Zacks Small-Cap Research
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Tiziana Life Sciences PLC (TLSA - NASDAQ)

Foralumab SPMS Trial & Additional Data

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 (5/26/2021)	$2.50
Valuation	**$7.50**

OUTLOOK

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 2027 regulatory approval and 2028 commercialization of foralumab for both pMS and CD in conjunction with partners.

SUMMARY DATA

52-Week High	**12.17**
52-Week Low	**1.76**
One-Year Return (%)	**1.0**
Beta	**-0.1**
Average Daily Volume (sh)	**377,939**
Shares Outstanding (mil)	**97.3**
Market Capitalization ($mil)	**243**
Short Interest Ratio (days)	**0.56**
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

WHAT'S NEW

Nasally-administered Foralumab Trial in SPMS Patient

On May 25, 2021, Tiziana Life Sciences PLC (NASDAQ: TLSA / LSE: TILS) announced that it had initiated a trial through the Individual Patient Expanded Access Program (EAP) of foralumab in a Secondary Progressive Multiple Sclerosis (SPMS) patient. This follows a previous release in late March that first introduced the effort that was cleared under the EAP. The first SPMS patient was dosed on May 24, 2021 with treatment to be administered over the following six months to examine long-term safety, tolerability and clinical response. Previous clinical work has been conducted in healthy volunteers and COVID-19 patients demonstrating the well-tolerated safety of nasally-administered foralumab, dosed up to 10 consecutive days, with no apparent severe adverse events. Treatment in these investigations also produced anti-inflammatory effects.

The SPMS patient will be treated at Brigham and Women's Hospital Harvard Medical School and will receive 50 mcg, or 25 mcg/nostril, in 3-week cycles. Dosing will be three times a week for the first two weeks followed by one week of rest in a repeating cycle that will continue for six months. The patient will be monitored during the period evaluating routine safety, tolerability and neurological behaviors. In addition, the study will also track microglial activation and will assess treatment response through immunological and neurodegenerative markers.

Other foralumab trials are planned. Tiziana expects to start a progressive Multiple Sclerosis (pMS) program and will evaluate Crohn's Disease, both in a Phase II study in coming quarters. A Phase II study for moderate to severe COVID-19 patients is scheduled to launch this year.

In the Space: Teplizumab FDA Advisory Committee Meeting

Foralumab rival teplizumab is scheduled for an FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting, with related briefing documents posted on May 25. The advisory committee meeting is scheduled for 9 AM ET on May 27 to review Provention Bio's (NASDAQ: PRVB) candidate. The meeting was called to discuss potential merits of teplizumab, which, like foralumab, is an anti-CD3 monoclonal antibody (mAb). In contrast to foralumab, teplizumab is indicated in type 1 diabetes and contains some murine elements, while fully human foralumab is indicated in a multitude of conditions with a focus on multiple sclerosis, Crohn's Disease and COVID-19 symptoms. News of the advisory committee meeting for teplizumab signals the FDA's efforts and consideration toward the novel anti-CD3 mAb, which can set a precedent for the drug class.

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 neurological 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.

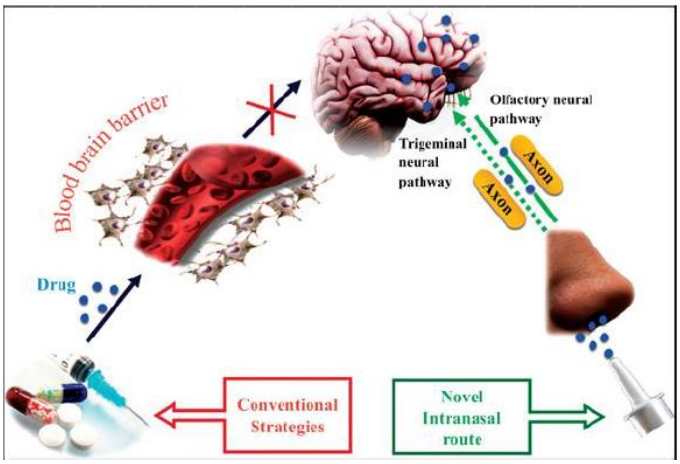
MS is clinically classified into four types: relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), primary-progressive multiple sclerosis (PPMS) and progressive-relapsing multiple sclerosis (PRMS).

