on our review of literature and resources addressing success probabilities. This is based on foralumab being a Phase II candidate in both pMS and CD.

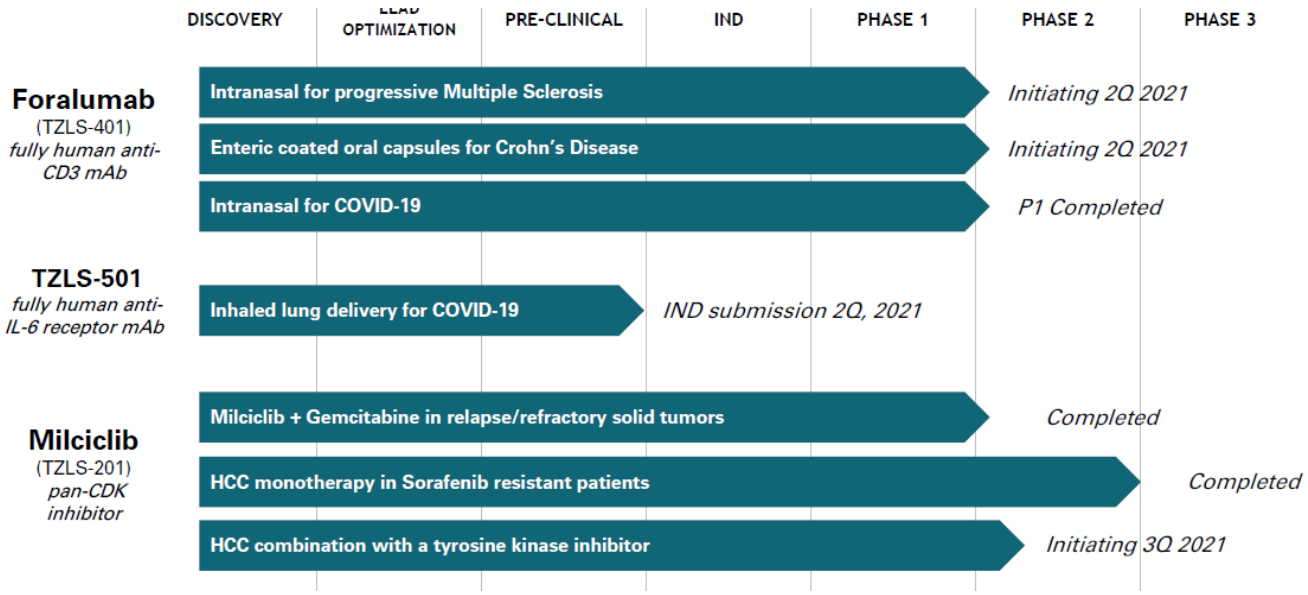
We assume general and administrative expense of £5.9 million in 2021 rising at an approximate 3% inflation rate over time. Research and development costs are forecast at £19.3 million in 2021, rising steadily to £24.3 million by 2025, then falling to zero a year after the last product becomes commercialized in 2029. We will add expected research and development costs and expected contributions from other programs when further details are provided and related clinical trials are launched.

[110] Based on a review of products provided by Evaluate Ltd. (accessed April 2021), there are over 10 different products either approved or in development for Crohn's Disease.
[111] Our model forecasts project product revenues in US dollars and coverts this amount to pounds sterling for our income statement estimates.

Outstanding warrants below our target price are assumed to be exercised with proceeds added to cash and exercised shares added to shares outstanding. We recognize the additional capital required to fund future trials and assume 50 million shares are issued near current price and dilute shares outstanding accordingly. Our penetration estimates are conservative, and could rise if study results demonstrate strong efficacy and safety for foralumab. We note that the determinant for many of the variables in our model will be the ultimate safety and efficacy profile and the degree to which the primary and secondary endpoints are achieved in the confirmatory trial. We will update our model accordingly as data is made available.

Based on the assumptions identified in our discounted cash flow model, we generate a current valuation of $7.50 per ADR share.

Exhibit XVII – Tiziana Development Pipeline[112]



[112] Source: Tiziana February 2021 Corporate Presentation.

CONCLUSION

Tiziana offers an impressive portfolio of three candidates that use evolved formulations of antibodies and receptor inhibitors administered via novel routes of administration to treat autoimmune, inflammatory and neoplastic disease. The company's lead candidate, foralumab, is a fully-human anti-CD3 monoclonal antibody that is being investigated in progressive multiple sclerosis (pMS), Crohn's Disease (CD) and COVID. The mAb binds to the CD3 receptor and modulates the presence of T cells, Tregs and other immune cells creating a tolerogenic environment. In contrast to other mAbs, foralumab can be administered orally, nasally and via inhalation allowing for more direct delivery to the disease site and avoiding systemic exposure. Tiziana's second most advanced candidate, milciclib, is a small molecule inhibitor of multiple cyclin-dependent kinases (CDKs), tropomyosin receptor kinases and Src family kinases. The product is planned for development in solid tumors in combination with a tyrosine kinase inhibitor. The third candidate in the company's portfolio is TZLS-501, an anti-interleukin-6 receptor mAb. The biologic can reduce chronic inflammation associated with autoimmune disease and can be used with other agents against COVID, multiple myeloma, arthritis, lupus and cancer.

