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Tonix Pharmaceuticals Holding Corp. (TNXP-NASDAQ)

TNXP: Targeting Organ Transplant Rejection with TNX-1500; Phase 1 Trial to Initiate 2H22…

Based on our probability adjusted DCF model that takes into account potential future revenues from TNX-102 SL in fibromyalgia, TNX-1500, TNX-1900 and TNX-1300, TNXP is valued at $1.50/share. This model is highly dependent upon continued clinical success of the company's assets and will be adjusted accordingly based upon future clinical results.

Current Price (03/31/22)	$0.22
Valuation	**$1.50**

OUTLOOK

On March 14, 2022, Tonix Pharmaceuticals Holding Corp. (TNXP) announced financial results for the fourth quarter and full year 2021 and provided a business update. The company recently highlighted data for TNX-1500, an anti-CD40L monoclonal antibody (mAb), showing long-term rejection free graft survival in heart and kidney allografts in non-human primates (NHPs). CD40L is a member of the tumor necrosis alpha (TNF-α) superfamily and helps to mediate T cell helper function. TNX-1500 is a third-generation anti-CD40L mAb that has been engineered to reduce the risk of thrombosis while maintaining robust efficacy. We anticipate the company initiating a Phase 1 clinical trial for TNX-1500 in the second half of 2022. Additional indications for the asset include the prevention of xenograft (pig-to-human) rejection, allogeneic (human-to-human) transplant rejection, amyotrophic lateral sclerosis (ALS), and the treatment of autoimmune disease.

SUMMARY DATA

52-Week High	**$1.39**
52-Week Low	**$0.17**
One-Year Return (%)	**-82.69**
Beta	**1.23**
Average Daily Volume (sh)	**45,581,480**
Shares Outstanding (mil)	**534**
Market Capitalization ($mil)	**$118**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**17**
Insider Ownership (%)	**2**
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 2018 Estimate	**-1.4**
P/E using 2019 Estimate	**-1.5**

Risk Level	**Above Avg.**
Type of Stock	**Small-Value**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2021	0 A	0 A	0 A	0 A	0 A
2022	0 E	0 E	0 E	0 E	0 E
2023					0 E
2024					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2020	-$0.07 A	-$0.07 A	-$0.05 A	-$0.07 A	-$0.26 A
2021	-$0.05 E	-$0.05 E	-$0.05 E	-$0.06 E	-$0.20 E
2022					-$0.20 E
2023					-$0.18 E

WHAT'S NEW

Business Update

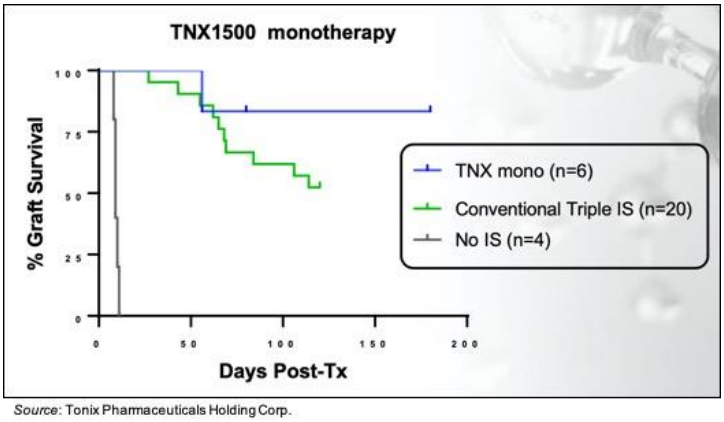
TNX-1500 to Enter Phase 1 Clinical Trial in 2H22

Tonix Pharmaceuticals Holding Corp. (TNXP) recently highlighted new preclinical data for TNX-1500 showing long-term rejection free graft survival in heart and kidney allografts in non-human primates (NHPs). The studies were conducted at Massachusetts General Hospital/Harvard Medical School. TNX-1500 is a third-generation anti-CD40 ligand (CD40L) monoclonal antibody (mAb) that is being developed for the prevention of allograft rejection, xenotransplantation, and the treatment of autoimmune disease.