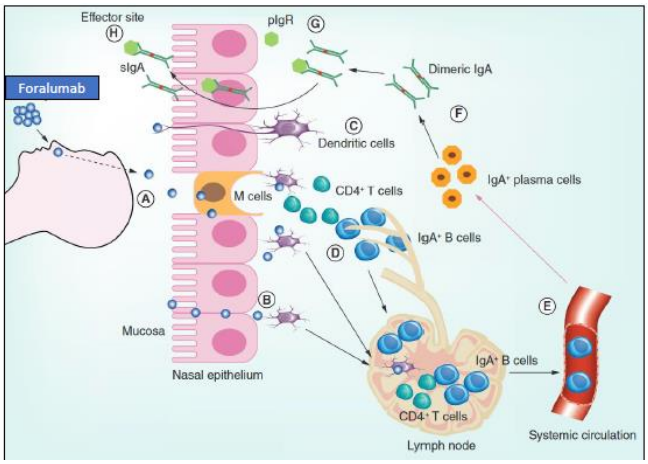
- RRMS is the most common disease course, patients have symptoms and respond well to treatments, leading to long episodes of remission. Patients experience defined attacks of new or increasing neurologic symptoms which are followed by periods of remission. During remission, where some or all of the symptoms 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.[1]
- 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.

Phase I Further Analysis

In January of 2020, Tiziana announced foralumab clinical data showing that the antibody was well tolerated in a Phase I study. The single-site, double-blind, placebo-controlled, single ascending dose study administered the mAb orally, via enteric coated capsules, at 1.25, 2.5 and 5.0 mg per dose. No drug-related safety issues were observed, even at the highest dose. In a follow up to this initial analysis, an update was released on May 26, 2021 with additional observations and further analysis of the Phase I trial.

Exhibit I – Nasal Administration / Activation of Mucosal Immunity in Cervical Lymph Node[2]





The new release shared analysis of lymphocyte subsets from blood samples in healthy volunteers. Researchers observed immunomodulatory effects of foralumab on CD8+ cytotoxic T-lymphocytes and other inflammatory biomarkers.

[1] https://www.nationalmssociety.org/What-is-MS/Types-of-MS
[2] Source: May 2021 Tiziana Corporate Presentation. Image on right adapted from Marasini, Nirmal, Mariusz Skwarczynski, and Istvan Toth. "Intranasal delivery of nanoparticle-based vaccines." Therapeutic Delivery 8.3 (2017): 151-167.

Additional analysis highlights:

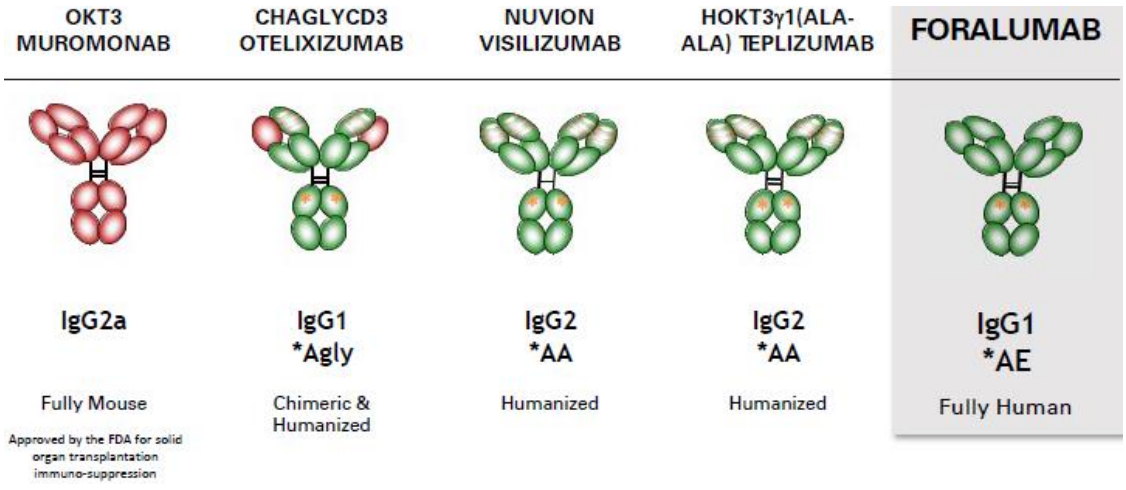
- Nasally administered foralumab was well tolerated and there were no apparent symptoms of severe toxicity or cytokine release syndrome;
- Systemic levels of foralumab were below the lower quantitation limit of 8 ng/mL suggesting that nasally administered foralumab appears to exert its effects via nasal epithelium utilizing local and lymphatic immune systems directly;
- Most prominent effects among cytotoxic T-cell subsets were observed in the 50 mcg group compared to 10 mcg, 250 mcg and placebo groups;
- The observed effects in the 50 mcg dose group were the following:
    - Statistically significant reductions from baseline in CD8_Tem cytotoxic T cell subset through 14 days and CD8_TEMRA, CD8_GranzymeB, CD8_Perforin subsets through 21 days;
    - Statistically significant increase from baseline in CD8_naive subset through day 21;
    - Statistically significant stimulation in production of anti-inflammatory cytokine IL-10 along with suppressed production of pro-inflammatory cytokine IFN-γ, suggested a positive trend for immunomodulation and anti-inflammatory effect.

The observations from the Phase I in healthy patients reinforce the takeaways from the COVID-19 foralumab trial conducted in Brazil. We discuss the available takeaways from this trial in an article here. The primary conclusions were that the anti-inflammatory effects of foralumab may be useful against an aggressive inflammatory response to a virus, direct delivery of the drug to nasal passages and respiratory tract has a rapid impact on inflammation, foralumab-treated patients showed improved sense of smell and taste and multiple pro-inflammatory biomarkers were reduced.

Foralumab

Foralumab is an anti-CD3 monoclonal antibody that reduces T cell activation and cytokine release by 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.[3]

Exhibit II – Evolution of Anti-CD3 mAbs[4]



[3] 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).
[4] Source: Tiziana Life Sciences Corporate Presentation, January 2021.

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**
    - **IND development underway**
- **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**

Summary

Tiziana has initiated a trial for its innovative, nasally-administered monoclonal antibody foralumab. The trial has enrolled its first patient and will evaluate the long-term safety and tolerability as well as monitor clinical efficacy through microglial activation and biomarkers relating to immunology and neurodegeneration. The trial was enabled through the Individual Patient EAP evaluating a patient with SPMS. SPMS is a subtype of multiple sclerosis characterized when symptoms arise during a stage in remission and are not resolving with treatments. Multiple sclerosis itself is a neurological condition that affects the white matter of the central nervous system. We are watching teplizumab, another anti-CD3 mAb indicated in Type 1 diabetes that has a target action date of July 2, 2021. An approval could establish a positive precedent for the drug class.

We were also introduced to additional analysis of foralumab administered to healthy patients. The assessment determined that nasally administered foralumab was well tolerated, systemic levels of the drug were minimal and that 50 mcg produced the most prominent effects. The 50 mcg dose produced favorable immunomodulation and diminished inflammatory responses over a two to three week period.

We recently initiated on Tiziana. 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. We maintain our target price of $7.50 per share.

