Zacks Small-Cap Research

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Tonix Pharmaceuticals Holding Corp. (TNXP-NASDAQ)

TNXP: Ready to File IND to Study TNX 102-SL in Agitation in Alzheimer's Disease…

Based on our probability adjusted DCF model that takes into account potential future revenues from TNX-102 SL PTSD, TNXP is valued at $13/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 (01/08/18)	$3.59
Valuation	**$13.00**

OUTLOOK

Tonix Pharmaceuticals Holding Corp. (TNXP) recently announced the company completed a pre-IND meeting with the U.S. FDA for TNX-102 SL as a clinical candidate for agitation in Alzheimer's disease. We believe the company is in a position to file an IND in the first quarter of 2018.

Agitation in patients suffering from Alzheimer's disease is one of the top reasons for institutionalization and is a significant burden on the healthcare system in the U.S. TNX-102 SL can help improve sleep quality, and poor sleep quality is linked to agitation thus providing supportive rationale for its use in the indication.

SUMMARY DATA

52-Week High	**$6.32**
52-Week Low	**$2.85**
One-Year Return (%)	**-37.10**
Beta	**2.92**
Average Daily Volume (sh)	**59,233**
Shares Outstanding (mil)	**8**
Market Capitalization ($mil)	**$28**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**18**
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 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Value**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0 A	0 A	0 A	0 A	0 A
2017	0 A	0 A	0 A	0 E	0 E
2018					0 E
2019					0 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$7.41 A	-$4.97 A	-$2.90 A	-$2.08 A	-$15.41 A
2017	-$1.27 A	-$0.65 A	-$0.77 A	-$0.74 E	-$3.23 E
2018					-$2.55 E
2019					-$1.99 E

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WHAT'S NEW

Business Update

Tonix Pharmaceutical Holdings Corp. recently announced the company had completed a pre-IND meeting with the U.S. Food and Drug Administration (FDA) regarding the use of TNX-102 SL (cyclobenzaprine HCl sublingual tablet) for agitation in Alzheimer's disease (AD). The company is planning to file an IND in the first quarter of 2018 such that it can initiate a Phase 2 study once additional financing is in place. 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) 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 $5\text{-}HT_{2A}$ 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 $5\text{-}HT_{2A}$ receptor antagonist, however unlike other atypical antipsychotics it has a 60-fold difference in affinities for the $5\text{-}HT_{2A}$ receptor and D_2 receptors, which may improve effectiveness and lead to a more benign side effect profile.

Conclusion

Tonix is interested in testing TNX-102 SL in a number of different indications, with agitation in AD being the first. We believe this is a prudent choice given the lack of any approved therapeutics, the large market opportunity, and the fact that cyclobenzaprine could potentially impact the three main areas that drive agitation. The company is fully focused on the Phase 3 study of TNX-102 SL in posttraumatic stress disorder (PTSD), which will have an interim analysis in the third quarter of 2018, however we see agitation in AD as a good next step in the life cycle of TNX-102 SL. We anticipate additional details regarding the Phase 2 study following submission of the IND in the first quarter of 2018. With Phase 3 data in PTSD anticipated later in 2018 we continue to believe Tonix is undervalued and our current valuation is $13 per share.

PROJECTED FINANCIALS

Tonix Pharmaceuticals Holding Corp.
Income Statement

Tonix Pharmaceuticals	2016 A	Q1 A	Q2 A	Q3 A	Q4 E	2017 E	2018 E	2019 E
TNX-102 SL (PTSD)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Research & Collaborations	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
CoGS	$0.0	$0	$0	$0	$0	$0.0	$0.0	$0.0
Product Gross Margin	-	-	-	-	-	-	-	-
R&D	$28.5	$3.0	$2.8	$3.9	$3.5	$13.2	$12.0	$13.0
SG&A	$10.4	$2.1	$2.0	$1.9	$2.1	$8.1	$8.5	$9.0
Operating Income	($39.0)	($5.1)	($4.8)	($5.8)	($5.6)	($21.3)	($20.5)	($22.0)
Operating Margin	-	-	-	-	-	-	-	-
Interest & Other Income	$0.1	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1
Pre-Tax Income	($38.8)	($5.1)	($4.8)	($5.8)	($5.6)	($21.2)	($20.4)	($21.9)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($38.8)	($5.1)	($4.8)	($5.8)	($5.6)	($21.2)	($20.4)	($21.9)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($15.41)**	**($1.27)**	**($0.65)**	**($0.77)**	**($0.74)**	**($3.23)**	**($2.55)**	**($1.99)**
YOY Growth	*-46.2%*	-	-	-	-	*-79.0%*	*-21.0%*	*-21.9%*
Weighted Shares Outstanding	2.5	4.0	7.3	7.5	7.5	6.6	8.0	11.0

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

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