EDISON

Tonix Pharmaceuticals

PTSD awareness day and earnings update

Financial and development update

Pharma & biotech

Tonix recently held a post-traumatic stress disorder (PTSD) awareness day to highlight the current standards of care, the unmet medical need of the disease as well as the development plan for TNX-102 SL to treat it. The first Phase III trial in military-related PTSD will enroll up to 550 patients and will have one to two interim analyses, which would allow for early stoppage due to efficacy or a sample size adjustment. The trial is expected to start in Q117, with the first interim analyses expected in H217. A second trial in predominantly civilian PTSD is expected to follow.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/14	0.0	(27.6)	(2.77)	0.0	N/A	N/A
12/15	0.0	(48.1)	(2.86)	0.0	N/A	N/A
12/16e	0.0	(37.6)	(1.45)	0.0	N/A	N/A
12/17e	0.0	(29.0)	(0.71)	0.0	N/A	N/A

Note: *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

PTSD remains an unmet medical need

There are only two FDA-approved drugs for PTSD, both of which are SSRIs that are used for depression. The majority of patients do not achieve remission with therapy, with remission rates especially low among military-related PTSD sufferers. Approximately 55% of patients receive a benzodiazepine despite recommendations against their use in PTSD as well as the risk of dependence, withdrawal, long-term cognitive decline and the worsening of PTSD.

First Phase III interim analysis expected in H217

The Phase III in military-related PTSD patients is expected to begin in Q117 and will enroll up to 550 patients with a CAPS-5 baseline of ≥33 to receive either 5.6mg of TNX-102 SL or placebo. Due to its adaptive design, an interim analysis is expected to occur in H217 and to encompass approximately 180 patients. At that point the trial may be stopped for efficacy (though the exact statistical hurdle rate has not been determined yet) or the sample size adjusted.

Breakthrough designation possible

Due to the AtEase data where the 5.6mg dose of TNX-102 SL had a statistically significant benefit over placebo, it is possible that Tonix will get breakthrough designation for its program as the therapy data shows it may successfully treat a serious condition. This could allow for FDA approval following one Phase III trial.

Valuation: Reduced to $207m or $5.27 per basic share

We have reduced our valuation from $208m or $8.05 per basic share, to $207m or $5.27 per basic share, mainly due to the dilution from the 9.5m share offering in October. Tonix ended the third quarter with $26.7m in cash and raised an additional $4.6m in October. We expect a funding requirement of $80m before profitability in 2023, up from $70m previously.

1 December 2016

Price	**US$0.40**
Market cap	**US$16m**

Net cash (US$m) at 30 September 2016	26.7
Shares in issue	39.2m
Free float	86.2%
Code	TNXP
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(10.5)	(83.9)	(94.5)
Rel (local)	(13.7)	(84.1)	(94.8)

52-week high/low	US$7.8	US$0.4

Business description

Tonix Pharmaceuticals is an emerging specialty pharmaceutical company focused on psychiatric and neurological disorders. It is advancing TNX-102 SL for the treatment of PTSD for both the military and civilians, following positive Phase II results.

Next events

Military-related PTSD Phase III start	Q117
Phase III interim analysis	H217

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PTSD: A serious unmet need

Post-traumatic stress disorder is a large though somewhat underserved market. Anyone who has had a traumatic experience (eg child abuse, rape, seeing a loved one die) can exhibit symptoms of the disease. Lifetime prevalence for adults is 8%,[1] which goes up to as high as 31% for veterans.[2]

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), to be diagnosed with PTSD sufferers have to exhibit symptoms across four categories: intrusions, avoidance, mood and cognition, and arousal (see Exhibit 1).

Exhibit 1: Diagnostic criteria for PTSD

Intrusions (1+ symptoms present)	Avoidance (1+ symptoms present)	Mood & cognition (2+ symptoms present)	Arousal (2+ symptoms present)
Recurring nightmares, flashbacks	Avoid people, places, things	Alterations in cognition (negative)	Exaggerated startle response
Intrusive memories (images)	Avoid thoughts/conversations	Alterations in mood (negative)	"On guard" all the time
Physiological and psychological reactions to reminders		Loss of interest	Irritability or angry outbursts
		Social withdrawal	Difficulty sleeping, concentrating

Source: DSM-5

There are a number of shortcomings associated with available treatments for PTSD. There are currently only two products approved for the disorder, paroxetine and sertraline, both SSRIs with the associated side effects and only modest effect size. Based on the Cohen's d statistic, where 0.2 is considered a small effect size, 0.5 is considered moderate and 0.8 is considered large,[3] both approved therapies have only small to moderate impacts (see Exhibit 2).