The CD40/CD40L signaling pathway is involved in the activation of both the innate and adaptive immune response. CD40 is predominantly expressed on antigen presenting cells (APCs) and delivers intracellular activating signals. CD40L, which does not contain any signaling capacity, is found on multiple cell types, including T cells, B cells, natural killer (NK) cells, macrophages, and platelets (Schönbeck *et al*., 2001). The CD40/CD40L pathway is essential for humoral immune responses to T cell-dependent antigens (Lederman *et al*., 1992), the production of proinflammatory cytokines (Cella *et al*., 1996), and generating effective cytotoxic T cell responses (Liu *et al*., 2013).

For the heart allograft study in NHPs, TNX-1500 was dosed at 30 mg/kg twice weekly on days 0, 3, 7, and 14 followed by weekly dosing of 20 mg/kg from days 21 to 175. Results showed that in 4/5 heart transplants, there was no acute cellular injury (as judged by H&E staining) or chronic antibody injury (as judged by CD4 immunohistochemistry). The animals are currently being observed following cessation of therapy, but thus far there is prolonged organ acceptance. These results are similar to what was seen with hu5c8, a mouse/human IgGk1 chimeric anti-CD40L mAb, however treatment with hu5c8 caused thrombosis in some animals, which was not seen with TNX-1500.

For the kidney allo-transplantation study in NHPs, TNX-1500 was dosed at 20 mg/kg on days 0, 2, 7 and then weekly until day 180. The following chart shows that of the six recipients, no rejection was observed in five of them. This compares to treatment with conventional immunosuppressive therapy, in which 10 of 20 recipients showed organ rejection by day 120. The four recipients that did not receive any therapy all rejected the organ within a few days.



Source: Tonix Pharmaceuticals Holding Corp.

Another strategy being employed to facilitate long-term tolerance induction is the use of a combined kidney and bone marrow transplant (CKBMT; Kawai *et al*., 2008, Kawai *et al*., 2014). The end goal of this procedure is to have long-lasting, durable tolerance without the need for immunosuppressive therapy. The first step in the procedure is to severely deplete the recipients mature T cells. New protocols for T cell depletion are being developed that utilize anti-CD40L and/or anti-CTLA mAbs. In an NHP CKBMT trial, an NHP recipient received a conditioning regiment consisting of low dose total body irradiation, thymic irradiation, venetoclax, and thymoglobulin followed by a CKBMT. Four doses of TNX-1500 were administered over seven days and immunosuppressive treatment continued

until day 28. At one year, the kidney biopsy showed no signs of rejection, meaning the recipient achieved long-term immunosuppression-free survival.

In addition to its potential utility in preventing allograft rejection, TNX-1500 may also be utilized to prevent rejection in xenograft transplants. Given the shortage of human donor organs currently available, xenografts utilizing organs procured from genetically modified pigs may become a viable alternative. Multiple changes to the pig's genome aid in preventing tissue rejection, however following the transplant it is still necessary for the patient to be administered costimulation pathway blockers to prevent cell-mediated immune rejection. Previous work has shown that blockade of the CD40-CD40L interaction is associated with the longest pig-to-primate xenograft survivals (Samy *et al*., 2017).

Lastly, TNX-1500 may be utilized as a treatment for autoimmune diseases such as rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus (SLE), and Crohn's disease. In mice, genetic knockout of CD40L results in protection from multiple experimental autoimmune diseases, including experimental allergic encephalomyelitis (Grewal *et al*., 1996). In addition, CD40L expression is increased on a number of cell subsets in patients with systemic lupus erythematosus (Desai-Mehta *et al*., 1996) and on circulating T cells from patients with rheumatoid arthritis and psoriatic arthritis (Daoussis *et al*., 2006), thus supporting its role in autoimmune disease. Development of first-generation anti-CD40L mAbs had to be halted after multiple reports of thromboembolic complications (Kawai *et al*., 2000). This risk is thought to result from the IgG constant region interacting with FcγRIIA (Robles-Carrillo *et al*., 2010). Second- and third-generation anti-CD40L mAbs have been engineered to reduce binding to FcγRIIA, and while second-generation molecules have exhibited decreased efficacy, TNX-1500 is designed to preserve FcRn function and deliver efficacy without an increased safety risk.

