

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): December 18, 2019

TONIX PHARMACEUTICALS HOLDING CORP.
(Exact name of registrant as specified in its charter)

Nevada
(State or Other Jurisdiction
of Incorporation)

001-36019
(Commission
File Number)

26-1434750
(IRS Employer
Identification No.)

509 Madison Avenue, Suite 1608, New York, New York 10022
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (212) 980-9155

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
 Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
 Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
 Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Global Market

Item 7.01 Regulation FD Disclosure.

Tonix Pharmaceuticals Holding Corp. (the “Company”) updated its investor presentations, which are used to conduct meetings with investors, stockholders and analysts and at investor conferences, and which the Company intends to place on its website, which may contain nonpublic information. Copies of the presentations are filed as Exhibit 99.01 and 99.02 hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01 and 99.02 attached hereto, shall not be deemed “filed” for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the “Exchange Act”) or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d)	Exhibit No.	Description.
	<u>99.01</u>	Corporate Presentation by the Company for December 2019 (Long Form)
	<u>99.02</u>	Corporate Presentation by the Company for December 2019 (Abbreviated Form)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: December 18, 2019

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer



Investor Presentation



December 2019

Version P0213 12-17-19 (Doc 0577)

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Cautionary Note on Forward-Looking Statements

2

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, substantial competition; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and risks related to failure to obtain U.S. Food and Drug Administration clearances or approvals and noncompliance with its regulations. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission (the "SEC") on March 18, 2019, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.



Who we are:

- A clinical stage biopharmaceutical company dedicated to developing innovative treatments for patients and making meaningful contributions to society
- Focusing on small molecules and biologics to treat psychiatric, pain and addiction conditions

What we do:

- Target therapeutic areas with high need for improvement
 - Conditions with no, or inadequate, treatments
 - Significant patient populations not well served by existing therapies
- Develop innovative treatment options with possibility to be a “game changer”
 - Scientifically unique and innovative
 - Strong scientific rationale supported by preliminary clinical evidence and published literature
 - Proven regulatory pathways and established clinical endpoints
 - Built on a foundation of proprietary intellectual property

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CNS Candidates in Clinical Development

Psychiatry, Pain and Addiction

TNX-102 SL and TNX-601 owned outright with no royalties due

4

Pipeline Product	Indication	Phase 1	Phase 2	Phase 3	NDA ³ /BLA ⁴	Market
TNX-102 SL¹ Cyclobenzaprine HCl sublingual tablets Protectic [®] formulation technology	<i>Bedtime Treatment for PTSD – Tonmya^{®2}</i>	→			Interim analysis results expected 1Q 2020 Topline data expected 2Q 2020	
	<i>Bedtime Treatment for Fibromyalgia</i>	→			Interim analysis results expected 2H 2020	
	Bedtime Treatment for Agitation in Alzheimer's	→				
	Bedtime Treatment for Alcohol Use Disorder (AUD) ⁵	→				
TNX-1300⁶ Cocaine esterase (recombinant from bacteria) i.v. formulation	Cocaine intoxication / overdose	→				
TNX-601 CR⁷ Tianeptine oxalate oral controlled release formulation	Daytime Treatment for PTSD	→				
	Daytime Treatment for Major Depressive Disorder (MDD)	→				
	Neurocognitive Dysfunction from Corticosteroids	→				

¹ TNX-102 SL (cyclobenzaprine HCl) sublingual tablets is an investigational new drug and has not been approved for any indication; ² Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD; ³ NDA- New Drug Application; ⁴ BLA - Biologic Licensing Application; ⁵ Pre-Investigational New Drug (IND) meeting completed in October with FDA. Upon receiving FDA clearance of an IND application, TNX-102 SL for AUD will be Phase 2 ready as it is expected to qualify for the 505(b)(2) pathway for approval; ⁶ TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, i.v. solution) is an investigational new biologic and has not been approved for any indication; ⁷ TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 study for formulation development was recently completed outside of the U.S.

Pipeline Product	Indication(s)	Category
TNX-1600 Triple reuptake inhibitor ²	Daytime Treatment for PTSD	Psychiatry
TNX-1500³ Anti-CD154 monoclonal antibody	Prevention and treatment of organ transplant rejection Treatment for autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis	Transplant Autoimmunity
TNX-1700 rTFF2 ⁴	Treatment for gastric and pancreatic cancers	Oncology
TNX-801³ Live horsepox virus (HPXV) vaccine from cell culture	Smallpox-preventing vaccine	Biodefense
TNX-701³ Radioprotection drug oral capsules	Protection from radiation injury	Biodefense

¹ (Experimental new medicines and biologics, not approved for any indication)

² (2S,4R,5R)-5-(((2-aminobenzo[d]thiazol-6-yl)methyl)amino)-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol) is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine)

³ Programs owned outright with no royalties due

⁴ recombinant Trefol Family Factor 2



TNX-102 SL Proposed Mechanism: Improving Sleep Quality

6

The focus of TNX-102 SL development is both unique and innovative

- Testing the therapeutic benefit of sleep ('sleep quality')
 - Restorative sleep, in contrast to time spent sleeping ('sleep quantity')
- Targeting clinical conditions for which improved sleep quality may have a therapeutic benefit
 - Reduction in disease-specific symptoms, with sleep improvement as a secondary endpoint

Therapeutic Area	Target Indication	Status
Psychiatry	Posttraumatic stress disorder (PTSD)	Phase 3
Rheumatology	Fibromyalgia (FM)	Phase 3
Psychiatry / Neurology	Agitation in Alzheimer's Disease (AAD)	Phase 2 ready
Addiction	Alcohol Use Disorder (AUD)	Pre-IND
Chronic pain	TBD	Life-cycle opportunity
Sleep disorders	TBD	Life-cycle opportunity

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TNX-102 SL Intellectual Property – U.S. Protection expected until 2035

7

Composition of matter (eutectic): Protection expected to 2034/2035

- United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9636408 in May 2017, U.S. Patent No. 9956188 in May 2018, U.S. Patent No. 10117936 in Nov 2018, and U.S. Patent No. 10,357,465 in July 2019
- European Patent Office (EPO) issued Patent No. 2968992 in December 2019
- China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019
- Indonesian Patent Office issued Indonesian Patent No. IDP000055516 in January 2019
- Saudi Arabian Patent Office issued Saudi Patent No. 6088 in September 2018
- Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018
- New Zealand Intellectual Property Office (NZIPO) issued New Zealand Patent No. 631152 in August 2017
- 35 patent applications pending (5 being allowed in U.S, Australia, Europe, Taiwan, South Africa)

Composition of matter (sublingual): Protection expected to 2033

- NZIPO issued New Zealand Patent No. 631144 in March 2017 and Patent No. 726488 in January 2019
- Taiwanese Intellectual Property Office issued Taiwanese Patent No. 1590820 in July 2017 and Patent No. 1642429 in December 2018
- Australian Patent Office issued Australian Patent No. 2013274003 in October 2018
- JPO issued Japanese Patent No. 6259452 in Dec 2017
- 21 patent applications pending

Method of use (PTSD) for cyclobenzaprine: Protection expected to 2030

- Hong Kong Patent Office issued Hong Kong Patent No. HK1176235 in September 2018
- USPTO issued U.S. Patent No. 9918948 in March 2018
- European Patent Office (EPO) issued European Patent No. 2501234B1 in Sept 2017 (validated in 37 countries). In response to an opposition filed in June 2018, EPO's Opposition Division determined in October 2019 that it will uphold this patent.
- 1 patent application pending



Overview of Posttraumatic Stress Disorder (PTSD)

8

PTSD is a chronic disabling disorder in response to experiencing traumatic event(s)

Symptoms of PTSD fall into four clusters:

1. Intrusion (aversive memories, nightmares, flashbacks)
2. Avoidance (avoiding persons, places or situations)
3. Mood/cognitions (memory block, emotional numbing, detachment from others)
4. Hyperarousal (anxiety, agitation & sleep disturbance)

Diagnosis, symptom severity, as well as treatment effect, is determined by CAPS-5*

- Recognized as the standard for rating PTSD severity in clinical trials
- Takes into account all four symptom clusters
- Higher Total CAPS-5 score reflects more severe PTSD symptoms

* Clinician-administered PTSD scale for Diagnostic Statistical Manual version 5 (DSM-5)



Impact of PTSD on People

9

Consequences:

- Impaired daily function and substantial interference with work and social interactions
- Reckless or destructive behavior
- Increased health care utilization and greater medical morbidity

PTSD as a risk factor for:

- Depression
- Alcohol or substance abuse
- Absenteeism/unemployment
- Homelessness
- Violent acts
- Suicidal thoughts and suicide

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PTSD: U.S. Prevalence and Index Traumas

10

PTSD is a chronic response to traumatic event(s)

- A majority of people will experience a traumatic event at some point in their lifetime¹
- 20% of women and 8% of men in the U.S. who experience significant trauma develop PTSD¹

Adult Civilians:

- Lifetime prevalence: 6.1% (14.4 million adults in the U.S.)²
 - Persistent - >1/3 fail to recover, even after several years following the trauma²
- Twelve month prevalence: U.S. 4.7% (12 million adults)²
EU 2.3% (~10.0 million adults)³

Most common forms of trauma¹

- Witnessing someone being badly injured or killed
- Natural disaster
- Life-threatening accident
- Sexual or physical assault

¹ Kessler et al., Arch Gen Psychiatry 1995; 52:1048

² Goldstein et al., 2016 (adjusted for 2019)

³ The European Union Market Potential for a New PTSD Drug. Prepared for Tonix Pharmaceuticals by Procella Consultants Ltd, September 2016



Prevalence of PTSD Among Civilians and Veterans

11



Approximately **12 million** American adults annually¹



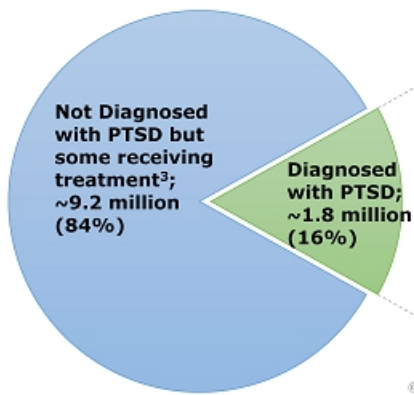
Women more likely to develop than men¹

¹Goldstein et al., 2016 (adjusted for 2019); ²Norris, *PTSD Res Quar.* 2013; ³Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015, Washington, DC; Among 1.9M separated OEF/OIF/OND veterans, 1.2M have obtained VA healthcare; 685k evaluated by VA with possible mental disorder, and 379k diagnosed with PTSD.

