Zacks Small-Cap Research

March 31, 2014
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Tonix Pharmaceuticals

(TNXP-NASDAQ)

TNXP: Nice Buying Opportunity In Tonix Pharmaceuticals…

Current Recommendation	**Buy**
Prior Recommendation	Neutral
Date of Last Change	11/13/13
Current Price (03/31/14)	$10.30
Target Price	**$16.00**

We continue to be positive on shares of Tonix Pharmaceuticals. We believe the company's novel sublingual formulation of cyclobenzaprine has significant utility in the treatment of fibromyalgia and PTSD. We discuss the candidate for both indications below, as well as introduce TNX-201, the company's new candidate for tension headaches. We have conducted a sum-of-parts valuation for Tonix Pharmaceuticals that incorporates our three forecasts for sales of TNX-120SL in fibromyalgia and PTSD and TNX-201 in ETTH noted below. We believe the shares are fairly-valued at between $16 to $18 per share, and recommend purchase at today's price.

SUMMARY DATA

52-Week High	**$18.67**
52-Week Low	**$2.50**
One-Year Return (%)	**44.44**
Beta	**1.86**
Average Daily Volume (sh)	**185,808**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$101**
Short Interest Ratio (days)	**0.37**
Institutional Ownership (%)	**8**
Insider Ownership (%)	**N/A**
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 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

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

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	0 A	0 A	0 A	0 A	0 A
2014	0 E	0 E	0 E	0 E	0 E
2015					0 E
2016					0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.93 A	-$0.95 A	-$0.87 A	-$0.74 A	-$3.37 A
2014	-$0.35 E	-$0.39 E	-$0.42 E	-$0.45 E	-$1.62 E
2015					-$1.54 E
2016					-$1.33 E

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WHAT'S NEW

Financial Update

On March 31, 2014, Tonix Pharmaceuticals (TNXP) reported financial results for the fourth quarter and full year ending December 31, 2014. The company did not report any revenues in 2013, in-line with expectations and our financial model. Net loss in the fourth quarter totaled $3.7 million, or 74 cents per share. Loss was driven by $1.3 million in R&D and $2.4 million in SG&A. SG&A expense in the quarter was around $1.0 million higher than expected and up substantially from the three previous quarters in 2013. During the fourth quarter, the company recorded approximately $0.5 million in stock-based compensation. For the full year 2013, net loss totaled $10.9 million, or $3.37 per share. Loss was driven by $4.7 million in R&D and $6.2 million in SG&A expense. Stock-based compensation for the full year 2013 totaled $1.7 million, which we consider to be high for a company with only six full time employees, only three of which are executives.

Tonix exited December 31, 2013 with $8.2 million in cash and investments. Operating burn in the fourth quarter totaled $3.6 million. For the full year 2014, operating burn totaled $8.5 million. In January 2014, Tonix raised approximately $40.7 million in cash through a public offering. Tonix offered approximately 2.9 million shares at an offering price of $15.00 per share. Besides this public offering, Tonix has also received approximately $4.8 million in warrant exercises during the first quarter 2014. With an expected operating burn of $3.0 million in the first quarter 2014, we now expect the company to report cash and investments of $50.8 million in cash and investments. As of March 24, 2014, we calculate the (reasonable) fully-diluted share count as 12.7 million, meaning Tonix has approximately $4.00 in current cash per share on hand.

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Update On TNX-102SL In Fibromyalgia

Enrollment in the Phase 2b/3 BESTFIT trial continues ahead of plan. In fact, enrollment is ahead of schedule and management has made the decision to expand the current Phase 2b portion from 120 patients to 200 patients. We believe this is a testament to the size and under-served nature of the disease. BESTFIT is a randomized, double-blind, placebo-controlled 12-week safety and efficacy studies in fibromyalgia patients who will take either a TNX-102 SL (cyclobenzaprine HCl 2.8 mg) tablet or placebo at bedtime.

The primary endpoint of both trials will be the change in pain from baseline to Week 12 as measured by the Numeric Rating Scale (NRS). We note the primary endpoint planned for these trials is similar to that utilized by Pfizer and Eli Lilly to gain approval for Lyrica and Cymbalta, respectively, for the treatment of fibromyalgia syndrome. Placebo response will be a key issue to watch. Tonix plans to include a 1-2 week wash-out period prior to randomization. We note the Pfizer phase 3 study with Lyrica showed a placebo response rate of nearly 50%. The company will also collect information on secondary endpoints, including NRS scores at other time points during the 12 week study, the Fibromyalgia Impact Questionnaire (FIQ), and the Patient Global Impression of Change (PGIC). Despite increasing the size of the trial by 66%, management still expects top-line data in the fourth quarter 2014.

…Feeling Good About The Trial…

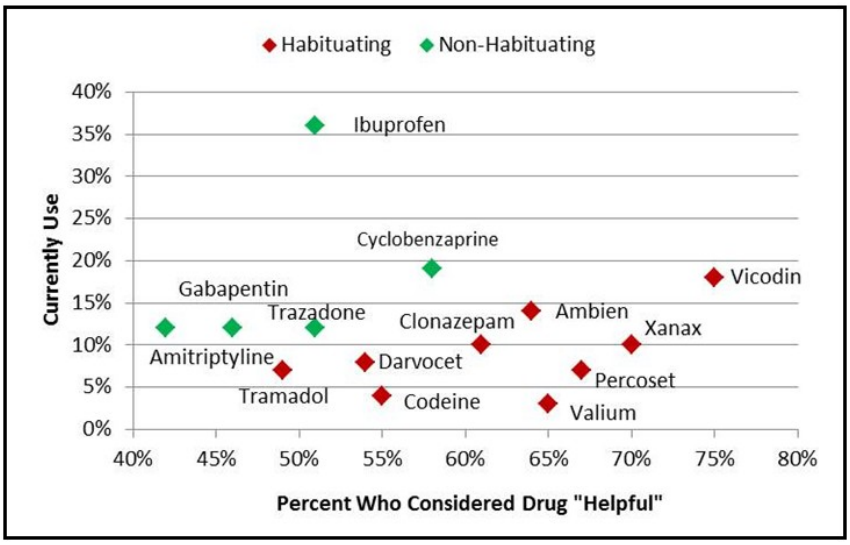
We continue to be confident in the outcome of the BESTFIT trial based on the significant clinical and real-world efficacy of cyclobenzaprine for the treatment of fibromyalgia. For example, a paper by Bennett (2007) describes an internet survey of 2,596 fibromyalgia patients. This study unfortunately occurred before Lyrica, Cymbalta, or Savella were approved in this indication, but is informative regarding patient perceptions of relative effectiveness of the other drugs. The scatterplot below shows the responses of patients to questions regarding the effectiveness of various drug treatments as well as what drugs they are currently taking. Several factors stand out:

- ⇨ Ibuprofen is widely used but not being considered exceptionally effective. This outcome likely reflects prescriber perceptions of a relatively benign side effect profile for this drug.

- ⇨ Medications receiving the highest effectiveness ratings from patients include:
  - → The narcotic painkillers Vicodin and Percoset;
  - → Anxiolytic benzodiazepines such as Xanax, Clonzaepam, Valium, and
  - → The sleep aid Ambien, which in many patients loses effectiveness over time

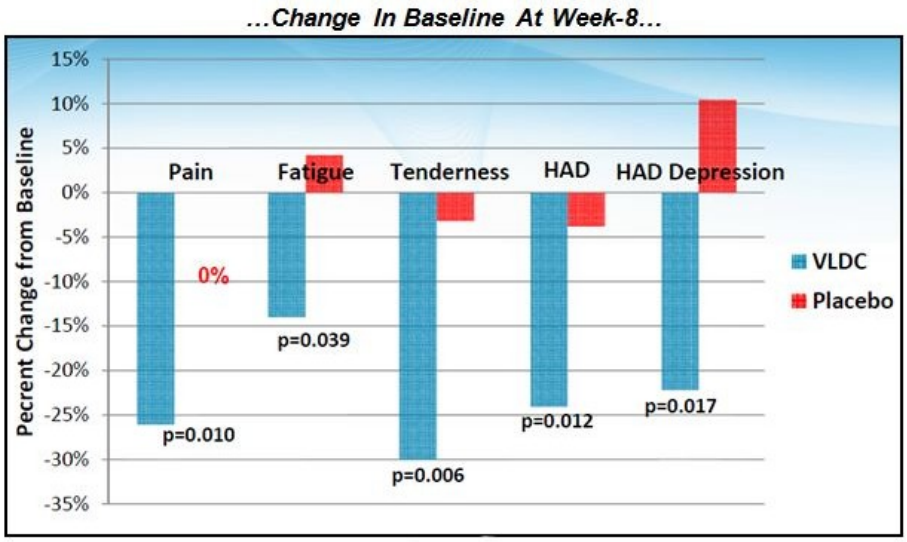
The medications most widely regarded as effective by patients are not the most widely used, as they tend to be those which raise prescriber concerns regarding the potential for habituation or need for escalating doses to maintain the same level of efficacy (tachyphylaxis). Among the medications with limited habituation and tolerance liabilities, cyclobenzaprine stands out as being perceived as effective by the highest percentage of patients.

Current Medication Use Vs. Patient-Percieved Effectiveness



Findings by Bennett are backed-up by market research conducted by Frost & Sullivan. Frost & Sullivan concluded the total prescription market for fibromyalgia in 2010 was approximately $1.2 billion, with an annual growth rate of 18% between 2007 and 2010. According to Frost & Sullivan, 48 million doses of the cyclobenzaprine (branded and generic) products were prescribed off-label for fibromyalgia in 2010. These figures indicate that muscle relaxants in general, and CBP in particular, have been widely adopted in fibromyalgia despite the lack of an approval for this disorder. This marries well with research from Decision Resources. The firm estimates that approximately $1.1 billion of the $1.3 billion market in 2011 was on-label sales of Lyrica (~$450M), Cymbalta (~$550M), and Savella (~$100M), with the other $0.2 billion coming from off-label use of drugs like Tramadol, naltrexone, and cyclobenzaprine. We note that dollar sales of off-label cyclobenzaprine are muted by the low cost of the generic molecules. In actual prescription numbers, Tonix management estimates that cyclobenzaprine is third most commonly prescribed drug for the disease.

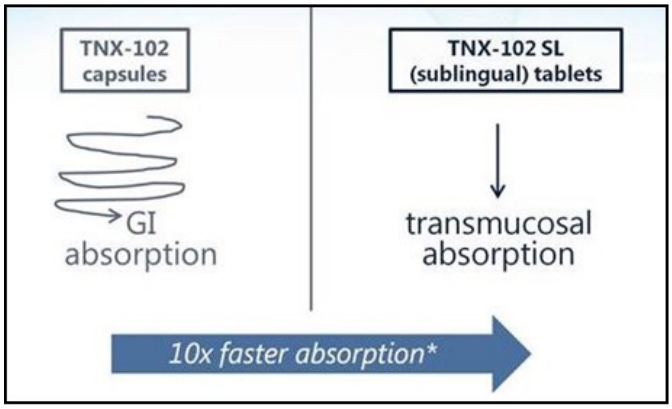
In December 2011, data from a phase 2a study with a low dose formulation of cyclobenzaprine was published by the Sleep Disorders Clinics of the Centre for Sleep and Chronobiology, University of Toronto, Ontario, Canada (supported by Tonix Pharmaceuticals) in the Journal of Rheumatology (38(12):2653-63). The paper is called, "Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study" and strongly supports clinical utility of the drug for the treatment of fibromyalgia. The trial was a randomized, double-blind, placebo-controlled, dose-escalating, parallel-design study in patients with fibromyalgia and disrupted sleep. A total of 36 patients (1:1 very low dose (VLD) cyclobenzaprine vs. placebo) were treated for 8 weeks. We present the key findings form the data below in graph form.