Exhibit 2: Effect size for various PTSD therapies

Class	Drug	Sample size	Effect size (Cohen's d)
SSRI	Paroxetine	1,070	0.42
	Sertraline	1,123	0.26
	Fluoxetine	889	0.31
	Citalopram	35	-0.34
SNRI	Venlafaxine	687	0.12
TCA	Amitriptyline	33	0.9
	Imipramine	41	0.24
MAOI	Brofaromine	48	0.58
	Phenelzine	37	1.06
Anti-psychotic	Olanzapine	34	0.14
	Risperidone	419	0.26
Anti-convulsant	Topiramate	142	0.96
	Divalproex	85	0.06
	Tiagabine	232	0.02
Other pharmacological therapy	Prazosin	50	0.4
	Bupropion	30	-0.23
	Mirtazapine	29	0.27
	TNX-102 SL (5.6mg in pts w/CAPS-5 ≥33)	**38**	**0.53**
Psychotherapy	Cognitive processing therapy	299	1.4
	Cognitive therapy	221	1.22
	Cognitive behavior therapy – exposure	387	1.27
	Cognitive behavior therapy – exposure	825	1.09
	Eye movement desensitization and reprocessing	117	1.08
	Narrative Exposure Therapy	227	1.25

Source: UK NICE National Clinical Practice Guidelines, US Department of Health and Human Services Agency for Healthcare Research and Quality, Tonix Pharmaceuticals

1 Kessler et al, Arch Gen Psych 2005;62:617-627

2 Dohrenwend et al, Science. 2006 Aug 18; 313(5789): 979–982

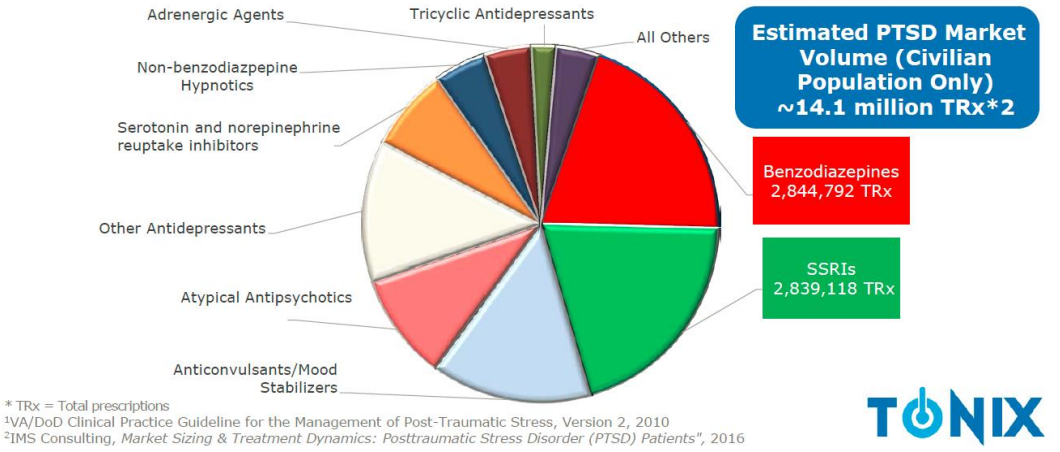
3 Cohen J, Psychological Bulletin, 0033-2909, July 1, 1992

There have been 11 published positive randomized control trials (RCTs) for SSRIs, mostly in predominantly female civilian populations. There were also six negative RCTs in PTSD, mainly in predominantly veteran, male populations.

Among other pharmacological therapies, some of which are used off label after SSRI failure, meaningful effect sizes were generally seen only in small trials (the effect size for topiramate is heavily skewed by a 67-patient trial in Iran where the drug was tested as adjunct therapy rather than monotherapy for PTSD).

