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Tonix Pharmaceuticals Holding Corp. (TNXP-NASDAQ)

TNXP: 50% Enrollment Reached in HONOR Trial; Interim Analysis in Mid-Summer…

Based on our probability adjusted DCF model that takes into account potential future revenues from TNX-102 SL PTSD, TNXP is valued at $11/share. This model is highly dependent upon continued clinical success of TNX-102 SL in PTSD and will be adjusted accordingly based upon future clinical results.

Current Price (05/29/18)	$3.09
Valuation	**$11.00**

OUTLOOK

Tonix Pharmaceuticals Holding Corp. (TNXP) recently announced financial results for the first quarter of 2018 and provided a business update. In April 2018, the company announced that the HONOR trial of TNX-102 SL in patients suffering from posttraumatic stress disorder (PTSD) is now 50% enrolled. A pre-specified interim analysis will be conducted following conclusion of the 12-week treatment period for those patients, with the results to be announced in mid-summer (third quarter of 2018). Potential outcomes from the interim analysis include 1) stopping the trial for success; 2) continuing to enroll the full study as planned; 3) continuing to enroll with a specified increase in the total number of participants in the full study.

SUMMARY DATA

52-Week High	**$4.83**
52-Week Low	**$2.76**
One-Year Return (%)	**-30.72**
Beta	**2.84**
Average Daily Volume (sh)	**87,863**
Shares Outstanding (mil)	**8**
Market Capitalization ($mil)	**$26**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**14**
Insider Ownership (%)	**4**
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	**-1.7**
P/E using 2019 Estimate	**-1.7**

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)
2017	0 A	0 A	0 A	0 A	0 A
2018	0 A	0 E	0 E	0 E	0 E
2019					0 E
2020					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$1.27 A	-$0.65 A	-$0.77 A	-$0.70 A	-$3.17 A
2018	-$0.88 A	-$0.63 E	-$0.63 E	-$0.63 E	-$2.77 E
2019					-$1.98 E
2020					-$2.03 E

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WHAT'S NEW

Business Update

HONOR Study 50% Enrolled

On April 3, 2018, Tonix Pharmaceuticals Holding Corp. (TNXP) announced that the Phase 3 HONOR trial of TNX-102 SL (cyclobenzaprine HCl sublingual tablet) in patients with posttraumatic stress disorder (PTSD) is now 50% enrolled. A pre-planned interim analysis is scheduled to take place following the 12-week treatment period concludes for those patients. We believe those results will be announced in mid-summer (third quarter of 2018).

Potential outcomes for the interim analysis, which will be conducted by an unblinded Independent Data Monitoring Committee (IDMC), include: 1) the study being stopped for success; 2) the trial continuing to enroll the full study (approximately 550 patients); 3) the trial continuing to enroll with a specified increase in the total number of subjects. The company is guiding for a *P* value of <0.01 being required for stopping the trial at the interim analysis for efficacy and a *P* value <0.045 for success of the full study when those results are announced in the first quarter of 2019.

Of the potential outcomes, we peg the probability for each outcome as follows: 25% - stopping the study early for success; 65% - continuing to enroll the fully study; 10% - continuing to enroll with an increased number of subjects. The first outcome is clearly positive, however we view the second outcome as positive as well since the study is 90% powered to reach statistical significance with 550 subjects. We view the last outcome, the necessity of enrolling additional patients, as neutral to negative (depending upon the number of additional patients to enroll).

We believe there are a number of reasons that the HONOR study is likely to be successful (either at the interim analysis or following analysis of the full results), including:

A) The homogeneity of the study population. Military-related PTSD is overwhelmingly comprised of men in their 30's who all experienced a relatively recent (average of ~7 years based on AtEase study) combat-related traumatic event. For a mental disorder, this is a remarkably homogenous population, meaning that results from one study to another are likely to be similar. Thus, since the demographics of the HONOR study are going to be very similar to the AtEase study, this increases the likelihood for success in the HONOR study.
B) CAPS-5 ≥ 33. For the Phase 2 study, the inclusion criteria included a CAPS-5 score of ≥ 29. Previous PTSD trials utilized CAPS-IV, and the CAPS-IV to CAPS-5 conversion was not a straight forward calculation, thus the ≥ 29 cutoff was determined partially arbitrarily. A post-hoc analysis of the Phase 2 AtEase trial showed that using a cutoff for the CAPS-5 of ≥ 33 increased the effect size from 0.36 to 0.52. Thus, we believe including only those with a CAPS-5 score ≥ 33 will result in an effect size more in line with the post-hoc analysis.
C) Increased number of patients. The Phase 2 AtEase study reached statistical significance even though the trial compared only 49 subjects on 5.6 mg TNX-102 SL to 92 subjects on placebo. For the interim analysis of the HONOR study, there should be approximately 140 subjects each treated with placebo or TNX-102 SL. Based on an approximate 25% dropout rate (which was what was seen for placebo patients in Phase 2 AtEase trial), that should result in approximately 100 patients evaluated in both the treated and placebo group.