...Sublingual Administration Provides a Pharmacokinetic Profile Ideal for Bedtime Dosing...

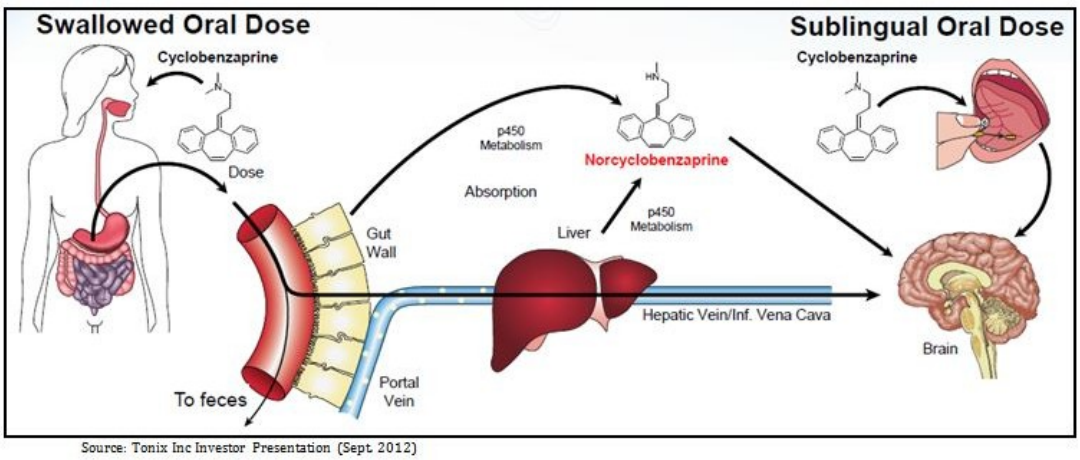
In order to obtain a pharmacokinetic profile that is optimized for addressing sleep disruption in fibromyalgia, Tonix is developing a sublingual very low dose cyclobenzaprine formulation, TNX-102-SL. This novel sublingual formulation is designed specifically for bedtime dosing in patients with FM. TNX-102-SL is a novel formulation with rapid absorption and minimal next-day somnolence.

When cyclobenzaprine is administered by the traditional oral route, the time to peak serum concentrations is delayed due in part to the time required for the drug to travel through the digestive system to the intestines. It must then cross the lining of the intestine and be absorbed into the blood flow of the portal vein. It then travels into the liver before entering the general circulation. As described in the Flexeril package insert, the amount of cyclobenzaprine absorbed into the bloodstream varies between 33% and 55% of the dose ingested. The variability in absorption may be due to several factors, including effects of the stomach pH (acidity or base on the dissolution of the tablets, as well as the context of either an empty stomach or a recent meal. The uncertainties in absorption rates make it challenging for a physician contemplating a bedtime treatment for fibromyalgia to ensure the intended therapeutic effect is achieved without risking side effects like next-day drowsiness, which could result if the patient has too much cyclobenzaprine remaining in the bloodstream the next day.



Tonix management believes that a rapid and more predictable cyclobenzaprine product, like TNX-102SL, would see significant use by physicians and be in high demand by fibromyalgia patients with respect to the generic 5 mg Flexeril tablet. We concur, but do not fully rule-out generic substitution in our financial model. However, we note another added benefit to Tonix' SL formulation compared to the generic cyclobenzaprine.

Within the liver, cyclobenzaprine encounters drug metabolizing enzymes and is in part converted to des-methyl norepinephrine, a metabolite with similar biological activity and an extended serum half-life of 31 hours. A portion of the cyclobenzaprine is also excreted into the bile and thus back into the intestine. A fraction of this excreted material may be reabsorbed in a process called enterohepatic recirculation. This slows the transfer of drug from the intestines to the general circulation, such that a full four hours passes between taking the drug and peak serum levels. Overall, oral administration of cyclobenzaprine leads to a lengthy delay until peak serum levels are achieved, and once established, high serum levels persist for up to a full day. Furthermore, a long-lived biologically active metabolite is formed that exacerbates the effects of the persistently high serum levels of the parent drug.



Source: Tonix Inc Investor Presentation (Sept. 2012)

For rapid sleep onset, the patient must remember to take a tablet several hours before bedtime. Thus, a patient may then remain groggy and sedated around the clock due to the slow absorption of the drug and the extended half-life of the nor-methyl metabolite. Daytime sedation is particularly problematic for fibromyalgia patients, who already struggle with chronic fatigue. Previous pharmacokinetic results demonstrated by Tonix show that more rapid effects compared with current generic cyclobenzaprine products, increased dosage precision and decreased potential for morning grogginess / residual effect. We believe these are key prescribing factors that will lead to market share gains for Tonix' drug once commercialized.

...Safety Extension Study...

In December 2013, Tonix announced that patients who have completed the BESTFIT trial will be eligible for enrollment in the F203 study, a 12-month open-label long-term safety exposure study. The primary objective of F203 is to evaluate the long-term safety and tolerability of TNX-102 SL taken sublingually at bedtime once-daily in patients with fibromyalgia. The secondary objective is to evaluate the long term efficacy of TNX-102 SL on the symptoms of fibromyalgia.