What is most concerning is that there are 2.9m prescriptions per year for benzodiazepines in the civilian PTSD market alone, representing about 20% of all prescriptions for PTSD (see Exhibit 3) and indicating that 55% of patients receive a drug class that may actually worsen PTSD (note that a single patient may have multiple prescriptions from different classes).

Exhibit 3: Drug classes used in PTSD



Source: Tonix Pharmaceuticals

The Department of Veteran's Affairs/Department of Defense Clinical Practice Guidelines go so far as to strongly recommend against the use of benzodiazepines to treat PTSD due to negative cognitive effects and withdrawal symptoms, some of which mirror PTSD symptoms like nightmares and insomnia (and can start while the patient is still on-drug at a stable dose due to the building of tolerance). The guidelines state:

"Although benzodiazepines have been frequently used "as needed" and continuously for anxiety disorders, including to augment evidence-based treatment modalities in PTSD, there is theoretical, animal, and human evidence to suggest that benzodiazepines may actually interfere with the extinction of fear conditioning or *potentiate* the acquisition of fear responses and worsen recovery from trauma. Benzodiazepine should be used especially cautiously in combat veterans with PTSD because of the very high co- morbidity of combat-related PTSD with alcohol misuse and substance use disorders (upwards of 50 percent of co-morbidity) and potential problems with tolerance and dependence. Once initiated, benzodiazepines can be very difficult, if not impossible, to discontinue due to significant withdrawal symptoms compounded by the underlying PTSD symptoms."

With proper education, it may be possible to convince physicians to switch out benzodiazepines with TNX-102 SL, which has a much more innocuous toxicity profile and does not have the tolerance/withdrawal issues. The toxicity profile is so innocuous that not a single patient withdrew due to an adverse event from the high-dose arm, while three withdrew for that reason from placebo (in total 16% withdrew from any reason from the 5.6mg arm, compared to 27% from placebo).

Upcoming Phase III trial designs

The company provided additional clarity on the design of its Phase III program. It will involve two large Phase III trials, the first being in military-related PTSD and the second in predominantly civilian PTSD (though with a military component). The first trial will be a randomized, double-blind, placebo-controlled trial with up to 550 patients who will receive either 5.6mg of TNX-102 SL or placebo. The entrance criteria will be stricter than in the AtEase trial, with a minimum CAPS-5 score of 33 required for entry, instead of 29. This will help ensure that the participants in the trial actually have PTSD. The endpoint will be mean change from baseline in total CAPS-5 score at week 12.

Tonix plans to conduct one to two unblinded interim analyses with the first occurring after approximately 180 patients are enrolled (~90 in each arm), after which the study can be stopped due to efficacy or the sample size can be adjusted. As the exact statistical plan has not yet been approved by the FDA, the p-value hurdle necessary for an efficacy stop is unknown, but it is likely to be high. This first Phase III trial is expected to begin in Q117 with an interim analysis in H217. We continue to expect the full data readout in 2018 and do not expect an early halt due to efficacy.

The second trial will have the same design as the first except that it will be a predominantly civilian sample. The company expects over half of the participants to be female, which leads to an expectation of around 25% of the trial participants suffering from military-related PTSD. Note that historically female PTSD patients have been more responsive to medical therapy. The target start date for this trial is yet to be determined but it will follow the military-related trial initiation.

It is possible that Tonix will be able to obtain breakthrough designation for its program as the therapy has data showing TNX-102 SL may successfully treat a serious condition. This could allow for FDA approval following one Phase III trial; however, we continue to model a requirement for two Phase III trials for approval.

Valuation

We have reduced our valuation from $208m or $8.05 per basic share, to $207m or $5.27 per basic share, mainly due to the dilution from Tonix's 9.5m share offering in October. We expect to update our valuation with the advancement of the PTSD program and/or regulatory actions such as breakthrough therapy designation.