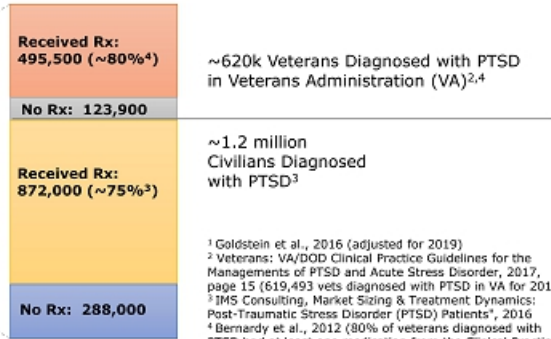


PTSD Prevalence and Market Characteristics

Prevalent Population with PTSD (U.S.) ~12 million¹ (civilians plus veterans)



Majority of diagnosed patients receive pharmacotherapy treatment



~620k Veterans Diagnosed with PTSD in Veterans Administration (VA)^{2,4}

~1.2 million Civilians Diagnosed with PTSD³

¹ Goldstein et al., 2016 (adjusted for 2019)
² Veterans: VA/DOD Clinical Practice Guidelines for the Management of PTSD and Acute Stress Disorder, 2017, page 15 (619,493 vets diagnosed with PTSD in VA for 2016)
³ IMS Consulting, Market Sizing & Treatment Dynamics: Post-Traumatic Stress Disorder (PTSD) Patients, 2016
⁴ Bernardy et al., 2012 (80% of veterans diagnosed with PTSD had at least one medication from the Clinical Practice Guidelines)

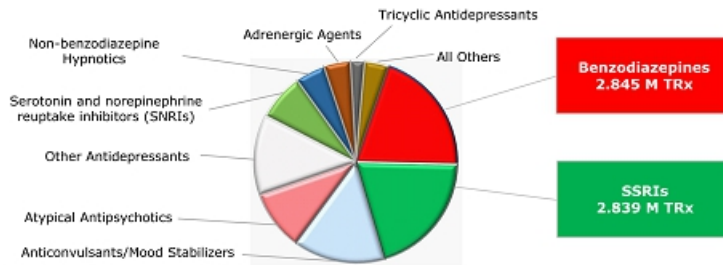


What Drug Classes are Used to Treat PTSD?

Market highly fragmented, with benzodiazepines widely prescribed (but not indicated)¹

- Multiple medications per patient (or "Polypharmacy") is the norm
 - Approximately 55% of patients receive a benzodiazepine, and 53% receive a selective serotonin reuptake inhibitor (SSRI)
- SSRIs are the only FDA-approved drug class

Estimated PTSD Market Volume (Civilian Population Only) ~14.1 million TRx*²



* TRx = Total prescriptions

¹ VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress, Version 2, 2010

² IMS Consulting, *Market Sizing & Treatment Dynamics: "Post-Traumatic Stress Disorder (PTSD) Patients"*, 2016
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PTSD: Not Well-Served by Approved Treatments

14

FDA-approved SSRIs, paroxetine and sertraline, are indicated as a treatment for PTSD

- Neither drug has shown efficacy in military-related PTSD
- Majority of male PTSD patients unresponsive or intolerant to current treatments
- Side effects relating to sexual dysfunction, sleep disturbance and weight gain are commonly reported

Characteristics of an ideal drug therapy that would be compatible and complementary with behavioral therapy

- Lack of retrograde amnesia (e.g., unlike off-label use of benzodiazepines and non-benzodiazepines)
- Lack of interference on sleep (e.g., unlike approved SSRIs)

TNX-102 SL is being investigated in both military and civilian PTSD and is expected to be indicated as a “treatment for PTSD”



Why Initially Targeted Military-Related PTSD?

15

Military-related PTSD not well-served by existing FDA-approved therapies

- **No clear treatment response observed in U.S. military population**

Sertraline: failed to show efficacy in a large multicenter trial in U.S. military (placebo numerically better)¹
Paroxetine: no large trials conducted with predominantly military trauma

- **Inconsistent treatment response observed in males**

Sertraline: FDA-conducted post-hoc analysis concluded no effect for male civilian subgroup²
Paroxetine: no sex-related difference in treatment outcomes³

- **Important tolerability issues with SSRIs in this population**

Sexual dysfunction^{2,3}
Insomnia^{2,3}
SSRI withdrawal syndrome⁴

¹ Friedman et al., J Clin Psychiatry 2007; 68:711

² Zoloft Package Insert, August, 2014

³ Paxil Package Insert, June, 2014

⁴ Fava et al., Psychother Psychosom 84:72-81, 2015



Growing Economic and Social Burden to Care for Veterans with PTSD

16

Health care costs associated with PTSD for OEF/OIF/OND veterans:

Direct costs

\$3,000-5,000
per patient per year for
OEF/OIF Veterans¹

**~ 1.9M Veterans
out of 2.7M**
Service members deployed
between 10/1/2001 and
3/31/2015³



Indirect costs

\$2-3 billion
estimated yearly cost
to society²

Families, social care
agencies, schools,
employers, welfare system²

¹ CBO Report 2012; ² Tanielian, *Invisible Wounds of War*. 2005; ³ *Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015*, Washington, DC; OEF/OIF/OND, Operations Enduring Freedom, Iraqi Freedom and New Dawn.
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First investigational new drug to show treatment effect in military-related PTSD in two potential pivotal efficacy studies

- Phase 2 study (P201/AtEase) showed TNX-102 SL 5.6 mg had a strong signal of treatment effect at Week 12 as measured by CAPS-5¹
- Phase 3 study (P301/HONOR) provided evidence of effectiveness as early as 4 weeks after treatment but diminished over time due to high placebo response
 - Retrospective analysis showed persistent effectiveness at Week 12 in subgroup with Time Since Trauma ≤ 9 years from screening
- Both studies can be used as supportive evidence of efficacy and safety for TNX-102 SL NDA submission
- No serious or unexpected adverse events related to TNX-102 SL were reported

Phase 3 study (P302/RECOVERY) initiated in March 2019 and currently enrolling

¹ CAPS-5 = Clinician-Administered PTSD Scale for DSM-5



No Recognized Abuse Potential in Clinical Studies

18

Active ingredient is cyclobenzaprine, which is structurally related to tricyclic antidepressants

- Cyclobenzaprine interacts with receptors that regulate sleep quality: 5-HT_{2A}, α_1 -adrenergic and histamine H₁ receptors
- Cyclobenzaprine does **NOT** interact with the same receptors as traditional hypnotic sleep drugs, benzodiazepines or non-benzodiazepines that are associated with retrograde amnesia
- Cyclobenzaprine-containing product was approved 40 years ago and current labeling (May 2016) indicates no abuse or dependence concern

TNX-102 SL NDA can be filed without drug abuse and dependency assessment studies

- April 2017 meeting minutes from the March 2017 FDA meeting



TNX-102 SL: Sublingual Formulation is Designed for Bedtime Administration

19

TNX-102 SL: Proprietary sublingual formulation of cyclobenzaprine (CBP) with transmucosal absorption

- Innovation by design with patent protected CBP/mannitol eutectic
- Rapid systemic exposure
- Increases bioavailability during sleep
- Avoids first-pass metabolism
- Lowers exposure to long-lived active major metabolite, norcyclobenzaprine (norCBP)

CBP undergoes extensive first-pass hepatic metabolism when orally ingested

- Active major metabolite, norCBP¹
 - Long half-life (~72 hours)
 - Less selective for target receptors (5-HT_{2A}, α_1 -adrenergic, histamine H₁)
 - More selective for norepinephrine transporter and muscarinic M₁