Pharmacokinetic Study Complete

On May 24, 2018, Tonix announced the results of a Phase 1 pivotal bridging pharmacokinetic study on TNX-102 SL with AMRIX® (cyclobenzaprine HCL extended release [ER]) as the reference listed drug (RLD). The study was designed to compare the plasma levels of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) administered sublingually to the recommended dose of the RLD (AMRIX® 30 mg ER capsule) for 20 consecutive days of dosing on an empty stomach in healthy adults age 18-65. As expected, results showed that plasma levels of TNX-102 SL 5.6 mg are lower than AMRIX® 30 mg ER after 20 days of dosing. In addition, adverse events (AEs) were generally mild and transient and there were no discontinuations due to AEs. This study was a requirement before an NDA could be filed for TNX-102 SL and, as expected, the results signify that it qualifies to be filed under the 505(b)(2) pathway.

IND Clearance for Alzheimer's Agitation

Tonix recently announced that the FDA has cleared the IND for a Phase 2 clinical trial testing TNX-102 SL in patients with agitation in Alzheimer's disease (AD). While the company has yet to disclose how the study will be funded, we believe a partnership is the most likely scenario.

Agitation in Alzheimer's Disease

Agitated behaviors (e.g., irritability, restlessness, aggression) are a significant issue in patients with AD. Reports indicate that agitation occurs in approximately 50% of AD patients (Alzheimer's Association) and is a leading cause of institutionalization (Cohen *et al*., 1997). These behavioral disturbances have been linked with both cognitive decline (Teri *et al*., 1990) as well as increased caregiver burden, thus decreasing or eliminating them could be beneficial for both the patients and those taking care of them.

Agitation among dementia patients typically occurs in the late afternoon or evening and thus additional terms used to describe the condition include "sundown syndrome", "sundowning", and "nocturnal delirium". The terms all collectively refer to a set of neuropsychiatric symptoms that occur in elderly patients with dementia near sunset. The International Psychogeriatric Association defines Alzheimer's agitation as excessive motor activity such as pacing and restlessness, verbal aggression such as screaming and shouting, or physical aggression such as grabbing, pushing, and hitting that 1) is frequently recurrent for at least two weeks and 2) results in excess disability (e.g., impairment in interpersonal relationships). Due to the lack of a clear definition until recently, some prior studies referring to "sundown syndrome" included behaviors only in late afternoon while some included behaviors occurring throughout the night, thus making it difficult to draw comparisons across different studies.

The symptoms of agitation are generally seen in alterations of three main areas: mood, anxiety, and psychosis.

- Mood refers to emotional states such as sadness, happiness, irritability, and lability. In dementia patients, mood is typically disregulated and in addition to agitation this can also lead to depression.

- Anxiety is driven by an overactive "fight or flight" response, which is analogous to what is seen in patients with posttraumatic stress disorder (PTSD), particularly hyperarousal and hypervigilance.

- Psychosis, which results in disturbed perceptions, delusions, and disorganized thought processes, occurs in many dementia patients due to paranoid ideation.

There is no agreed upon theory as to the cause of agitation in AD, although there are a number of hypotheses, including:

- Unmet physical or psychological needs as a result of isolation at night (Cohen-Mansfield *et al*., 1990), fatigue (Cohen-Mansfield *et al*., 1995), or some other nonspecific unmet need (Evans, 1987).

- Disordered circadian rhythm manifested as increased nocturnal activity, later peak of daytime activity, and less correlation in body temperature with a 24-hour cycle (Volicer *et al*., 2001).

- Sleep disorders caused by the degradation of neuronal pathways that initiate and regulate sleep (Bliwise *et al*., 2004). Staedt *et al*. provide a comprehensive overview of the biological causes of sleep disruption in AD patients (Staedt *et al*., 2005). An additional factor affecting sleep may be restless leg syndrome, which was found to correlate with agitation in patients with AD (Rose *et al*., 2011).

Treatment of Agitation in AD

Currently there are no FDA approved therapies for agitation in AD and the treatments that are used are either not effective, have a number of potential serious side effects, or both. Treatment typically involves changes in the patient's environment and/or the off-label use of pharmaceutical agents.

Environmental Treatments: This typically takes the form of behavioral intervention and/or making sure that the individual's needs are being met and at this point is the first line of treatment for most patients. Caregivers are taught ways to help maintain a regular schedule for the patient, how best to reassure an agitated patient, and to increase attention to the patient's physical needs (incontinence, constipation, pain, etc.) to help mitigate potential triggers of agitation.