F203 has been accepted by the FDA as an abbreviated long-term safety exposure evaluation study is being conducted to support a 505(b)(2) new drug application for TNX-102 SL as a chronic medication for the management of fibromyalgia. We believe this is an important study with respect to the potential label for Tonix' drug because current generic formulations of cyclobenzaprine are limited to prescriptions lasting on "*up to two or three weeks*" based on the current prescribing information. We expect Tonix can gain approval for chronic use of TNX-102SL, thus providing another meaningful advantage of its candidate over generic substitutions.

Update On TNX-102SL In PTSD

In the third quarter 2014, Tonix plans to initiate a Phase 2 study with TNX-102SL for the treatment of post-traumatic stress disorder. This is the same formulation of sublingual low-dose cyclobenzaprine being used in the company's Phase 2b/3 BESTFIT study. Tonix was previously waiting for support from the U.S. Department of Defense (DOD) before they filed the IND for TNX-102SL in PTSD. However, with $45+ million cash raised during the first quarter 2014, management can now push-forward without DOD support. That's not to say the DOD may not still be involved in the planned Phase 2 trial, but Tonix doesn't have to wait for them. Almost all-things government related were at a stand-still in November and December 2013, so the ability to push-forward alone is huge for Tonix.

As for PTSD, there is enormous overlap between Fibromyalgia and PTSD. According to Tonix, 50% of the FM or PTSD patient population meets the criteria for the other disorder. Plus, the manifestations and treatment paradigms are similar, and include disturbed sleep and painkiller abuse and addition.

...Medical & Psychiatric Comorbidity...

Medical	Prevalence	Psychiatric	Prevalence
Chronic Fatigue Syndrome	20-80%	Major Depressive Disorder	62%
Irritable Bowel Syndrome	32-80%	Bipolar Disorder	11%
Temporomandibular Disorder	75%	Panic Disorder	29%
Tension / Migraine Headaches	10-80%	Post-Traumatic Stress Disorder	21%
Chemical Sensitivities	33-35%	Social Phobias	19%
Interstitial Cystitis	13-21%	Obsessive Compulsive Disorder	7%
Chronic Pelvic Pain	18%		

Source: Aaron LA, et al. *BestPract Res Clin Rheumatol.* 2003;17:563-574; & Arnold LM, et al. *J Clin Psychiatry.* 2006;67:1219-1225.

Roughly 3.5% of the U.S. adult population suffers from PTSD. The numbers are shockingly high for U.S. military service personal, a population with high incidence of suicide and opioid addiction. It's a sad and growing problem, and there have been no new approved medications for PTSD in over a decade. Tonix is preparing to start a Phase 2 study of TNX-102SL in PTSD associated with military / combat service in the third quarter 2014. Although management has narrowed the PTSD population, eliminating things like car accidents and sexual assault, the homogenous population should lead to improved data collection. Plus, the growing attention of the U.S. government in this area should eventually lead to grants or additional funding in the future. It's an astute development plan in our view.

Intellectual Property

The patent portfolio for TNX-102 SL includes patent applications directed to pharmaceutical compositions containing cyclobenzaprine and various formulations thereof, along with methods for treating fibromyalgia and other CNS conditions utilizing cyclobenzaprine. The portfolio includes issued U.S. Patents Nos. 6,541,523, 6,395,788 and 6,358,944, and corresponding issued foreign counterpart patents or applications. These U.S. are listed below and expected to expire in 2020, unless they are eligible for patent term extensions on the basis of FDA approvals.

Number	Name	Expiration
US 6,541,523	Methods for Treating or Preventing Fibromyalgia Using Very Low Doses of Cyclobenzaprine - USA	August 11, 2020
US 6,395,788	Methods and Compositions for Treating or Preventing Sleep Disturbances and Associated Illnesses Using Very Low Doses of Cyclobenzaprine - USA	August 11, 2020
US 6,358,944	Methods and Compositions for Treating Generalized Anxiety Disorder - USA	August 11, 2020

This may look like an area of concern for investors considering we are not expecting a NDA filing on TNX-102SL until 2017 and approval in 2018. However, Tonix has a number of applications pending. Management has stated that they have applied for patent protection for the unique pharmacokinetic profile of very low dose cyclobenzaprine administered sublingually, and for the eutectic mixture that makes this formulation possible. Specifically, U.S. Patent Application No. 13/918,692 seeks claims that would not expire until 2033.

We believe that these applications have a high probability of being granted and that they will be highly defensible. A eutectic mixture is a mixture of two compounds that is low melting, and thus rapidly-dissolving. Such mixtures are typically found by serendipity, and it would be very difficult for a competitor to identify an alternative mixture with similar properties. The pharmacokinetic application covers the actual rate and extent of absorption of the drug substance into the bloodstream. Thus the very profile required by the FDA for an ANDA filing is protected by the IP, even if a generic competitor is able to produce a non-infringing formulation that is bioequivalent. Purdue Pharma used this type of patent to protect its lucrative OxyContin franchise for many years, and it withstood multiple Paragraph IV challenges.

Other pending applications include U.S. application 13/157,270, “Methods and Compositions for Treating Fatigue Associated with Disordered Sleep Using Very Low Dose Cyclobenzaprine”, which was filed in 2011. Given its 2010 priority date, this application is expected to provide protection through 2030.

Reimbursement and Generic Competition

Important concerns for any company seeking to develop a reformulation of a generic drug are those of competition from the original formulation and the willingness of payers to reimburse for the new one. Recent examples in which reformulations failed to get traction with physicians and/or payers include the insomnia drugs Intermezzo, a sublingual reformulation of zolpidem for sleep maintenance insomnia, and Silenor, a low dose reformulation of doxepin for sleep onset insomnia. Launched in the first quarter of 2010, Silenor and Intermezzo have been complete commercial failures.