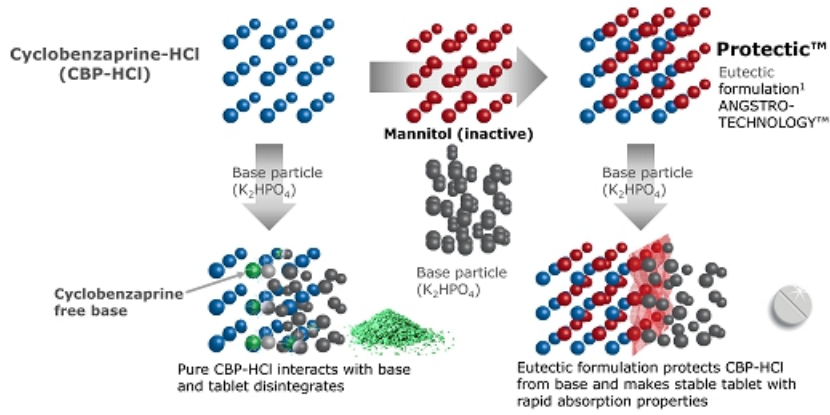
TNX-102 SL 505(b)(2) NDA approval can rely on the safety of the reference listed drug (AMRIX®)²

¹ Daugherty et al., Abstract 728, Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015, Toronto Ontario, Canada
² FDA Minutes (November 26, 2018)



Proprietary Cyclobenzaprine Hydrochloride Eutectic Mixture Stabilizes Sublingual Tablet Formulation

20



¹ U.S. Patent issued May 2, 2017



TNX-102 SL: Hypothesized Novel Mechanism Targets Sleep Quality for Recovery from PTSD

21

PTSD is a disorder of recovery

- Most people exposed to extreme trauma recover over a few weeks
- In PTSD, recovery process impeded due to insufficient sleep-dependent memory processing^{1,2}

Memory processing is essential to recovery

- Vulnerability to memory intrusions and trauma triggers remains if no consolidation of new learning (extinction)

TNX-102 SL targets sleep quality³

- The active ingredient in TNX-102 SL, cyclobenzaprine, interacts with receptors that regulate sleep quality: strongly binds and potently blocks 5-HT_{2A/2C}, α_1 -adrenergic and histamine H₁ receptors, permissive to sleep-dependent recovery processes

¹Straus LD, Acheson DT, Risbrough VB, Drummond SPA. Sleep Deprivation Disrupts Recall of Conditioned Fear Extinction. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017; 2(2):123-129. ²Murkar ALA, De Koninck J. Consolidative mechanisms of emotional processing in REM sleep and PTSD. *Sleep Med Rev*. 2018; 41:173-184. ³Daugherty et al., Abstract 728, Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015, Toronto Ontario, Canada



Proposed Mechanism of Action of TNX-102 SL in the Treatment of PTSD: Focus on Nocturnal 5-HT_{2A} Receptor Blockade in REM

22

- Generally, serotonin (5-HT) activity promotes the awake state and inhibits REM sleep; whereas once in REM sleep, the 5-HT system is normally quiescent
- Extinction learning is critical to recovery from trauma, and such new learning is consolidated (moving from labile short term to established long term memory) during particular stages of sleep^{1,2}
- Recent rodent research shows how particular brain wave patterns during REM sleep, known as "P-waves" are critical to extinction consolidation³
- 5-HT activation of pontine brainstem region richly expressing 5-HT_{2A} receptors inhibits P-wave generation during REM⁴
- Nocturnal blockage of 5-HT_{2A} receptors may restore extinction consolidation by inhibition of errant 5-HT stimulation during REM (see model in next 2 slides)

1. Pace-Schott, et al. *Biology of Mood & Anxiety Disorders*. 2015;5(3):1-19.

2. Straus et al. *Biol Psychol: CNMI*. 2017;2(2):123-129.

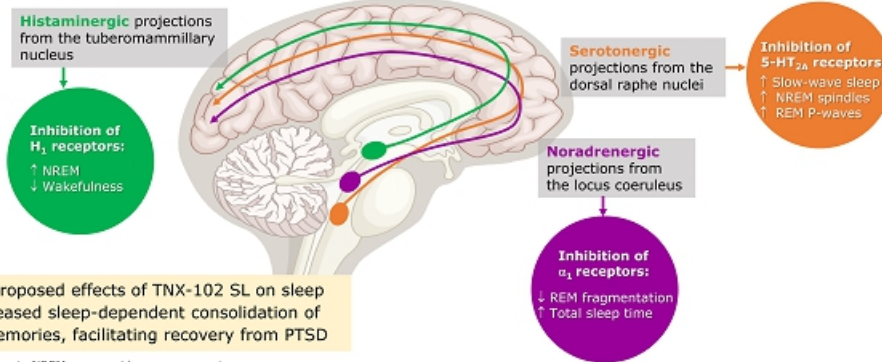
3. Datta S, et al. *J Neurosci*. 2013;33(10):4561-4569.

4. Datta S, et al. *Sleep*. 2003;26(5):513-520.



Proposed Mechanism of Action of TNX-102 SL in the Treatment of PTSD: The Effects of Nocturnal Neuroreceptor Blockade on Sleep

Cyclobenzaprine is a functional antagonist at serotonergic 5-HT_{2A} receptors, noradrenergic α_1 receptors, and histaminergic H₁ receptors



The overall proposed effects of TNX-102 SL on sleep leads to increased sleep-dependent consolidation of extinction memories, facilitating recovery from PTSD

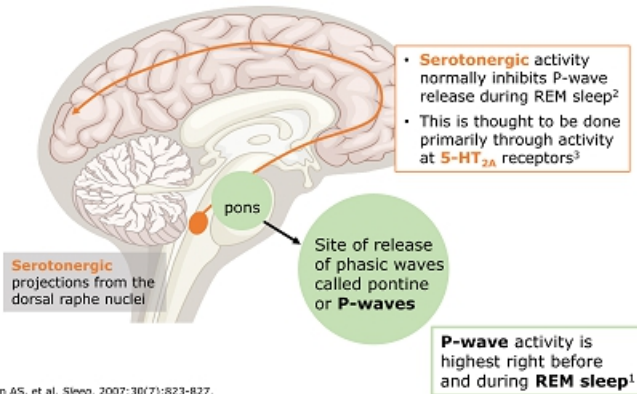
REM, rapid eye movement; NREM, non-rapid eye movement; P-waves, ponto-geniculo-occipital waves

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Fear Extinction Memory Consolidation: The Proposed Role of P-Waves, REM Sleep, and Serotonergic Neuroreceptor Activity

24



- Increased P-wave activity during REM sleep is critical for fear extinction memory consolidation in rats⁴
- By blocking 5-HT_{2A} receptors, cyclobenzaprine may sustain P-wave activity during REM sleep
- This blockade may lead to better quality of REM sleep with increased fear extinction consolidation in individuals with PTSD, facilitating recovery

P-waves, ponto-geniculo-occipital waves; REM, rapid eye movement

1. Lim AS, et al. *Sleep*. 2007;30(7):823-827.
2. Datta S, et al. *Sleep*. 2003;26(5):513-520.
3. Tamas K, Gyorgy B. Effect of 5-HT_{2A/2B/2C} receptor agonists and antagonists on sleep and waking in laboratory animals and humans. In: Monti JM, Pandi-Perumal SR, Jacobs BL, Nutt DJ, eds. *Serotonin and sleep: Molecular, functional, and clinical aspects*. Basel, Switzerland: Birkhäuser Basel; 2006.
4. Datta S, et al. *J Neurosci*. 2013;33(10):4561-4569.



Phase 2 P201/AtEase¹ Study in Military-Related PTSD

25

Placebo at bedtime once-daily
N= 92*

TNX-102 SL at bedtime once-daily
2.8 mg N= 90*

TNX-102 SL at bedtime once-daily
5.6 mg (2 x 2.8 mg) N= 49*

- Randomized, double-blind, placebo-controlled trial in military-related PTSD
 - Efficacy analysis from 231* patients; 24 U.S. clinical sites
 - Enrolled patients with baseline CAPS-5² ≥ 29
 - Primary Efficacy Analysis:
 - Difference in CAPS-5 score change from baseline between TNX-102 SL 2.8 mg and placebo at Week 12
 - Key Secondary Measures:
 - PROMIS Sleep Disturbance, CGI-I, SDS
- 12-week open-label extension

12 weeks

¹ClinicalTrials.gov Identifier: NCT02277704
²CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
*Modified intent-to-treat population



P201 was a large adequate well-controlled Phase 2 study in military-related PTSD

- Primary endpoint (Week 12 CAPS-5) did not separate from placebo for TNX-102 SL 2.8 mg
- No safety or tolerability issue discovered
- Retrospective analyses showed TNX-102 SL 5.6 mg had a strong signal of treatment effect at Week 12 CAPS-5 (P=0.053) and CGI-I (P=0.041) scores
- Retrospective analyses suggested CAPS-5 \geq 33 enrollment criteria for Phase 3



P201/AtEase Study – Summary of Primary and Secondary Analyses (Week 12)

Assessment	Domain	Analysis	p-Values	
			2.8 mg (N=90)	5.6 mg (N=49)
CAPS-5	Total	MMRM (Primary Analysis)	0.259 [^]	0.053
	Total	MMRM with Multiple Imputation	0.211	0.031*
	Total	MMRM w/ Hybrid LOCF/BOCF	0.172	0.037*
	Total	ANCOVA	0.090	0.038*
CAPS-5 clusters/items	Arousal & Reactivity cluster (E)	MMRM	0.141	0.048*
	Sleep item (E6)	MMRM	0.185	0.010*
	Exaggerated Startle item (E4)	MMRM	0.336	0.015*
CGI-I	Responders	Logistic Regression	0.240	0.041*
PGIC	Mean score	MMRM	0.075	0.035*
Sheehan Disability Scale	Work/school item	MMRM	0.123	0.050*
	Social/leisure item	MMRM	0.198	0.031*