Tonix will be conducting a pre-IND meeting with the FDA such that a Phase 1 clinical trial can be initiated in the second half of 2022. The first indication for TNX-1500 will be kidney allotransplantation, with the goal of replacing nephrotoxic calcineurin inhibitors. Additional indications will include heart or kidney xenotransplantation, the treatment of the rare neurodegenerative condition amyotrophic lateral sclerosis (ALS), and autoimmune diseases. The company has filed composition of matter patents for TNX-1500 and manufacturing of the antibody is in progress in preparation for the first clinical trial.

Update on TNX-102 SL for Fibromyalgia

On March 21, 2022, Tonix announced that, as expected based on a previously reported pre-specified interim analysis, TNX-102 SL did not achieve the primary endpoint of reducing fibromyalgia (FM) daily pain at Week 14 in the Phase 3 RALLY trial. The RALLY study was a 14-week randomized, double blind, placebo controlled trial of TNX-102 SL 5.6 mg in which 514 subjects with FM were randomized 1:1 to receive either TNX-102 SL 2.8 mg or placebo for the first two weeks followed by TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or two placebo tablets for the remaining 12 weeks.

In December 2020, Tonix announced positive topline results for the Phase 3 RELIEF study of TNX-102 SL 5.6 mg (primary endpoint, *P*=0.010). The disparate outcomes between the RELIEF study and RALLY study are hard to reconcile, however a look at the results of the RALLY study may offer some insight into why it was unsuccessful.

There was a 79% and 77% increase in the number of adverse event-related participant discontinuations in the drug treatment group and placebo group, respectively, in the RALLY study compared to the RELIEF study, as shown in the following table.

Table 1. Increases in AE-Related Discontinuations in RALLY Compared with RELIEF in Both Placebo and TNX-102 SL Groups

	RALLY (F306)	RELIEF (F304)	RALLY (F306)	RELIEF (F304)
	Placebo		TNX-102 SL	
Patients with at least one TEAE leading to early discontinuation	6.2%	3.5%	15.2%	8.5%
Ratio of patients with at least one TEAE leading to early discontinuation in F306 to F304 (F306/F304)	1.77		1.79	

TEAE = treatment-emergent adverse event

Source: Tonix Pharmaceutical Holdings Corp.

To account for missing data (i.e., when a patient discontinues the data that would have been collected for them is considered 'missing'), the statistical analysis is performed using a method called 'multiple imputation' (MI), which ultimately results in a negative impact from the missing data. For example, the following table shows the results when performing the statistical analysis with and without MI. Without MI, the results of the RELIEF and the RALLY trials appear consistent.

Table 2: Comparisons of Analytic Methods on Primary and Secondary Endpoints at Week 14 Between the RALLY and RELIEF Phase 3 Studies of TNX-102 SL 5.6 mg in Fibromyalgia