We expect to see Tiziana advance foralumab into multiple clinical trials this year. Three Phase II studies are expected to launch this year in pMS, CD and COVID. Each of these indications has an unmet need that foralumab's distinct target and method of administration may address. In pMS there is only one other disease modifying therapy available that has limited effectiveness, providing substantial demand for an improved treatment. We estimate a market of about 100,000 patients in the United States and almost twice that number outside the US. CD lacks a definitive cure and existing treatment only manages symptoms. An improved approach is needed and foralumab's action on CD3 is upstream of existing therapies potentially providing improved response. We estimate that there is an addressable market of just under one million in the United States and about three million in the rest of the developed world. COVID and ARDS are serious conditions that can lead to death if the immune response gets out of control. With over half a million deaths in the US and almost three million around the world over the prior year, there is a dramatic need to have additional treatments beyond the imperfect ones that are now available for COVID. If COVID disappears, Tiziana's foralumab and TZLS-501 may also continue to address respiratory issues with ARDS where there are an estimated 111,000 cases in the US every year and almost 340,000 in the rest of the developed world, providing a continuing need for immune modulating drugs.

Tiziana held an estimated £44 million on its balance sheet at the end of last year taking into account the ~£44 million capital raise and existing funds less estimated cash burn. This amount is sufficient to support modeled program costs over the next 18 months. We anticipate that the foralumab programs will complete Phase II work and advance into Phase III efforts in 2023, assuming successful Phase II results. If safety and efficacy endpoints are met in Phase III trials, Tiziana can make BLA, MAA and other regulatory submissions to obtain marketing approval for pMS and CD by 2027 and 2028. Intellectual property protection is expected to last until the early 2040s allowing over a decade of access to nasal and oral anti-CD3 indications without generic competition.

Key reasons to own Tiziana shares:

- **Multiple Phase II-ready assets pursuing unmet needs**
  - **Fully human anti-CD3 - foralumab**
    - **Multiple Sclerosis**
    - **Crohn's Disease**
    - **COVID-19 / ARDS**
  - **Pan-CDK Inhibitor - milciclib**
    - **Non-small cell lung carcinoma (NSCLC)**
    - **Hepatocellular carcinoma (HCC)**
  - **Fully human anti-IL-6 receptor – TZLS-501**
    - **ARDS, ILD, COVID-19 and other diseases**
- **Oral, nasal and inhaled administration of antibodies**
  - **Improved ease of use**
  - **No need for hospital-based infusion**
  - **Lower doses required for efficacy**
  - **Reduced systemic exposure and toxicity**
  - **Fewer side effects with reduced systemic exposure and toxicity**
  - **Focused distribution at the target organs in CD and severe lung disorders**
  - **Higher lung drug retention and efficacy while minimising toxicity to other organs**
- **Validation of intranasal foralumab technology in Phase I COVID-19 trial**
  - **Phase II trial announced**

Tiziana's portfolio of candidates has the potential to address numerous unmet needs in multiple autoimmune diseases, dysregulated responses to underlying viruses and in oncology. We see multiple clinical trials launching in the near term which are targeting large markets with an unmet need around the globe. Over the next several years we anticipate registrational work will be successful and foralumab will be commercialized. Beyond foralumab, Tiziana has two other candidates that will advance upon sufficient supportive data and availability of funding. As we initiate on Tiziana Life Sciences PLC, our analysis and forecasts generate a valuation of $7.50 per ADR share.