BOCF, baseline observation carried forward; CGI-I, Clinical Global Impression - Improvement scale; LOCF, last observation carried forward;

MMRM, mixed model repeated measures; PGIC, Patient Global Impression of Change

[^]Primary analysis p-value not significant comparing Tonmya 2.8 mg versus placebo

*p<0.05



P301/HONOR¹ Study –Evidence of Efficacy at Week 4 Discontinued Due to High Placebo Response at Week 12

28

General study characteristics:

Randomized, double-blind, placebo-controlled, adaptive design, planned 550 military-related PTSD participants with baseline CAPS-5² ≥ 33 in approximately 40 U.S. sites

TNX-102 SL once-daily at bedtime

5.6 mg (2 x 2.8 mg tablets)

N= 125*

Placebo once-daily at bedtime

N= 127*

————— 12 weeks —————>|..... 12-week and/or 40-week open-label extension studies

Primary endpoint CAPS-5²:

- Mean change from baseline at Week 12 (TNX-102 SL 5.6 mg vs. placebo)

Unblinded interim analysis at 274 randomized participants (mITT³ N= 252)

- Study stopped due to not meeting a pre-specified study continuation threshold at Week 12
- Participants discontinued in HONOR or 12-week open-label extension (OLE) studies can enroll in the 40-week OLE study

¹ClinicalTrials.gov Identifier: NCT03062540

²CAPS-5 = Clinician-Administered PTSD Scale for DSM-5

*Modified intent-to-treat population



P301/HONOR Study- Primary Analysis in mITT Population

29

Visit Statistic	Placebo N=127		TNX-102 SL 5.6 mg N=125		Difference
	CAPS-5 Value	MCFB	CAPS-5 Value	MCFB	
Week 4					
LS Mean (SE)	31.0 (1.62)	-11.2 (1.62)	27.5 (1.73)	-14.7 (1.73)	-3.6 (1.51)
95% CI	(27.8,34.2)	(-14.4,-8.0)	(24.1,30.9)	(-18.1,-11.4)	(-6.5,-0.6)
p-value					0.019
Week 8					
LS Mean (SE)	29.4 (1.76)	-12.8 (1.76)	27.6 (1.86)	-14.6 (1.86)	-1.8 (1.77)
95% CI	(25.9,32.8)	(-16.3,-9.4)	(24.0,31.3)	(-18.2,-10.9)	(-5.2,1.7)
p-value					0.321
Week 12					
LS Mean (SE)	28.0 (1.80)	-14.2 (1.80)	27.0 (1.90)	-15.2 (1.90)	-1.0 (1.88)
95% CI	(24.5,31.5)	(-17.7,-10.7)	(23.3,30.8)	(-18.9,-11.4)	(-4.7,2.7)
p-value					0.602

MMRM with Multiple Imputation

In P301 study both TNX-102 SL and placebo-treated groups improved but the greater improvement on TNX-102 SL compared with placebo diminished over time

- TNX-102 SL did not separate from placebo at primary endpoint

LS Mean (SE) = Least Squares Mean (Standard Error)

CI = Confidence Interval

MCFB = Mean Change From Baseline

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Differences Between P201/AtEase and P301/HONOR Studies Design

30

Categories	P201	P301
No. of US Sites Randomizing \geq 1	24	43
No. of Treatment Arms	3	2
Baseline Entry CAPS-5 Threshold	\geq 29	\geq 33
Range of Includable Ages, years	18-65	18-75
Depression Rating Scale Employed	MADRS	BDI-II
Minimum Time Since No TFT	1 month	3 months
Primary Endpoint Analytic Method	MMRM	MMRM with MI
No. of In-Clinic Study Visits	9	5
No. of CAPS-5 Administrations	6	5
Key Secondary Endpoints	CGI-I, SDS, PROMIS SD	CGI-I, SDS

Phase 2 and 3 studies were very similar – both studied military related PTSD at multiple sites in the US

- CAPS-5 \geq 33 entry criteria used in Phase 3

BDI-II= Beck Depression Inventory-II; CGI-I=Clinical Global Impression – Improvement; MI= multiple imputation; MMRM=mixed model repeated measures; MADRS=Montgomery-Åsberg Depression Rating Scale; PROMIS SD=Patient-Reported Outcomes Measurement Information System – Sleep Disturbance; SDS=Sheehan Disability Scale; TFT=trauma-focused therapy

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P201/AtEase and P301/HONOR Demographics and Characteristics

31

Variable	P201			P301	
	Placebo N=92	TNX 2.8 mg N=90	TNX 5.6 mg N=49	Placebo N=127	TNX 5.6 mg N=125
Females, %	6.50%	6.70%	8.20%	13.40%	8.00%
Age, yrs. (SD)	32.0	34.5	34.8	35.5	35.9
Body Mass Index, kg/m ²	28.9	29.0	29.0	29.3	29.9
Employment (current), %	58.7%	62.2%	67.3%	63.0%	55.2%
Unable to work due to PTSD, %	9.8%	11.1%	14.3%	12.6%	16.8%
Active Duty/Reservists/Veterans, No.	8/4/79	9/5/71	5/7/37	17/0/110	9/0/116
Time since trauma, mean years	7.1	7.3	6.2	9.2	9.2
Time since trauma, median years	7.0	7.2	6.0	9.3	9.5
Combat index trauma, %	80.4%	85.6%	93.8%	77.2%	83.2%
Number of deployments	2.2	2.3	2.6	3.0	2.6
Baseline CAPS-5 Scores	39.5	39.5	39.3	42.4	42.0
Baseline BDI-II Scores	NA	NA	NA	23.0	25.6
Baseline MADRS Scores	17.3	17.6	16.1	NA	NA

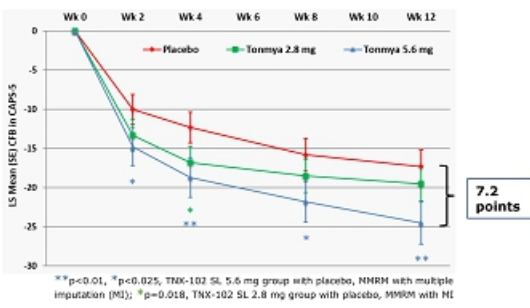
The striking difference between P201 and P301 was time since trauma

- Phase 2 P201 study recruited many participants from the surge in Iraq who were mostly <9 years since trauma

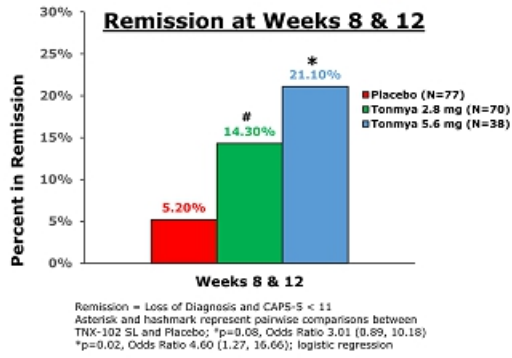


TNX-102 SL Phase 2 Dose-Effect in Military-Related PTSD¹

PTSD Symptoms (CAPS-5² Score)



Remission at Weeks 8 & 12



¹ Completed Phase 2 P201/MEase study: Retrospective analysis of TNX-102 SL 5.6 mg on CAPS-5 ≥33 (high-moderate) subgroup. Primary analysis of P201/MEase, based on TNX-102 SL 2.8 mg in participants with entry CAPS-5 ≥29 (moderate PTSD severity), was not statistically significant.
² CAPS-5 = Clinician administered PTSD Scale for DSM-5



Primary Outcome (CAPS-5) in Phase 3 Study: mITT and ≤ 9 Years Time Since Trauma Subgroup

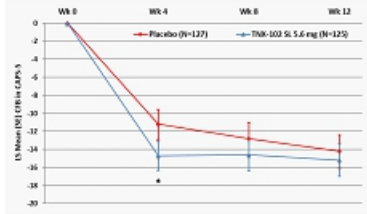
Phase 3 P301/HONOR Study¹

PTSD Symptoms (CAPS-5 Score)

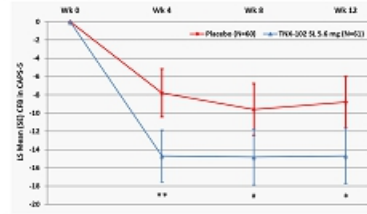
PTSD Symptoms (CAPS-5 Score)

Modified intent to treat (mITT) population

Time Since Trauma (TST) ≤ 9 yrs



~50% mITT Population



* $p=0.019$, TNX-102 SL 5.6 mg group v. placebo, using mixed model repeated measures (MMRM) with multiple imputation (MI)

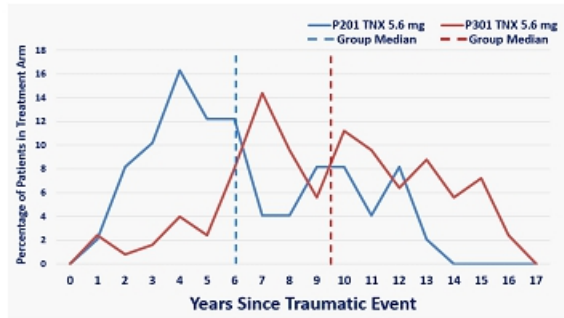
** $p=0.004$, * $p=0.069$, * $p=0.039$, TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

¹ Phase 3 P301/HONOR study: stopped in July 2018. Separation on primary endpoint did not cross pre-specified study continuation threshold at Week 12 in the interim analysis at ~50% randomization; no safety or tolerability issues discovered.