	RALLY (F306)			
	MMRM+MI*		MMRM**	
Endpoints	LSMD (SE)	*p*-value	LSMD (SE)	*p*-value
Pain by Diary	-0.2 (0.16)	**0.115**[#]	-0.4 (0.16)	0.014
FIQR Symptom domain	-1.9 (1.52)	0.216	-3.4 (1.55)	0.030
FIQR Function domain	-0.4 (1.46)	0.797	-1.6 (1.48)	0.266
PROMIS Sleep Disturbance	-2.3 (0.80)	0.004	-3.3 (0.73)	<0.001
PROMIS Fatigue	-1.2 (0.74)	0.101	-2.0 (0.73)	0.007
Sleep Quality by Diary	-0.3 (0.16)	0.094	-0.4 (0.16)	0.008
	RELIEF (F304)			
	MMRM+MI*		MMRM**	
Endpoints	LSMD (SE)	*p*-value	LSMD (SE)	*p*-value
Pain by Diary	-0.4 (0.16)	**0.010**[#]	-0.5 (0.16)	0.004
FIQR Symptom domain	-4.3 (1.60)	0.007	-5.6 (1.60)	<0.001
FIQR Function domain	-4.4 (1.69)	0.009	-5.2 (1.63)	0.001
PROMIS Sleep Disturbance	-2.9 (0.82)	<0.001	-3.3 (0.82)	<0.001
PROMIS Fatigue	-1.8 (0.76)	0.018	-2.1 (0.79)	0.007
Sleep Quality by Diary	-0.6 (0.17)	<0.001	-0.7 (0.17)	<0.001

Source: Tonix Pharmaceutical Holdings Corp.

FIQR = Fibromyalgia Impact Questionnaire-Revised; LSMD = least squares mean difference (between TNX-102 SL and placebo); MMRM = mixed model repeated measures; MI = multiple imputation; PROMIS = Patient-Reported Outcomes Measurement Information System; SE = standard error

* MMRM with MI was the pre-specified primary analysis

**MMRM without MI was a pre-specified analysis

[#] Primary efficacy endpoint: change from baseline in the weekly average of daily diary pain severity numerical rating scale scores

What could account for the dramatic increase in discontinuations in the RALLY study? While there are many potential reasons, one notable difference between the RALLY and RELIEF studies is that the RALLY study was taking place during the height of the COVID-19 pandemic when vaccines were being administered across the country. This may have contributed to a more challenging environment for participants in the trial.

Regardless, the company will now turn its attention to the Phase 3 RESILIENT study now that the COVID-19 pandemic is entering the endemic phase, which will hopefully lead to adverse event-related discontinuations returning to levels seen in the RELIEF and posttraumatic stress disorder (PTSD) studies. We anticipate the RESILIENT trial initiating in the first half of 2022.

Multiple Clinical Trials to Initiate Over the Next Year

Tonix has built a diverse pipeline that includes development candidates for COVID, biodefense, immunology, and multiple central nervous system (CNS) diseases. The company is expected to initiate a clinical trial for TNX-1300 in the near term, with multiple other trials initiating for other development candidates over the next year:

- TNX-1300: The company will be initiating a Phase 2 clinical trial of TNX-1300 for the treatment of cocaine overdose in the first half of 2022. TNX-1300 is a recombinant enzyme derived from the *CocE* gene of a *Rhodococcus* species that utilizes cocaine as a sole source of carbon and nitrogen (Bresler *et al*., 2000). Results from a previous Phase 2 clinical trial showed that the recombinant CocE enzyme (then called RBP-8000, now TNX-1300) rapidly degraded plasma cocaine levels in volunteer cocaine users and was safe and well tolerated.
- TNX-102 SL: Phase 3 RESILIENT trial in FM: Initiation – 1H22
- TNX-102 SL: Phase 2 trial in PTSD (in Kenya): Initiation – 1H22
- TNX-102 SL: Phase 2 trial in Long COVID: Initiation – 1H22
- TNX-1900: Phase 2 trial for chronic migraine: Initiation – 2H22
- TNX-601 CR: Phase 2 trial in Major Depressive Disorder: Initiation – 1Q23
- TNX-2100: First-in-human trial: Topline Data – 1H23

Financial Update

On March 14, 2022, Tonix announced financial results for the fourth quarter and full year 2021. As expected, the company did not report any revenues for the fourth quarter or full year 2021. Net loss for the fourth quarter of 2021 was $29.6 million, or $0.07 per share, compared to a net loss of $17.0 million, or $0.10 per share, for the fourth quarter of 2020. The weighted average common shares outstanding for the fourth quarter of 2021 were approximately 451.2 million compared to approximately 163.9 million for the fourth quarter of 2020.