The commercial failure of Silenor (3 mg or 6 mg doxepin) is a direct result of the lack of differentiation between Silenor and generic 5 mg or 10 mg doxepin. To date, sales of Intermezzo (1.75 mg or 3.5 mg zolpidem tartrate SL) have been a significant disappointment to Transcept Pharmaceuticals and commercial partner, Purdue Pharma L.P. We believe this creates a significant perception hurdle for Tonix with investors, because Transcept did studies to show differentiation between Intermezzo 3.5 mg and generic 10 mg zolpidem (Ambien®), and uptake is still far below what both Transcept and Purdue had hoped.

We believe, however, that there are several important differences between the insomnia market and the fibromyalgia market. First, very few fibromyalgia patients describe their symptomatic relief as adequate in spite of taking an average of 2.5 medications supplemented by various forms of non-pharmacological therapy. These patients are profoundly ill, and the lack of satisfactory treatment options creates a tremendous driving force to try new therapies, even in the case of physicians who might normally regard reformulated drugs with skepticism. Furthermore, the ability to enhance sleep with drug formulation that provides minimal daytime exposure is a powerful marketing message in a therapeutic area in which fatigue is one of the most prominent patient complaints.

A second strong differentiator from the situation encountered by reformulated drugs for insomnia is that while the insomnia patient bears the great majority of the burden of inadequately treatment on their own, the costs of inadequately treated fibromyalgia are borne to a significant extent by payors. The cost of treating patients with fibromyalgia was examined in a Spanish study reported by Rivera et al (2012). Two hundred thirty two patients referred to rheumatology clinics with a diagnosis of fibromyalgia were evaluated at baseline for to determine their recent healthcare utilization. They were compared to a demographically matched control group of 110 healthy patients selected from clinic staff or accompanying relatives, both before and after optimization of medicinal therapies by a rheumatologist.

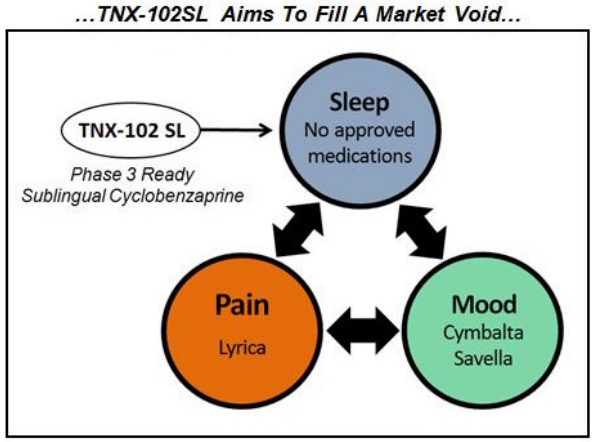
The study found that at baseline, total healthcare expenditures for the fibromyalgia patients averaged €423 per month, approximately 3.6-fold that of the healthy controls. At baseline, these expenses consisted primarily of physician visits and non-pharmacological therapies such as physical therapy, hydrotherapy, and psychotherapy. After three months of optimized medical therapy, total average expenditures fell to €335, a decrease of 21%.

The final differentiator is the willingness of the patient to seek pharmacological help. W note that over 50% of fibromyalgia patients visit their treatment physician over five times a year. Contrast this with the insomnia market where only roughly 10% seek pharmacological help, and the majority are satisfied with generic zolpidem. For these therapy seekers, nearly three-fourths spend between $100 and $500 per month on OTC medications and nearly two-thirds spend the same amount on prescription medications.

Revenue Model

Averaging the data obtained from the NIH, AFSA, and NFA, we estimate there are approximately 8 million Americans living with FM. Over 90% of these patients have sleep problems. Approximately 70% of these patients report difficult in conducting normal daily tasks, such as light housework due to chronic fatigue. According to Decision Resources, U.S. sales of prescription drugs specifically for the treatment of FM totaled $1.3 billion in 2011. This figure includes sales of Cymbalta, Lyrica, and Savella of $595 million, $504 million, and $110 million, respectively.

Despite the availability of FDA approved products, we believe the current treatment options for fibromyalgia continue to leave many patients dissatisfied. Existing approved fibromyalgia medications such as Lyrica and Cymbalta, which focus on reducing fibromyalgia -associated pain and mood disorder, respectively, do little to improve sleep quality. Insomnia medications such as Ambien and Lunesta improve total sleep time, but do little to improve the chronic fatigue associated with fibromyalgia.



If Tonix can gain approval for TNX-102-SL in fibromyalgia using standardized pain (NRS) endpoints in its Phase 2b and Phase 3 program, while also demonstrating improvement in symptoms of fatigue and sleep quality, we believe a meaningful market opportunity exists. Frost & Sullivan estimate that 48 million tablets of cyclobenzaprine were sold specifically for fibromyalgia in 2010. We believe at least a third of FM patients would actively seek out prescription therapy, either as a monotherapy or an adjunctive therapy to Lyrica or Cymbalta, with their physicians support, and try a novel sublingual formulation of very low dose cyclobenzaprine.

Based on the generic market, the target population for Tonix with TNX-102-SL is over 2 million patients. We think that the sublingual formulation clearly contains meaningful advantages over the generic oral formulation. These include rapid absorption and minimal next-day residual effects ideal for a bedtime dose, and avoidance of first pass metabolism and build-up of norcyclobenzaprine ideal for chronic dosing. Of course, all this will need to be confirmed in clinical trials.

For the purpose of our model, we assume Tonix (and its partner) can capture 5% share – that's one out of every twenty patients currently on generic oral cyclobenzaprine for FM switching to TNX-102-SL. At a cost of $10 per pill, with decent tier-2 and tier-3 coverage, we see TNX-102-SL as a $650 million peak drug. We expect that by 2017, both Lyrica and Cymbalta will be generic, and that Tonix commercial partner will have one of the only (if not the only) branded prescription medications for fibromyalgia available.