Pharmaceutical Treatments: Different classes of pharmaceutical agents are utilized based upon what area(s) are contributing to the agitated behavior (i.e., mood, anxiety, and/or psychosis). However, a medication that helps control one aspect will typically not help control another, thus potentially necessitating multiple medications. An ideal agitation treatment would target multiple aspects of the condition.

For alterations in mood, mood stabilizers (valproic acid or carbamazepine) or antidepressants (typically selective serotonin reuptake inhibitors, SSRIs) are most commonly used. The FDA has not approved any drugs from either class for the treatment of agitation in dementia. There is evidence for efficacy of antidepressants, however their use is also associated with adverse side effects (Porsteinsson *et al*., 2014).

Anxiety is typically treated with benzodiazepines (e.g., lorazepam). While effective at calming patients, they have serious tolerability issues and can have a negative impact on cognition, balance (potentially leading to falls), and potentially increase the risk of death (Saarelainen *et al*., 2017).

Antipsychotics are the most common medications prescribed to treat psychosis. While some atypical antipsychotics have shown superiority over placebo in treating agitation in AD (Ballard *et al*., 2009), in 2005 the FDA published a document regarding deaths related to the use of antipsychotics in elderly patients with behavioral disturbances (FDA, 2005) that led to a "black box" warning for this class of drugs in 2008.

TNX-102 SL for the Treatment of Agitation in AD

TNX-102 SL is a small, rapidly disintegrating tablet containing 2.8 mg of cyclobenzaprine (CBP) administered as two tablets (5.6 mg) for sublingual administration and transmucosal absorption. CBP is the active ingredient of two products that are FDA approved in the U.S. for the treatment of muscle spasms. These products are sold as immediate-release tablets and extended-release capsules. The sublingual formulation has a differentiated pharmacokinetic profile from the oral immediate-release CBP tablet, including faster onset of absorption and higher bioavailability.

Cyclobenzaprine has multiple activities that include antagonism of the 5-HT_{2A} receptor, the alpha-1 adrenergic receptor, and histamine H_1 receptor, thus potentially being able to impact mood, anxiety, and psychosis. Antagonism of the 5-HT_{2A} receptor is particularly important as it is known to be involved in sleep and waking functions (Landolt *et al*., 2009). Mirtazapine, an atypical antidepressant that is a 5-HT_{2A} receptor antagonist, was shown to be effective in a small, open-label study in treating agitation in AD (Cakir *et al*., 2008). In addition, animal models show that restorative sleep is known to clear toxic proteins from the brain, including those linked to AD such as beta amyloid and tau (Xie *et al*., 2013).

TNX-102 SL could potentially have a number of advantages over other treatments, including other 5-HT_{2A} antagonists, as the sublingual administration can overcome difficulty in swallowing that many AD patients experience and dosing at bedtime could help alleviate any potential anticholinergic effects during the day.

Other Compounds Under Development

There are a number of companies with compounds under development for the treatment of agitation in AD. Each of them is using the Cohen-Mansfield Agitation Inventory (CMAI) as the primary endpoint of their respective studies (Cohen-Mansfield *et al*., 1989). The CMAI is a 29-item caregiver rating questionnaire that is used to quantify the frequency of agitated behaviors in elderly individuals with cognitive impairment. Each of the descriptions of 29 agitated behaviors is rated on a 7-point scale.

- Avanir Pharmaceuticals (AVNR) is testing AVP-786 in TRIAD, a Phase 3 program that initiated in Nov. 2015 consisting of two clinical trials (TRIAD-1 and TRIAD-2) with a total of 705 patients. AVP-786 consists of a deuterated form of dextromethorphan and an ultra-low dose of quinidine. Dextromethorphan is mainly used as an over-the-counter cough suppressant, however at higher doses it acts as a nonselective serotonin reuptake inhibitor, a sigma-1 receptor agonist, and an NMDA receptor antagonist. When taken as a single agent, dextromethorphan is rapidly metabolized and thus does not reach sufficient plasma concentration to exert effects on the CNS. Replacing some of the hydrogen atoms of dextromethorphan with deuterium ("heavy hydrogen") slows down its metabolism. The addition of quinidine (an antiarrhythmic agent) further slows its metabolism through inhibition of CYP2D6, leading to an increase in dextromethorphan's plasma concentration.

- Axsome Therapeutics (AXSM) is testing AXS-05 in a Phase 2/3 trial of 435 patients randomized 1:1:1 to AXS-05, bupropion (Wellbutrin®), or placebo. AXS-05 is a combination of dextromethorphan and bupropion.

Just as for AVP-786, the combination of bupropion and dextromethorphan results in decreased metabolism of dextromethorphan (leading to increased plasma concentration) due to bupropion's inhibition of CYP2D6. Bupropion may also exert some effects in the CNS.