Retrospective Comparison of Time Since Trauma in P201/AtEase versus P301/HONOR (TNX-102 SL 5.6 mg Groups)

34

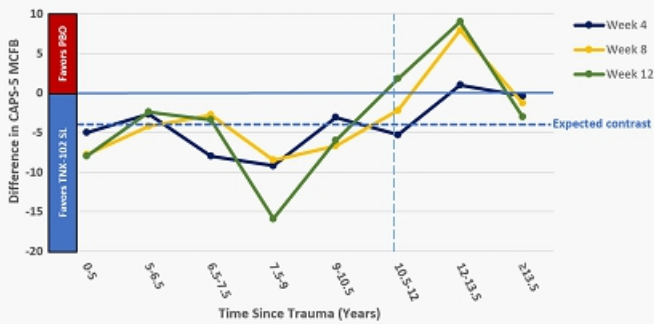


P301 study was initiated approximately two years later than Phase 2 P201

- The median time since trauma in P301 was 9.5 years compared to the median time since trauma in P201 of 6.0 years for TNX-102 SL 5.6 mg treated groups



CAPS-5 Mean Change from Baseline Difference from Placebo of TNX-102 SL 5.6 mg in TST Subgroups in P301¹



- The mITT population was divided into subgroups based on TST (1.5-2 years each as well as 0-5 years and ≥13.5 years subgroups)
- Graph shows the CAPS-5 differences in MCFB between TNX 5.6 mg and PBO for Weeks 4, 8, and 12 post-baseline timepoints
- "Expected contrast" horizontal dashed line indicates observed effect from Phase 2 P201 study
- For TST <10.5 years groups, TNX 5.6 mg showed good separation from PBO (left side of vertical dashed 10.5 year line)
- For TST >10.5 years groups, separation of TNX 5.6 mg from PBO was either small or worked in the favor of PBO (right side of vertical dashed 10.5 year line)

Group TST (yrs)	0-5	5-6.5	6.5-7.5	7.5-9	9-10.5	10.5-12	12-13.5	≥13.5
Placebo 'N'	12	23	11	13	21	18	15	18
TNX-5.6 mg 'N'	14	17	16	12	22	10	17	18

¹Time Since Trauma in PTSD: Phase 3 Multi-Center, Double-Blind, Placebo-Controlled Trial of TNX-102 SL, a Sublingual Formulation of Cyclobenzaprine, in Military-Related PTSD (Study TNX-CY-P301) Presented at CNS Summit in Boca Raton, FL November 1-4, 2018 and abstract published in *Innovations in Clinical Neuroscience*, November-December 2018;15(11-12,suppl):S10. <https://content.equisolve.net/tonixpharma/media/1d0c4055b2863fc74e1ef45f9dda442b.pdf>

MCFB=mean change from baseline; 'N'=number of participants in group; PBO=placebo; TST=time since trauma
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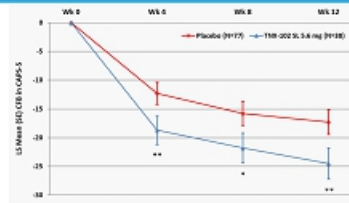
PTSD Treatment Response to TNX-102 SL in Phase 2 and Phase 3 Studies: Retrospective Analyses of P201 Entry CAPS-5 ≥ 33 and P301 ≤ 9 Years Since Trauma Subgroups

Change in CAPS-5 over course of treatment with TNX-102 SL

CAPS-5 is a structured interview assessing PTSD severity

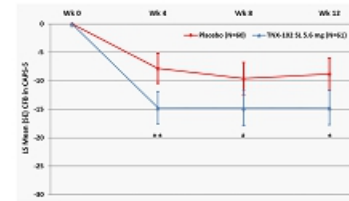
- Required primary endpoint for PTSD drug approval

Decrease in PTSD severity in Phase 3 subgroup ≤ 9 years since TST is similar to Phase 2 subgroup with baseline CAPS-5 ≥ 33



P201 Baseline CAPS-5 ≥ 33 (majority TST¹ ≤ 9 yr)

**p<0.01, *p=0.017, TNX-102 SL 5.6 mg group v. placebo, using mixed model repeated measures (MMRM) with multiple imputation (MI)



P301 TST ≤ 9 yr

**p=0.004, *p=0.039, #p=0.069 TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

¹Time since trauma;

²Majority of P201 participants were ≤ 9 years since trauma and ~80% of P201 participants and all of P301 participants were ≥ 33 CAPS-5 at baseline
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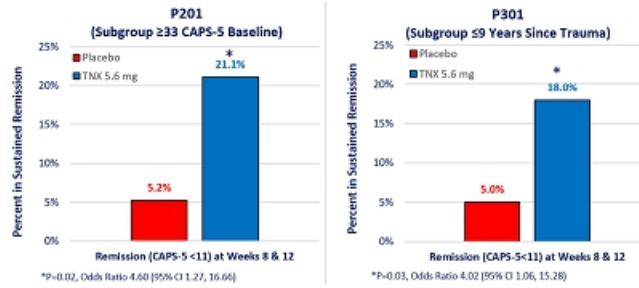
Sustained Remission in Phase 2 and Phase 3 Studies: Retrospective Analyses of P201 Entry CAPS-5 ≥ 33 and P301 ≤ 9 Years Since Trauma Subgroups

Remission is a clinical state that is essentially asymptomatic

In order to confirm remission:

- Determined rates of participants who met remission status at both Week 8 and Week 12

Rate of remission in ≤ 9 years since trauma group in P301 is similar to baseline CAPS-5 ≥ 33 group in P201¹



¹Majority of P201 participants were ≤ 9 years since trauma and ~80% of P201 participants and all of P301 participants were ≥ 33 CAPS-5 at baseline



Sustained Remission in P201/AtEase Study Retrospective Analyses of Phase 2 Subgroups with and without Oral AE's (ON/OT/NT)

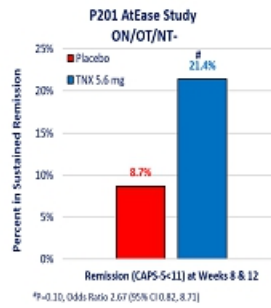
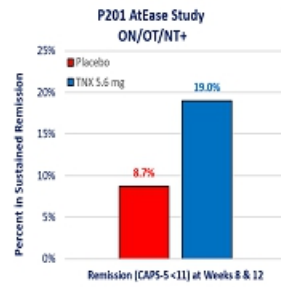
38

Oral numbness (ON), oral tingling (OT) and noticeable taste (NT) are local administration site reactions that are potentially unblinding

- Subgroups with and without ON/OT/NT were studied in participants who met remission status at *both* Week 8 and Week 12

Similar rates of remission were observed in participants in P201 with and without oral AE's

- Unblinding was unlikely to account for treatment effect



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Retrospective Analyses of ≤ 9 Years Since Trauma Subgroup on Primary and Secondary Endpoints in P301/HONOR Study

Measure			P301 mITT				P301 ≤ 9 Year Subgroup			
			PBO (N=127) v. TNX-5.6 (N=125)				PBO (N=60) v. TNX-5.6 (N=61)			
			Week 4		Week 12		Week 4		Week 12	
Analysis	LSMD	p-value	LSMD	p-value	LSMD	p-value	LSMD	p-value		
1°	CAPS-5	MMRM/MI	-3.6	0.019	-1.0	0.602	-6.9	0.004	-5.9	0.039
2°s	CGI-I	MMRM	-0.3	0.015	-0.1	0.403	-0.6	0.002	-0.5	0.021
	SDS	MMRM	-0.2	0.785	-1.6	0.101	-1.8	0.167	-4.3	0.007
	PGIC	MMRM	-0.2	0.238	-0.3	0.020	-0.4	0.045	-0.6	0.007
	PROMIS SD	MMRM	-3.1	0.015	-2.7	0.082	-4.5	0.029	-5.0	0.042
	BDI-II	MMRM	-1.1	0.330	-1.4	0.255	-5.2	0.008	-6.6	0.001

BOLDED p-values are all p<0.05; BDI-II=Beck Depression CAPS-5=Clinician-Administered PTSD Scale for DSM-5; CGI-I=Clinical Global Impression - Improvement scale; mITT=modified Intent-to-Treat sample; MMRM=mixed model repeated measures analysis; MI=multiple imputation; PGIC=Patient Global Impression of Change scale; PROMIS SD=Patient-Reported Outcome Measurement Information System Sleep Disturbance instrument (short form 8a); PBO=placebo; SDS=Sheehan Disability Scale; TNX-5.6=TNX-102 SL 5.6 mg; yrs=years; 1°=primary; 2°s=secondaries