R&D expenses for the fourth quarter of 2021 were $22.3 million, compared to $12.1 million for the fourth quarter of 2020. The increase was primarily due to increased clinical expenses, manufacturing expenses, non-clinical expenses, and employee-related expenses. G&A expenses for the fourth quarter of 2021 were $7.3 million, compared to $4.9 million for the fourth quarter of 2020. The increase was primarily due to an increase in employee-related expenses

For 2021, net loss available to stockholders was $92.3 million, or $0.26 per share, compared to a net loss of $52.2 million, or $0.55 per share, for 2020. The weighted average common shares outstanding for full year 2021 was approximately 360.2 million, compared to approximately 94.6 million for full year 2020. R&D expenses in 2021 were $68.8 million, compared to $36.2 million for 2020. The increase was primarily due to increased non-clinical expenses, manufacturing expenses, employee-related expenses, and regulatory/legal expenses. G&A expenses for 2021 were $23.5 million, compared to $14.4 million for 2020. The increase is primarily due to increased employee-related expenses, legal fees, investor relations expenses, and financial reporting expenses.

As of December 31, 2021, Tonix had approximately $178.7 million in cash and cash equivalents. Subsequent to the end of the year, the company sold 15.6 million shares of common stock in at-the-market (ATM) sales under a sales agreement with A.G.P. for net proceeds of approximately $4.3 million. In addition, the company sold 22.0 million shares under the purchase agreement with Lincoln Park for net proceeds of approximately $4.5 million. We estimate the company currently has sufficient capital to fund operations through the end of 2022. As of March 14, 2022, Tonix had approximately 533.9 million shares outstanding.