- Acadia Pharmaceuticals (ACAD) is testing pimavanserin (Nuplazid®) in the Phase 2 SERENE study, which was initiated in Nov. 2016 and is scheduled to enroll 432 patients. Pimavanserin is an atypical antipsychotic that is currently approved for the treatment of Parkinson's disease psychosis. Unlike other antipsychotics it is not a dopamine receptor antagonist, but instead is a highly selective antagonist of the 5-HT_{2A} receptor.

- Intracellular Therapeutics (ITCI) is testing ITI-007 in a Phase 3 clinical trial that initiated in June 2016 and is expected to enroll 360 patients. Like pimavanserin, ITI-007 is a 5-HT_{2A} receptor antagonist, however unlike other atypical antipsychotics it has a 60-fold difference in affinities for the 5-HT_{2A} receptor and D_2 receptors, which may improve effectiveness and lead to a more benign side effect profile.

Financial Update

On May 14, 2018, Tonix announced financial results for the first quarter of 2018. As expected, the company did not report any revenues. Net loss for the first quarter of 2018 was $6.9 million, or $0.88 per share, compared to a net loss of $5.1 million, or $1.27 per share, in the first quarter of 2017. R&D expenses were $5.2 million in the first quarter of 2018 compared to $3.0 million in the first quarter of 2017. The increase was predominantly due to a multiple-dose, randomized, open label, pharmacokinetic bridging study that was conducted primarily in the first quarter of 2018. G&A expenses were $1.8 million in the first quarter of 2018 compared to $2.1 million in the first quarter of 2017. The decrease was primarily due to a reduction in cash and stock-based compensation.

Tonix exited the first quarter of 2018 with approximately $19.3 million in cash and cash equivalents. Cash burn for the first quarter of 2018 was approximately $6.8 million, which was slightly higher than the previous few quarters due to the bridging study. We anticipate cash burn of approximately $5 million for each of the next three quarters. As of May 10, 2018, Tonix had approximately 8.5 million shares outstanding and when factoring in options and reasonably priced warrants a fully diluted share count of approximately 9.1 million.

Conclusion

We are looking forward to hearing the outcome from the interim analysis of the HONOR study this summer. We believe the most likely outcome is the study continuing to enroll as planned, with an outside shot at the study being stopped early for efficacy. Given the current enrollment pace we believe the full results from the study would be available during the first quarter of 2019.

The agitation in Alzheimer's indication provides an expansion of the company's pipeline and another potential area where the mechanism of action for TNX-102 SL could be utilized to assist patients that don't have any current treatment options. However, the company will need additional funding to initiate a clinical trial in Alzheimer's agitation, and with all focus on the PTSD study we don't believe anything will occur until the second half of 2018.

Our valuation for Tonix is derived from a probability adjusted discounted cash flow model that takes into account potential future revenues from the sale of TNX-102 SL in PTSD. Of the approximately 8 million individuals in the U.S. who suffer from PTSD, it's estimated that approximately 20% seek treatment. With a peak market share of only 6%, we currently estimate that peak sales of $650 million are possible. Using a discount rate of 18% and a 50% probability of approval leads to a net present value for the PTSD program of $83 million. Combined with the company's current cash position and dividing by a reasonable fully diluted share count of 9.1 million shares leads to a valuation of approximately $11 per share.

PROJECTED FINANCIALS

Tonix Pharmaceuticals	2017 A	Q1 A	Q2 E	Q3 E	Q4 E	2018 E	2019 E	2020 E
TNX-102 SL (PTSD)	$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	$13.3	$5.2	$3.5	$3.5	$3.5	$15.7	$14.4	$16.5
SG&A	$7.9	$1.8	$1.8	$1.9	$1.9	$7.4	$7.5	$8.0
Operating Income	($21.3)	($7.0)	($5.3)	($5.4)	($5.4)	($23.1)	($21.9)	($24.5)
Operating Margin	-	-	-	-	-	-	-	-
Interest & Other Income	$0.2	$0.1	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1
Pre-Tax Income	($21.1)	($6.9)	($5.3)	($5.4)	($5.4)	($22.9)	($21.8)	($24.4)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($21.1)	($6.9)	($5.3)	($5.4)	($5.4)	($22.9)	($21.8)	($24.4)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($3.17)**	**($0.88)**	**($0.63)**	**($0.63)**	**($0.63)**	**($2.77)**	**($1.98)**	**($2.03)**
YOY Growth	*-79.4%*	-	-	-	-	*-12.6%*	*-28.4%*	*2.6%*
Weighted Shares Outstanding	6.7	7.9	8.3	8.5	8.5	8.3	11.0	12.0

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

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