PROJECTED FINANCIALS

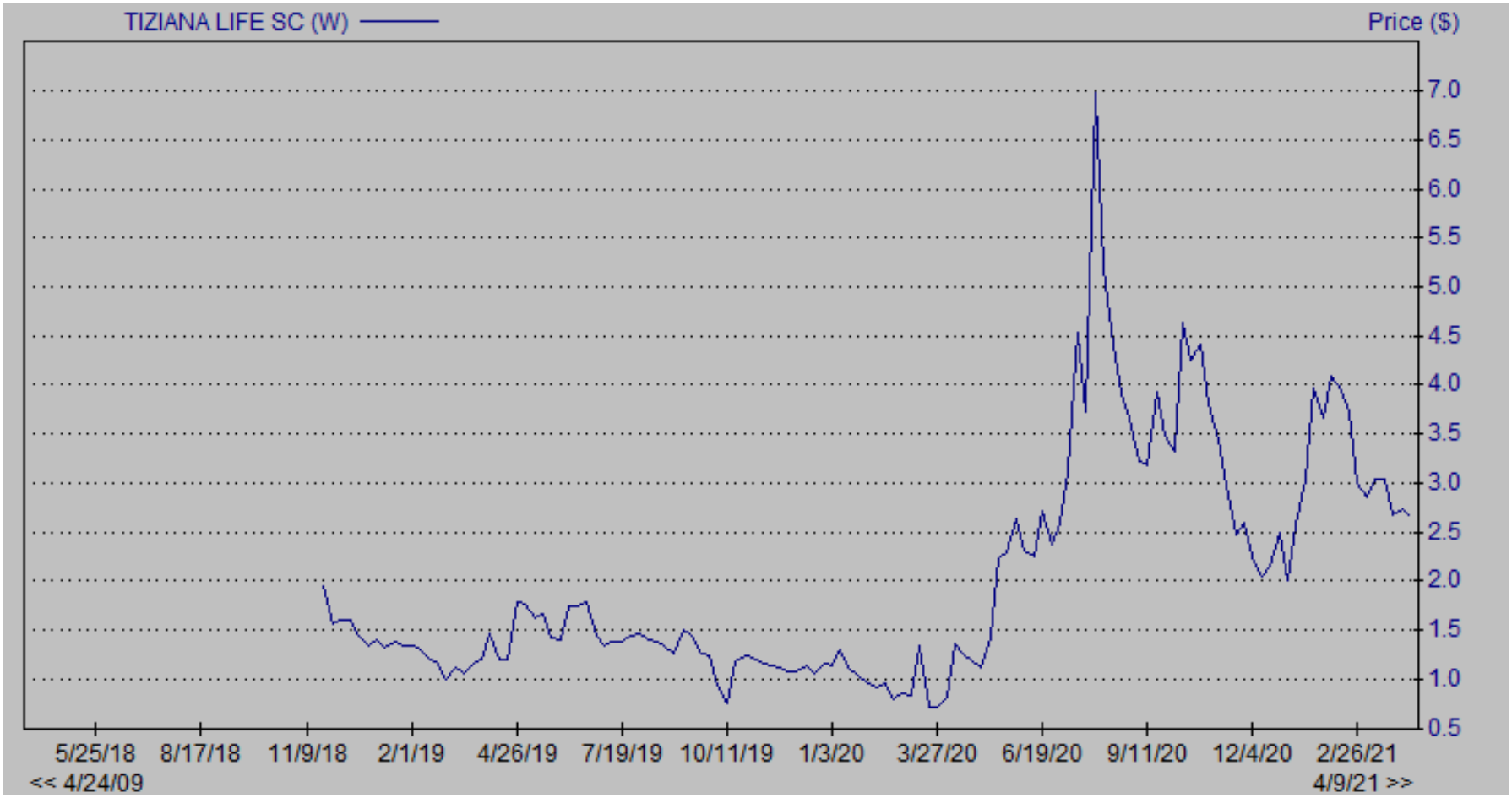
Tiziana Life Sciences PLC - Income Statement

Tiziana Life Sciences Plc	1H A	2H A	2019 A	1H A	2H A	2020 E	2021 E	2022 E
Total Revenues (£UK)	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
YOY Growth								
Research & Development	£1,507	£1,403	£2,910	£760	£3,875	£4,635	£19,312	£20,801
General & Administrative	£2,138	£2,726	£4,864	£3,169	£4,750	£7,919	£5,895	£5,968
Income from operations	-£3,645	-£4,129	-£7,774	-£3,929	-£8,625	-£12,554	-£25,207	-£26,769
Operating Margin						*# DIV/0!*	*# DIV/0!*	*# DIV/0!*
Other Expense	£5	£67	£72	-£5	£0	-£5	£0	£0
						£0	£0	£0
Pre-Tax Income	-£3,650	-£4,196	-£7,846	-£3,924	-£8,625	-£12,549	-£25,207	-£26,769
Provision for Income Tax	-£27	-£513	-£540	£0	-£1,500	-£1,500	£0	£0
Tax Rate	0.0%	0.0%	0.0%	0.0%	0.0%	12.0%	0.0%	0.0%
Net Income	**-£3,623**	**-£3,683**	**-£7,306**	**-£3,924**	**-£7,125**	**-£11,049**	**-£25,207**	**-£26,769**
Net Margin	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*
Reported EPS	**-£0.027**	**-£0.027**	**-£0.054**	**-£0.026**	**-£0.04**	**-£0.06**	**-£0.11**	**-£0.10**
YOY Growth			1.0%	-1.6%	35.7%	6.1%	101.8%	-10.1%
Basic Shares Outstanding	136,464	136,501	136,483	150,224	194,600	194,600	220,000	260,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

HISTORICAL STOCK PRICE

Tiziana Life Sciences PLC – Share Price Chart[113]



[113] Source: Zacks Research System

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