Secondary endpoints also showed strong treatment effects in ≤ 9 yrs TST

- Support CAPS-5 results and similar to Phase 2 P201 Study results



Adverse Events (AEs) in P201/AtEase and P301/HONOR Studies

Category of Adverse Reaction Preferred Term	P201			P301	
	Placebo (N=94)	TNX 2.8 mg (N=93)	TNX 5.6 mg (N=50)	Placebo (N=134)	TNX 5.6 mg (N=134)
Systemic Adverse Events**					
Somnolence	6.4%	11.8%	16.0%	9.0%	15.7%
Dry mouth	10.6%	4.3%	16.0%		
Headache	4.3%	5.4%	12.0%		
Insomnia	8.5%	7.5%	6.0%		
Sedation	1.1%	2.2%	12.0%		
Local Administration Site Reactions**					
Hypoesthesia oral	2.1%	38.7%	36.0%	1.5%	37.3%
Paraesthesia oral	3.2%	16.1%	4.0%	0.7%	9.7%
Glossodynia	1.1%	3.2%	6.0%		
Product Taste Abnormal				3.0%	11.9%

*only adverse events (AEs) are listed that are at a rate of $\geq 5\%$ in any TNX-treated group

**no values in a row for either study means the AE in the active group(s) in that study was at a rate of $<5\%$

No serious or unexpected AEs in P201 or P301 related to TNX-102 SL

- Systemic AEs comparable between studies and also consistent with those described in approved oral cyclobenzaprine product labeling
- Severity and incidence of oral hypoesthesia (oral numbness) are not dose related and similar in both studies



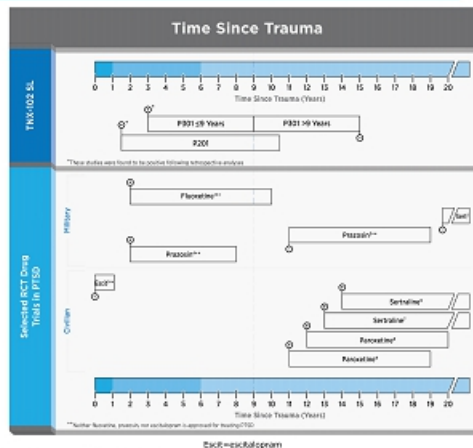
Published studies of prazosin suggested effects in military-PTSD prior to 9 years

- Loss of treatment effect >9 years

Paroxetine and sertraline studies supporting FDA approval were conducted on PTSD > 9 years

- SSRIs have a benefit long after trauma

¹Martenyi et al. *J Clin Psychiatry* 2002;63:199-206.
²Friedman et al. *J Clin Psychiatry* 2007;68:711-720.
³Raskind et al. *NEJM* 2018;378:507-517.
⁴Raskind et al. *Am J Psychiatry* 2013;170:1003-1010.
⁵Shalev et al. *Arch Gen Psychiatry* 2012;69:166-176.
⁶Davidson et al. *Arch Gen Psychiatry* 2001;58:485-492.
⁷Brady et al. *JAMA* 2000;283:1837-1844.
⁸Marshall et al. *Am J Psychiatry* 2001;158:1962-1968.
⁹Tucker et al. *J Clin Psychiatry* 2001;62:860-868.

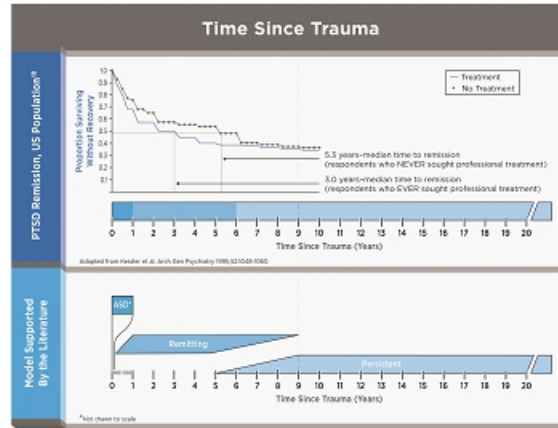




Time Since Trauma – Remitting and Persistent Phases of PTSD

Kessler et al¹ studied remission in PTSD with and without therapy

- Identified remitting and persistent phase of PTSD – with transition at approximately 6 years post trauma
- Supported by other studies²⁻⁶



¹Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.

²Armenta et al. *BMC Psychiatry* 2018;18:46.

³Gelzater-Ley et al. *PLOS ONE* 2013;8:e70084.

⁴Perkonig et al. *Am J Psychiatry* 2005;162:1320-1327.

⁵Santiago et al. *PLOS ONE* 2013;8:e59236.

⁶Davidson & Connor. *Eur Neuropsychopharmacol* 2001;11(Supp3):S148-S149. © 2019 Tonix Pharmaceuticals Holding Corp.



Response to TNX-102 SL for Female Participants in P301/HONOR Study¹

43

Females made up only 11% of the P301/HONOR study mITT population

Difference in mean change from baseline in CAPS-5 in females between placebo (N=17) and TNX-102 SL 5.6 mg (N=10) was:

- At 4 weeks -11.5 points
- At 12 weeks -9.1 points

Indicates substantial separation from placebo in the small number of female participants

Predicts therapeutic response to TNX-102 SL 5.6 mg likely in mixed civilian and military PTSD population to be studied in current P302/RECOVERY trial

- Civilian PTSD population tends to be about 2/3 female

¹ Presented at CNS Summit in Boca Raton, FL November 1-4, 2018; Poster 8A, Friday Nov. 2, 5:00-7:00 PM EDT, Reception and Poster Session, and abstract published in *Innovations in Clinical Neuroscience*, November-December 2018;15(11-12, suppl):S10.
<https://content.equisolve.net/tonixpharma/media/1d0c4055b2863fc74e1ef45f9ddaf42b.pdf>



Response to TNX-102 SL for Non-Combat Traumas in P301/HONOR Study in ≤ 9 Years Time Since Trauma Subgroup¹

44

Non-combat traumas studied are similar to traumas experienced in civilian populations with PTSD

To determine the therapeutic effects of TNX-102 SL 5.6 mg in a mixed civilian and military population, difference in MCFB in CAPS-5 was assessed in non-combat traumas in ≤ 9 years TST subgroup (placebo N=14, TNX-102 SL 5.6 mg N=10):

- At 4 weeks -4.8 points
- At 12 weeks -4.4 points

Non-combat traumas treated with TNX-102 SL 5.6 mg showed clinically meaningful separation from placebo at Weeks 4 and 12, suggesting a mixed civilian and military sample within 9 years of index trauma may show a therapeutic response to TNX-102 SL

¹ Presented at CNS Summit in Boca Raton, FL November 1-4, 2018; Poster 8A, Friday Nov. 2, 5:00-7:00 PM EDT, Reception and Poster Session, and abstract published in Innovations in Clinical Neuroscience, November-December 2018;15(11-12, suppl):S10. <https://content.equisolve.net/tonixpharma/media/1d0c4055b2863fc74e1ef45f9ddaf42b.pdf>
CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; MCFB = mean change from baseline; mITT = modified Intent-to-Treat sample; TST = time since trauma



Median time since trauma (TST) in TNX-102 SL 5.6 mg group in the P301/HONOR study (9.5 years) was longer than P201/AtEase study (6 years)

- Both studied military-related PTSD
- Time has passed since the surge in Iraq

In retrospective analysis, the ≤ 9 year TST subgroup of P301 study had similar results as the P201 study (primary and secondary)

- TST is important in placebo-controlled clinical study
- Potential enrichment in ≤ 9 years TST subgroup for treatment responders

The ≤ 9 year TST subgroup of P301 may be enriched for "Remitting Phase" of PTSD¹⁻⁴

- Expect remitting phase of PTSD is more amenable to drug studies

Results from retrospective analyses lead to improved Phase 3 study design

¹Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.

²Arnsperger et al. *BMC Psychiatry* 2018;18:48.

³Galatzer-Levy et al. *PLoS ONE* 2013;8:e70084.

⁴Perkonig et al. *Am J Psychiatry* 2005;162:1320-1327.