The U.S. PTSD population is estimated at a similar 8 million in size. We believe approximately 25% of these cases are associated with military service, about half of which seek medical treatment for the disease. This puts the U.S. military-associated PTSD population at around 1 million. Assuming similar pricing and market penetration as noted above for fibromyalgia, we believe TNX-102SL peak sales in PTSD are around $300 million.

TNX-201 Ready for Clinical Development

On March 3, 2014 Tonix Pharmaceuticals (TNXP) announced that they had recently held a pre-Investigational New Drug (pre-IND) meeting with the US. Food and Drug Administration (FDA) to discuss the development of TNX-201, a single isomer isometheptene (IMH) for the relief of episodic tension-type headache (ETTH).

…Tension Type Headaches…

Tension type headaches (TTH) are the most common type of headaches among adults and are also known as "stress headaches". These headaches were previously known by a number of terms, however the term "tension-type headache" was chosen by the International Classification Headache Diagnosis I (ICHD) in 1988 and later retained by ICHD II in 2004. The terms "tension" and "type" refer to the unknown nature of the underlying etiology, however a number of clinical studies have been performed that underscore their neurobiological basis.



ICHD II classified tension type headaches as either episodic (ETTH) or chronic (CTTH). ETTH are further subdivided into infrequent (occurring less than 12 days per year) or frequent (more than 12 days per year but less than 180 days per year). CTTH are characterized by an occurrence of more than 180 days per year. The clinical symptoms for the three types of headache are all similar and are only differentiated based on their frequency.

Approximately 20% of the world's population suffers from tension type headaches. Women are slightly more affected than men and the peak incidence occurs between the ages of 30-39 and decreases with increasing age. A 1997 study showed that lost workdays from TTH are as much as three times greater than from migraine headaches.

Despite numerous clinical studies, the exact cause of TTH remains elusive, however there are certain things that seem to trigger them including: stress and anxiety, squinting, poor posture, dehydration, noise, bright sunlight, tiredness and certain smells. TTH are known as primary headaches, which means that there is no underlying condition that causes them (such as a tumor or hemorrhage). Other types of primary headaches include migraines and cluster headaches.

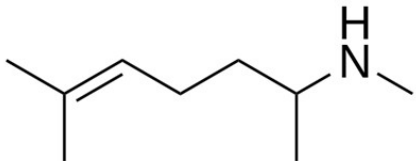
The pain associated with TTH is typically described as a dull pressure with the feeling of wearing a tight fitting band around the head. Clinical diagnosis of TTH is based on negative features (i.e., the absence of symptoms that characterize other headaches). Physical activity has no bearing on the intensity of the headache, which distinguishes TTH from migraine headaches where any type of physical activity worsens the pain. Nausea and vomiting, if present, precludes the diagnosis of TTH, while photophobia or phonophobia may be present but not concurrently.

Current treatment options for ETTH include over-the-counter analgesics such as ibuprofen, naproxen, acetaminophen, and aspirin, all of which have been shown to be more effective than placebo in controlled trials. Studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are most likely more effective than aspirin or acetaminophen, but these results are not unequivocal. Caffeine, codeine, sedatives, or tranquilizers are often combined with NSAIDs to increase their efficacy, however this can lead to the risk for dependency, abuse, and chronification of the headache.

The only currently FDA approved medications for the treatment of ETTH are fioricet and fiorinal, both of which contain butalbital, a barbiturate that can lead to dependency. These compounds have also been linked to Medication Overuse Headaches (MOH), also known as rebound headaches. These headaches occur through the overuse of pain medications to relieve primary headaches. They can occur frequently, can be very painful and are the third most common cause of headache. Regular use of over-the-counter medications such as ibuprofen and acetaminophen have also been linked to MOH, thus doctors typically advise limiting their use to not more than two days weekly. In addition to MOH, the overuse of acetaminophen has been linked to liver damage while the overuse of NSAID can cause gastrointestinal bleeding.

…A New Treatment Option…

Tonix has a stated mission of developing new pharmaceutical products for central nervous system (CNS) conditions that may be safer and more effective than what is currently available. The company does this by searching for potential therapeutic solutions among already existing pharmaceutical agents that have been used successfully in patients for other conditions. This strategy is being applied to the company's Phase 2/3 candidate, TNX-102SL, a low-dose cyclobenzaprine under investigation for the treatment of fibromyalgia, and now to the treatment of ETTH through the development of TNX-201, an improved formulation of isometheptene.



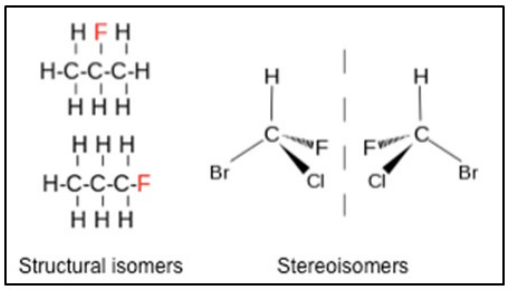
Isometheptene, 6-methylamino-2-methylheptene, is a compound that has been utilized to treat headaches for greater than 50 years. It is composed of two isomers, one believed to provide efficacy while the other only contributes to side-effects. It was first introduced into the clinic for the treatment of spasdic conditions of the biliary and urinary tracts but quickly became utilized in the treatment of migraine headaches. It is an indirect-acting agent and is thought to elicit an anti-headache action through a sympathomimetic effect leading to constriction of blood vessels in the head. It targets both the Alpha-1A adrenergic receptor and the synaptic vesicular amine transporter. Interaction with these cell surface targets elicits smooth muscle activation leading to vasoconstriction.