Conclusion

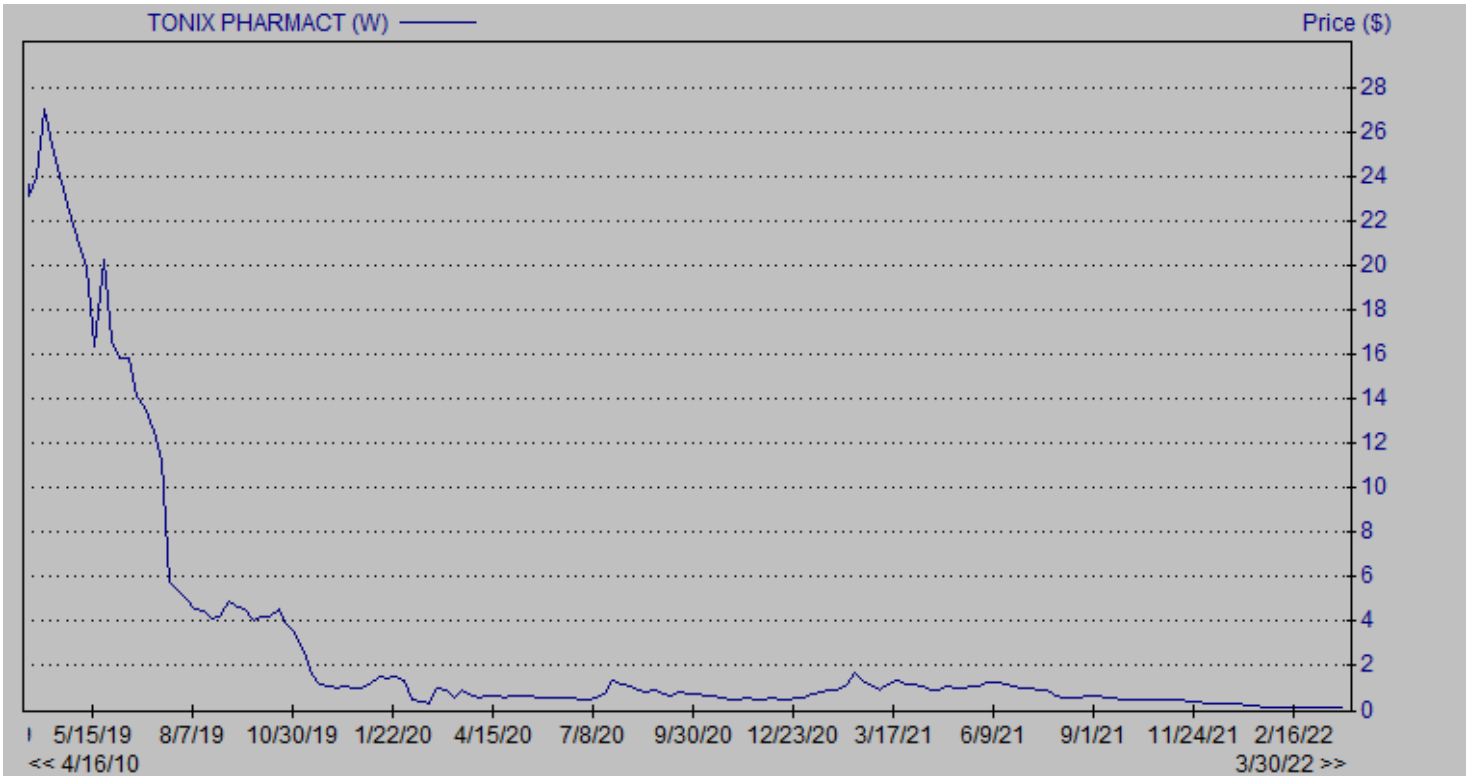
While it's unfortunate that the RALLY study did not meet the primary endpoint, we are glad to see Tonix moving ahead with the RESILIENT trial, as just one more successful Phase 3 trial is necessary before an NDA can be filed for TNX-102 SL in fibromyalgia. The company's move into monoclonal antibody development with TNX-1500 will be interesting to watch, as those assets typically draw partnering interests earlier than other types of compounds. Tonix recently raised $8.8 million from stock sales, and after accounting for the increased share count our valuation has decreased to $1.50.

PROJECTED FINANCIALS

Tonix Pharmaceuticals	2021 A	Q1 E	Q2 E	Q3 E	Q4 E	2022 E	2023 E	2024 E
TNX-102 SL (FM)	$0	$0	$0	$0	$0	$0	$0	$0
Research & Collaborations	$0	$0	$0	$0	$0	$0	$0	$0
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
CoGS	$0.0	$0	$0	$0	$0	$0.0	$0.0	$0.0
Product Gross Margin	-	-	-	-	-	-	-	-
R&D	$68.8	$18.0	$20.0	$22.0	$24.0	$84.0	$90.0	$95.0
SG&A	$23.5	$6.0	$6.5	$7.0	$7.5	$27.0	$30.0	$33.0
Operating Income	($92.3)	($24.0)	($26.5)	($29.0)	($31.5)	($111.0)	($120.0)	($128.0)
Operating Margin	-	-	-	-	-	-	-	-
Interest & Other Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1
Pre-Tax Income	($92.3)	($24.0)	($26.5)	($29.0)	($31.5)	($110.9)	($119.9)	($127.9)
Preferred Stock Deemed Dividend	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Warrant Deemed Dividend	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Taxes & Other	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($92.3)	($24.0)	($26.5)	($29.0)	($31.5)	($110.9)	($119.9)	($127.9)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.26)**	**($0.05)**	**($0.05)**	**($0.05)**	**($0.06)**	**($0.20)**	**($0.20)**	**($0.18)**
YOY Growth	*-53.6%*	-	-	-	-	*212.0%*	*-22.0%*	*-28.7%*
Weighted Shares Outstanding	360.2	530.0	540.0	550.0	560.0	545.0	600.0	700.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

HISTORICAL STOCK PRICE



Source: Zacks Small Cap Research

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