TNX-102 SL for PTSD: Phase 3 P302/RECOVERY Study Expecting Interim Analysis Results in 1Q 2020

46

General study characteristics:

- Randomized, double-blind, placebo-controlled study with baseline CAPS-5¹ ≥ 33 in approximately 30 U.S. sites
- Enrollment restricted to study participants with PTSD who experienced an index trauma ≤ 9 years from the date of screening
- Both civilian and military-related PTSD to be included

TNX-102 SL once-daily at bedtime
5.6 mg (2 x 2.8 mg tablets) *N= 125*

Placebo once-daily at bedtime
N= 125

12 weeks

Potential pivotal efficacy study to support NDA approval

Primary endpoint:

- CAPS-5¹ mean change from baseline at Week 12 (TNX-102 SL 5.6 mg vs. placebo)

Key Secondary endpoints include:

- Change from baseline Clinical Global Impression – Severity scale
- Change from baseline Sheehan Disability Scale total score

Interim analysis results expected 1Q 2020

Topline data expected 2Q 2020

¹CAPS-5 = Clinician-Administered PTSD Scale for DSM-5



Commercialization Options

47

Tonix is exploring a variety of options to commercialize TNX-102 SL, including commercializing on our own or partnering all or some indications in specific regions of the world

Tonix has participated in numerous partnering meetings

Commercial Considerations:

- Primary physician audience is well defined: psychiatrists (~30,000 in U.S.)
 - Small specialty sales force sufficient for coverage
- Primary market research with psychiatrists indicate strong interest in new therapeutic options



TNX-102 SL – Multi-Functional Mechanism Involves Antagonism at 3 Neuronal Receptors

48

Active ingredient, cyclobenzaprine, interacts with 3 receptors

- Antagonist at 5-HT_{2A} receptors
 - Similar activity to trazodone and Nuplazid® (pimivanserin)
- Antagonist at α_1 -adrenergic receptor
 - Similar activity to prazosin
- Antagonist at histamine H₁ receptors
 - Similar activity to Benadryl® (diphenhydramine) and hydroxyzine

Multi-functional activity suggests potential for other indications

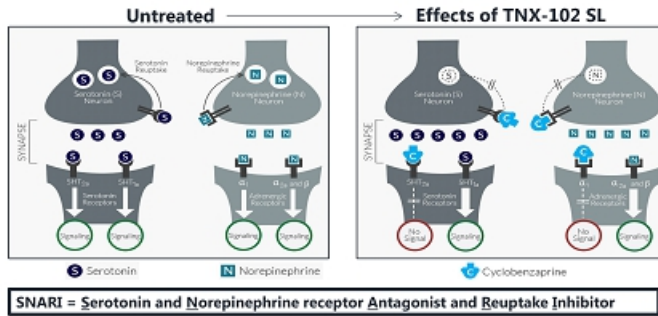
- TNX-102 SL was developed for the management of fibromyalgia (Phase 3)
- Sleep quality is a problem in other conditions



Cyclobenzaprine Effects on Nerve Cell Signaling

Cyclobenzaprine is a multi-functional drug - SNARI

- inhibits serotonin and norepinephrine reuptake
- blocks serotonin 5-HT_{2A} and norepinephrine α_1 receptors





Opportunities to Expand to Other Indications

51

Role of sleep disturbance more established in common psychiatric and neurological/pain disorders

- Recognized as a core symptom of many of these disorders
- Traditional sleep medications, which increase sleep quantity, may not provide benefit (benzodiazepines in major depression) or are contraindicated (benzodiazepines in PTSD)

Psychiatric Disorders

- Stress Disorders (PTSD)
- Mood Disorders (MDD)
- Anxiety Disorders
- Addiction (Alcohol Use Disorder)

Psychiatric Symptoms of Neurological Disorders

- Agitation in Alzheimer's
- Psychosis in Parkinson's, Alzheimer's and other dementias

Chronic Pain States

- Chronic wide-spread pain (fibromyalgia)
- Osteoarthritis

Growing recognition that there are many disorders where sleep disturbances may have a role in the pathophysiology (cardiovascular, metabolic, neurologic)

- Homeostatic role of sleep quality *in several disorders*

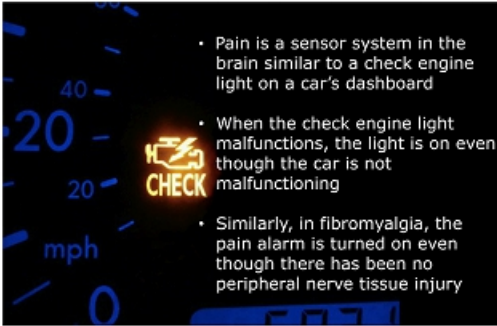


Management of Fibromyalgia (FM) – chronic pain condition

- TNX-102 SL 2.8 mg (half the dose being developed for PTSD) studied in Phase 2/3 trials– did not separate from placebo on primary endpoint: average pain improvement (responder analysis)
- Retrospective analysis showed average pain improvement (secondary endpoint) after 12 weeks of treatment showed statistical significance ($P < 0.05$, MMRM)
- Consistent improvement in sleep quality demonstrated
- TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) will be studied in new Phase 3 study to support product registration (April 2019 FDA meeting minutes)

Agitation in Alzheimer’s Disease

- Received Phase 2/potential pivotal efficacy study protocol comments from FDA in October 2018



Volkswagen Check Engine (Photograph). (2012, October 14). Wikipedia

- Pain is a sensor system in the brain similar to a check engine light on a car's dashboard
- When the check engine light malfunctions, the light is on even though the car is not malfunctioning
- Similarly, in fibromyalgia, the pain alarm is turned on even though there has been no peripheral nerve tissue injury

- Fibromyalgia is considered a neurobiological disorder characterized by¹: chronic widespread pain, non-restorative sleep, fatigue, diminished cognition
- Believed to result from inappropriate pain signaling in central nervous system in the absence of peripheral injury¹
- Causes significant impairment in all areas of life²
 - Lower levels of health-related quality of life – reduced daily functioning
 - Interference with work (loss of productivity, disability)
- Inflicts substantial strain on the healthcare system
 - Average patient has 20 physician office visits per year³
 - Annual direct medical costs are twice those for non-fibromyalgia individuals⁴

¹ Philips K & Clauw DJ, Best Pract Res Clin Rheumatol 2011;25:141.

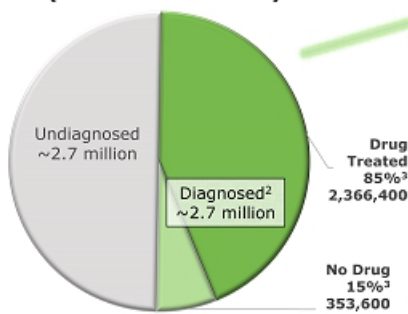
² Schaefer et al., Pain Pract, 2015.

³ Robinson et al, Pain Medicine 2013;14:1400.

⁴ White et al, J Occupational Environ Med 2008;50:13.



U.S. Prevalence Rate 2-4%¹ (~6-12 million adults)



Market Characteristics

Prevalence

- One of the more common chronic pain disorders

Diagnosed population

- Large population (~2.7 million) but underdiagnosed relative to prevalence rate
- Majority receive drug treatment

Treatment Pattern

- Polypharmacy the norm - average 2.6 drugs/patient³
- Rotation through therapy common: average ~5 drugs/year³
- Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year^{4,5}

Unmet Need

- Majority of patients do not respond or cannot tolerate therapy⁶

1. American Chronic Pain Association (www.theacpa.org, 2019)

2. Vincent et al., *Arthritis Care Res* 2013; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population

3. Robinson, et al., *Pain Medicine*, 2012; 85% received drug treatment

4. Vincent et al., *Arthritis Care Res* 2013;65:786

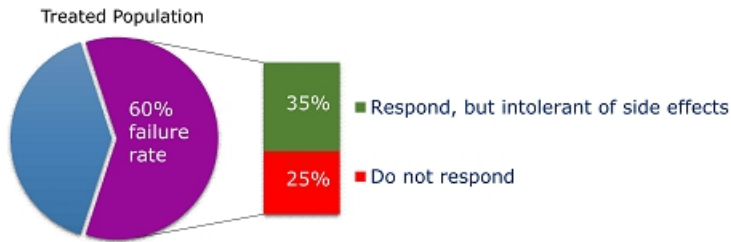
5. Product sales derived from IMS MIDAS; IMS MIDAS used to factor usage for fibromyalgia; data accessed April 2015.

6. Market research by Frost & Sullivan, commissioned by Tonix, 2011



Fewer than Half of Those Treated for Fibromyalgia Receive Complete Relief from the Three FDA-Approved Drugs¹

- The treatment objective is to **restore functionality** and **quality of life** by broadly improving symptoms while avoiding significant side effects
- The majority fail therapy due to **lack of a response** or **poor tolerability**²



¹ The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)
² Market research by Frost & Sullivan, commissioned by Tonix (2011)



Large Need for New Fibromyalgia Therapies that Provide Broad Symptom Improvement with Better Tolerability

56

- Currently-approved medications may have side effects that limit long-term use¹
 - Many patients skip doses or discontinue altogether within months of treatment initiation
- Medication-related side effects may be similar to fibromyalgia symptoms
- High rates of discontinuation, switching and augmentation
 - Attempt to treat multiple symptoms and/or avoid intolerable side effects
 - Average of 2-3 medications used simultaneously²
 - The typical patient has tried six different medications³
- Substantial off-label use of narcotic painkillers and prescription sleep aids³
 - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment⁴
- TNX-102 SL is a non-opioid, centrally-acting analgesic that could provide a new therapeutic option for fibromyalgia patients

¹ Nuesch et al, Ann Rheum Dis 2013;72:955-62.

² Robinson RL et al, Pain Medicine 2012;13:1366.

³ Patient Trends: Fibromyalgia[®], Decision Resources, 2011.

⁴ Berger A, Dukes E, Martin S, Edelsberg J, Oster G, Int J Clin Pract, 2007; 61(9):1498-1508.