There have been five controlled clinical trials with isometheptene either alone or in combination with dichlorophenazone and acetaminophen for the treatment of migraines and TTH (Diener, 2000). In two trials, the isometheptene combination was found to be superior to placebo. In one of those trials, isometheptene alone was also found to be superior to placebo and in another study was comparable to the isometheptene combination. Two studies examined the clinical efficacy of isometheptene combination in comparison with acetaminophen or isometheptene alone and found no significant advantage to the combination product. The fact that the combination product is not superior to isometheptene alone supports the development of TNX-201 as a stand-alone product.

…TNX-201 Offers An Improved Version of Isometheptene…

Tonix has developed a method for purifying a single isomer of isometheptene that the company believes can potentially reduce the toxicity associated with the racemic mixture (a mixture of the two isomeric forms). Isomers are molecules with the same molecular formula but that differ in their chemical structure. The two types of isomers are structural isomers, where the atoms of two isomers are joined together in different ways, and stereoisomers, where the molecules are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms, of which isometheptene is an example.

Historically, most drugs were developed as racemates (i.e., compounds with 50:50 proportions of enantiomers). There are many examples available where both members of an enantiomer pair are active (e.g., ibuprofen), where one member is active while the other is inactive (e.g., β-lactam antibiotics) and where one member is active while the other member has toxic effects (e.g., thalidomide and salbutamol). Isometheptene falls under the category of drugs where one isomer is believed to confer the anti-headache effect while the other isomer is responsible for the unwanted side effects.



In 1992, the FDA published guidelines on the development of new stereoisomeric drugs. The guidelines specifically cover the development of a single stereoisomer after a racemic mixture has been studied, which is the situation with the development of TNX-201. For pre-clinical testing, toxicological studies must be conducted that compare both the racemic mixture and the single stereoisomer. If no toxicological differences are seen between the mixture and the stereoisomer then no further studies are required. In the press release about the pre-IND meeting, Tonix indicated that no further pre-clinical testing will be required before filing of the IND, which we believe to mean that the company has seen no pharmacological or toxicological differences with the single stereoisomer preparation of isometheptrene compared to traditional racemic preparations of the compound. This is not surprising, as isometheptene has been administered to patients for greater than 50 years and has a relatively good safety profile.

…Isometheptene History & Regulatory Pathway…

Isometheptene has been sold for a number of years as a combination medication with dichloralphenazone and acetaminophen under the brand names Midrin, Duradrin, and Epidrine for the treatment of migraine headaches. However, these medications never went through the proper FDA approval process, as they were originally marketed before the 1962 amendment to the 1938 Food, Drug and Cosmetic Act. This amendment required manufacturers to show that their medications were both safe and effective, while the 1938 Food, Drug and Cosmetic Act had only required a safety requirement for selling pharmaceuticals.

To comply with the new law, in 1966 the FDA established the Drug Efficacy Study Implementation (DESI) list to test all compounds approved for sale between 1938 and 1962 and classify them as effective, ineffective, or further study required. Regardless of classification, in order to continue marketing any DESI drug the FDA requires clinical trials and a proper NDA filing. Thus far, no companies manufacturing compounds containing isometheptene have filed an NDA for their approval by the FDA. Thus, all products containing isometheptene are marketed as unapproved products in the U.S. and a marketing withdrawal has been sanctioned by the FDA since 2010.

Since the FDA has never approved isometheptene, Tonix will have to pursue the traditional 505(b)(1) NDA requirements, which includes the full complement of safety and efficacy studies in order to gain approval for TNX-201. With all pre-clinical work completed, the IND for TNX-201 should be filed in the third quarter of 2014 with a first-in-human clinical pharmacology study commencing in the fourth quarter of 2014. Assuming that the clinical trials go according to plan, we foresee TNX-201 clinical trials finishing in 2017 with an NDA filing in 2018.

…Strong IP Protection & Cash to Drive Development of TNX-201…

Tonix has an extensive patent portfolio for TNX-201. The intellectual property relates to isometheptene isomers and includes patent applications directed to a purified isomer of isometheptene, pharmaceutical compositions containing isometheptene, isometheptene formulations, methods for modulating headache and other CNS conditions and treating CNS conditions utilizing isometheptene isomers, and methods of manufacturing isometheptene isomers. The Isometheptene Technology patent portfolio includes U.S. patent applications such as U.S. Provisional Patent Application Nos. 61/754,281, 61/793,456, and 61/814,664. If U.S. and non-U.S. patents claiming priority from those applications issue, those patents would expire in 2034, excluding any patent term adjustments or extensions.

On January 29, 2014 Tonix announced the closing of a $43.5 million public offering of common stock. This large infusion of cash provides the company enormous flexibility and the opportunity to continue the development of TNX-201 in addition to continuing development of TNX-102 for fibromyalgia and post-traumatic stress disorder.

…Estimating Peak Sales for TNX-201…

Below we've provided a rough sketch of what peak sales for TNX-201 might be in 10 years:

- 45 million Americans have TTH (~20% of U.S. adult population)
- Approximately 80% are episodic in nature
- Approximately 10% are not adequately treated by OTC NSAIDs or aspirin
- Approximately 50% will seek medical Rx for TTH (not a migraine drug)
- Priced at $20 per pill – a discount to migraine drugs Cambia® and Treximet® that $33 and $28 per dose, respectively, but a sizable increase from OTC ibuprofen or generic isometheptene formulations that are not FDA approved and carry significant side effects.
- Assume the average episodic patient that seeks medical Rx experiences 52 per year (one a week), which is slightly more than the average migraine sufferer but still less than CTTH patients.
- Assume 10% market penetration

All this gets us to peak sales in 2024 of around $283 million. That is a nice sized product for a company like Tonix Pharmaceuticals that has a market capitalization of only $100 million. On an NPV basis we see TNX-201 worth $2 to $3 per share.