PROJECTED FINANCIALS

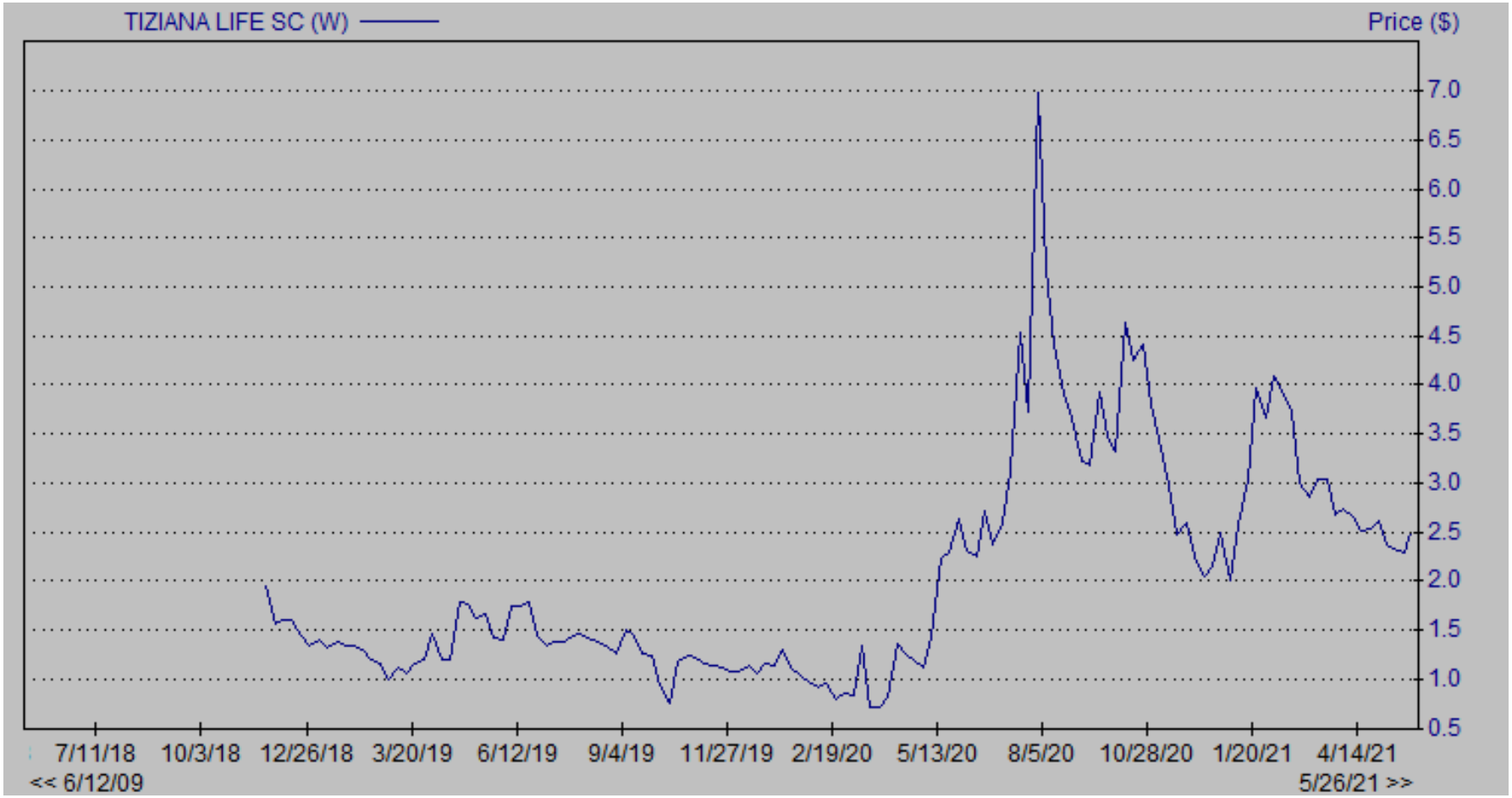
Tiziana Life Sciences PLC - Income Statement

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[5]



[5] Source: Zacks Research System

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