Exhibit 4: Tonix valuation table

Product	Main indication	Status	Prob. of success	Launch year	Peak sales ($m)	Patent protection	Royalty	rNPV ($m)
TNX-102 SL	PTSD	Phase II complete	50%	2020	803	2034	25.0%	175
Total								175
Cash and cash equivalents (Q316 + public offering) ($m)								31.3
Total firm value ($m)								207
Total basic shares (11 November 2016, m)								39.18
Value per basic share ($)								**5.27**
Dilutive warrants (m)								5.7
Weighted average exercise price ($)								1.22
Cash on exercise ($m)								6.90
Total firm value ($m)								213
Total number of shares (m)								44.9
Diluted value per share ($)								**4.76**

Source: Edison Investment Research

Financials

Tonix reported a loss of $7.6m in Q316, down from $9.8m in Q216, mainly due to the reduction of R&D expenses from $7.5m to $5.5m, predominantly associated with clinical development expenses. The net loss for the quarter, excluding non-cash expenditures, was $6.8m, down from a net loss of $12.4m, excluding non-cash expenditures in Q315. We expect spending to decrease for the remainder of the year to reflect fewer R&D commitments following the suspension of fibromyalgia development. The company ended the quarter with $26.7m in cash and added an additional $4.6m in an equity offering in October. We currently forecast that the company will need an additional $80m before profitability in 2023, up slightly from $70m previously.

Exhibit 5: Financial summary

US$000s	2013	2014	2015	2016e	2017e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
EBITDA	(10,888)	(27,656)	(48,162)	(37,796)	(29,115)
Operating Profit (before GW and except.)	(10,888)	(27,656)	(48,162)	(37,796)	(29,115)
Intangible Amortization	0	0	0	0	(9)
Other	0	0	0	0	0
Exceptionals	0	0	0	0	0
Operating Profit	(10,888)	(27,656)	(48,162)	(37,796)	(29,124)
Net Interest	4	40	108	149	107
Other	0	0	0	0	0
Profit Before Tax (norm)	(10,884)	(27,616)	(48,054)	(37,646)	(29,008)
Profit Before Tax (FRS 3)	(10,884)	(27,616)	(48,054)	(37,646)	(29,017)
Tax	0	0	0	0	0
Deferred tax	0	(0)	0	(0)	(0)
Profit After Tax (norm)	(10,884)	(27,616)	(48,054)	(37,646)	(29,008)
Profit After Tax (FRS 3)	(10,884)	(27,616)	(48,054)	(37,647)	(29,017)
Average Number of Shares Outstanding (m)	3.2	10.0	16.8	26.0	40.7
EPS - normalized ($)	(3.37)	(2.77)	(2.86)	(1.45)	(0.71)
EPS - FRS 3 ($)	(3.37)	(2.77)	(2.86)	(1.45)	(0.71)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	45	373	527	441	398
Intangible Assets	0	0	120	120	111
Tangible Assets	45	328	350	265	231
Other	0	45	57	56	56
Current Assets	8,202	38,184	43,016	21,301	15,494
Stocks	0	0	0	0	0
Debtors	0	0	0	0	0
Cash	8,202	38,184	43,016	21,301	15,494
Other	0	0	0	0	0
Current Liabilities	(765)	(1,487)	(3,049)	(944)	(944)
Creditors	(765)	(1,487)	(3,049)	(944)	(944)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(13)	(68)	(106)	(76)	(20,076)
Long term borrowings	0	0	0	0	(20,000)
Other long term liabilities	(13)	(68)	(106)	(76)	(76)
Net Assets	7,469	37,002	40,388	20,722	(5,128)
CASH FLOW					
Operating Cash Flow	(8,517)	(22,840)	(42,528)	(37,309)	(25,778)
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(15)	(319)	(238)	(66)	(30)
Acquisitions/disposals	0	0	0	0	0
Financing	10,042	47,836	47,685	15,641	0
Dividends	0	0	0	0	0
Other	0	0	(11)	0	0
Net Cash Flow	1,510	24,677	4,908	(21,734)	(25,808)
Opening net debt/(cash)	(1,785)	(8,202)	(38,184)	(43,016)	(21,301)
HP finance leases initiated	0	0	0	0	0
Exchange rate movements	(1)	(3)	(4)	(7)	0
Other	4,908	5,308	(72)	26	0
Closing net debt/(cash)	(8,202)	(38,184)	(43,016)	(21,301)	4,506

Source: Tonix Pharmaceuticals accounts, Edison Investment Research

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