Conclusion

We have conducted a sum-of-parts valuation for Tonix Pharmaceuticals that incorporates our three forecasts for sales of TNX-120SL in fibromyalgia and PTSD and TNX-201 in ETTH noted above. We believe the shares are fairly-valued at between $16 to $18 per share, and recommend purchase at today's price.

PROJECTED FINANCIALS

Tonix Pharma
Income Statement

Tonix Pharmaceuticals	2013 A	Q1 E	Q2 E	Q3 E	Q4 E	2014 E	2015 E	2016 E
TNX-102SL (FM)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
TNX-102SL (PTSD)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Pipeline	$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
Product Gross Margin	-	-	-	-	-	-	-	-
R&D	$4.7	$1.5	$1.8	$2.0	$2.4	$7.7	$10.0	$10.0
% R&D	-	-	-	-	-	-	-	-
SG&A	$6.2	$2.0	$2.1	$2.2	$2.2	$8.5	$9.4	$10.0
% SG&A	-	-	-	-	-	-	-	-
Operating Income	($10.9)	($3.5)	($3.9)	($4.2)	($4.6)	($16.2)	($19.4)	($20.0)
Operating Margin	-	-	-	-	-	-	-	-
Interest & Other Income	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1	$0.1	$0.1
Pre-Tax Income	($10.9)	($3.5)	($3.9)	($4.2)	($4.5)	($16.1)	($19.3)	($19.9)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($10.9)	($3.5)	($3.9)	($4.2)	($4.5)	($16.1)	($19.3)	($19.9)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($3.37)**	**($0.35)**	**($0.39)**	**($0.42)**	**($0.45)**	**($1.62)**	**($1.54)**	**($1.33)**
YOY Growth	*-39.6%*	-	-	-	-	*-52.1%*	*-4.4%*	*-14.1%*
Weighted Shares Outstanding	3.23	9.85	9.90	9.95	10.10	9.95	12.50	15.00

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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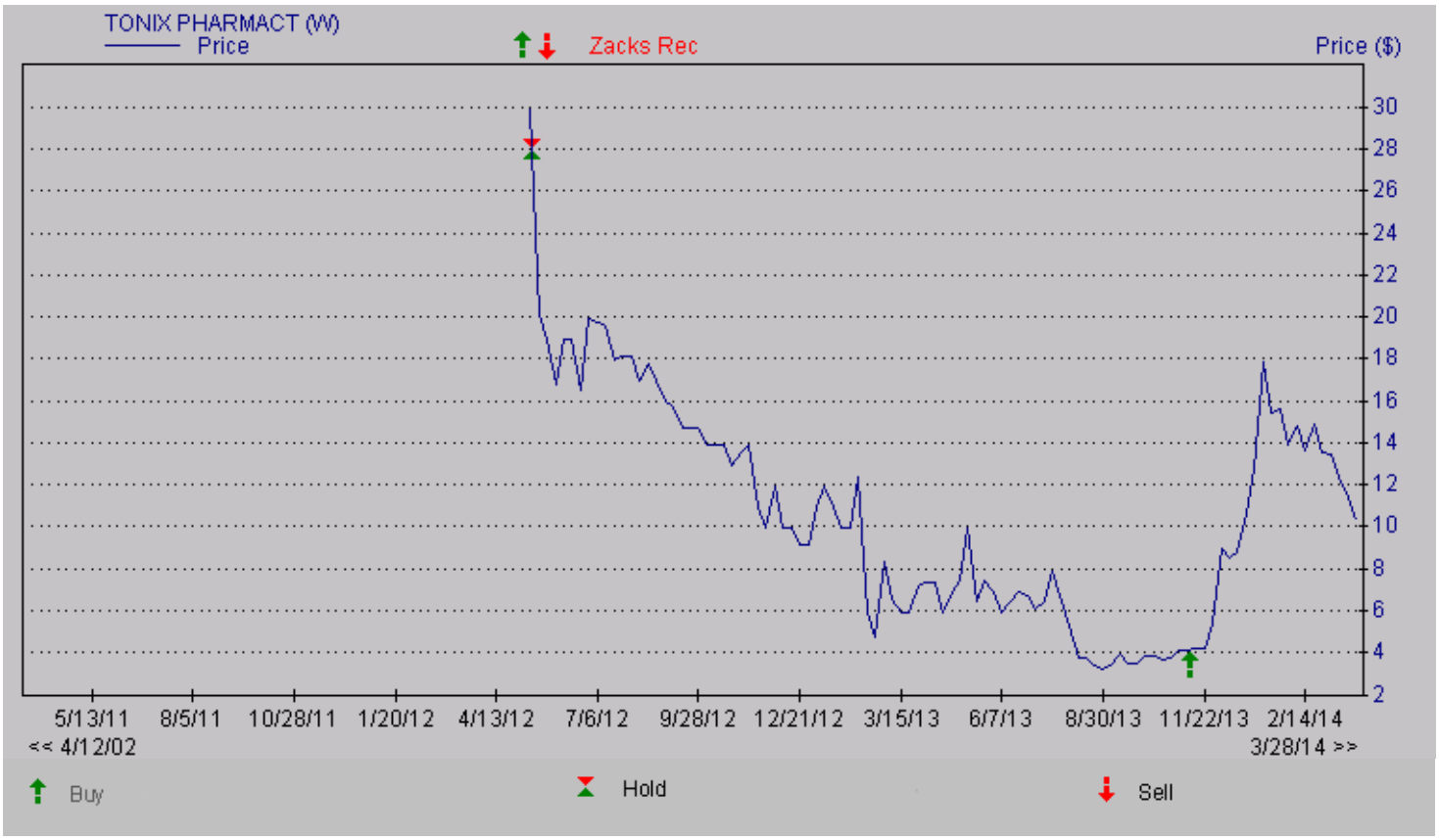

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