TNX-102 SL 2.8 mg for Fibromyalgia: Summary of Completed Phase 3 AFFIRM Study (F301) and Results

57

General study characteristics:

- Randomized, 12-week, double-blind, placebo-controlled Phase 3 study of TNX-102 SL 2.8 mg (half the dose being developed for PTSD) taken daily at bedtime (n=519)
- Patients had to satisfy the 2010 ACR Preliminary Diagnostic Classification Criteria
- **Primary endpoint:** Weekly average pain improvement as a 30% responder analysis
- **Secondary endpoints:** PGIC, FIQ-R Symptom Domain, FIQ-R Function Domain, Daily Sleep Quality Diary, PROMIS Sleep Disturbance

Efficacy results:

- Completers: 425 (81.9%) of 519 patients in Intent-to-Treat population
- The primary analysis (responder analysis) was not statistically significant (P=0.095). However, the pre-specified secondary analysis of average pain improvement after 12 weeks of treatment showed P<0.001, mixed model repeated measures (MMRM)
- Significant improvements observed in sleep quality, patient global impression of change and fibromyalgia-specific measures (secondary analyses)

PGIC = Patient Global Impression of Pain
FIQ-R = Fibromyalgia Impact Questionnaire - Revised
MMRM = mixed model repeated measures

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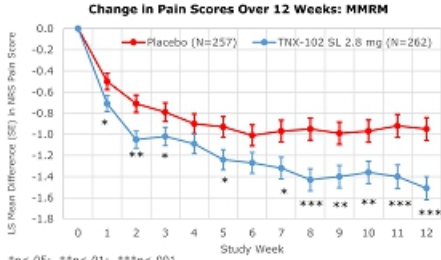
Phase 3 AFFIRM (F301) Study Results: Mean Pain Analyzed by Mixed Model Repeated Measures (MMRM), with and without Multiple Imputation

Pre-specified secondary analysis of AFFIRM:

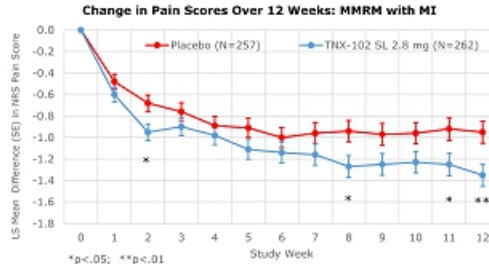
- Mean Pain Analysis, MMRM
- TNX-102 SL N=262; Placebo N=257
- Difference in LS Mean (SE): -0.6 (0.15); 95% CI (-0.8, -0.3); p<0.001

Retrospective analysis of AFFIRM:

- Mean Pain Analysis, MMRM with MI*
- TNX-102 SL N=262; Placebo N=257
- Difference in LS Mean (SE): -0.4 (0.14); 95% CI (-0.7, -0.1); p = 0.005
- Tonix intends to use MMRM with MI in calculating the primary endpoint for the new RELIEF (F304) study, in line with current FDA statistical guidance on handling of missing data



*p<.05; **p<.01; ***p<.001



*p<.05; **p<.01

*As will be the case for the RELIEF F304 primary analysis, all discontinuations due to Adverse Event and Lack of Efficacy are imputed using MI based on baseline values; all other discontinuations assumed to be Missing at Random and are imputed with MI using weekly data of subjects.
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TNX-102 SL 2.8 mg for Fibromyalgia: F301 Study Results and Program Updates

59

Safety results:

- Good tolerability and low rates of systemic AEs.
- The most common AEs were generally mild and transient events related to the sublingual administration of the study drug:
 - hypoesthesia (tongue or oral numbness)
 - glossodynia (burning sensation or other tongue discomfort)
 - oral paresthesias (tingling sensations)
 - abnormal product taste (bitter or noticeable taste)
- The severity and incidence of oral AEs are similar to those reported in our PTSD studies using TNX-102 SL 5.6 mg.

Conclusion:

- The results and efficacy findings support further investigation of TNX-102 SL at double the dose, 5.6 mg (2 x 2.8 mg tablets), as a chronic treatment for FM.

Program updates:

- Clear guidance received from FDA* to advance the FM program. The long-term safety exposure data from the PTSD program is expected to support the fibromyalgia NDA*.
- TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) daily at bedtime will be studied in new Phase 3 study to support product registration.

*March 2019 FDA meeting minutes

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TNX-102 SL 5.6 mg for Fibromyalgia: New Phase 3 RELIEF Study Initiated

General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia in approximately 40 U.S. sites (N=470)
- 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria for Inclusion
- Adaptive Design: one planned unblinded interim analysis based on 50% of randomized participants¹

TNX-102 SL once-daily at bedtime

5.6 mg (2 x 2.8 mg tablets)²

N= ~235

Placebo once-daily at bedtime

N= ~235

14 weeks

Primary endpoint (Week 14):

- Daily diary pain severity score change (TNX-102 SL 5.6 mg vs. placebo) from Baseline in the weekly average by numerical rating scale (NRS) analyzed by mixed model repeated measures analysis with multiple imputation (MMRM with MI)

Key Secondary endpoints (Week 14) include:

- Patient Global Impression of Change (PGIC): Proportion of patients with a rating of "very much improved" or "much improved"
- Fibromyalgia Impact Questionnaire – Revised (FIQR): Symptoms Domain
- FIQR Function Domain
- PROMIS^{*} Sleep Disturbance instrument T-score
- PROMIS Fatigue instrument T-score
- Daily diary sleep quality NRS (weekly average) score

Interim analysis results expected 2H 2020

Topline results expected 1H 2021 based on currently-planned sample size

Potential pivotal efficacy study to support NDA approval

¹Pending agreement with FDA

²Two week run in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose *PROMIS = Patient Reported Outcome Measurement Information System

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What is Agitation in Alzheimer's Disease?

61

Agitation is one of the most distressing and debilitating of the behavioral complications of Alzheimer's disease

- Includes emotional lability, restlessness, irritability and aggression¹

Link between disturbed sleep and agitation in Alzheimer's¹⁻³

- Agitation is commonly diurnal ("sundowning")

Prevalence

- Agitation is likely to affect more than half of the 5.3 million Americans who currently suffer from moderate to severe Alzheimer's disease, and this number is expected to nearly triple by 2050⁴

¹Rose, K. et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias*, 30:78

²Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association*, 18, 396.

³Canevelli, M., et al. (2016). *Frontiers in medicine*, 3.

⁴The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: <https://www.alz.org/facts/>



Outcomes

- Agitation is associated with significant poor outcomes for Alzheimer's patients and challenges for their caregivers

Common reason for institutionalization

- Development of agitation, or its worsening, is one of the most common reasons for patients having to transition from lower- to higher levels of care (nursing homes and other long-term care settings)¹

Cost

- The presence of agitation nearly doubles the cost of caring for patients with Alzheimer's disease, and agitation is estimated to account for more than 12% of the healthcare and societal cost of Alzheimer's disease, which is currently estimated to be \$256 Billion for the year 2017 in the United States¹

¹The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: <https://www.alz.org/facts/>



Agitation in Alzheimer's Disease – Additional Indication Being Developed for TNX-102 SL

63

Significant unmet need

- No FDA approved drugs for the treatment of agitation in Alzheimer's

Mechanism of improving sleep quality

- Sleep disturbance is a significant and common symptoms in Alzheimer's

Pharmacological advantages outweigh potential concerns of using TNX-102 SL in treating agitation in Alzheimer's disease

- Blocks 3 receptors, not just one (e.g., 5-HT_{2A})



TNX-102 SL for Agitation in Alzheimer's – Regulatory Status and Registration Strategy

64

Proposed Phase 2 IND study can potentially serve as a pivotal efficacy study to support NDA approval

- FDA comments on final protocol received October 2018

Registration Strategy of TNX-102 SL for agitation in Alzheimer's disease

- Efficacy Supplement (sNDA¹) may be leveraged from the PTSD/FM development program and supported by Initial NDA approval for PTSD/FM

¹Supplemental New Drug Application



TNX-102 SL Potentially Addresses Some of the Challenges in Treating Agitation in Alzheimer's

65

Sublingual route of administration (no swallowing)

- Swallowing can be an issue for a significant number of Alzheimer's patients

Low dose taken daily at bedtime

- Potentially minimize daytime anticholinergic side effects → improved tolerability and patient compliance

Role of sleep in clearing debris from the brain

- Animal studies have shown debris clearance from the brain during sleep including toxic proteins associated with Alzheimer's progression¹

¹T Xie L, et al. Science. (2013);342(6156):373



Connection between Sleep Disturbance and Agitation

- Agitation in Alzheimer's Disease is associated with sleep disturbance^{1,2}
- Evidence that improving sleep could improve agitation³

Supported by Potential Mechanism of Action

- TNX-102 SL is a multifunctional agent including antagonism of 5-HT_{2A}, α_1 -adrenergic and histamine H₁ receptors
- Certain 5-HT_{2A} antagonists have shown clinical efficacy against agitation in dementia including trazodone^{4,5}, and mirtazapine⁶
- The α_1 -adrenergic antagonist prazosin has shown efficacy in the treatment of agitation in dementia⁷
- The histamine H₁ antagonist hydroxyzine had historical use in treating agitation in dementia⁸

¹Bachmen, D. and Rabins, P. *Annu Rev Med.* 2006;57:499.

²Rose, K et al. *Am J Alzheimers Dis Other Dement.* 2015 30(1):78.

³Figueiro MG *Sleep Med.* 2014 15(12):1554-64.

⁴Lebert F. et al. *Dement Geriatr Cogn Disord.* 2004;17(4):355.

⁵Sulzer DL et al. *Am J Geriatr Psychiatry.* 1997 5(1):60.

⁶Cakir S. et al., *Neuropsychiatr Dis Treat.* 2008 4(5):963.

⁷Wang, LY et al., *Am J Geriatr Psychiatry.* 2009 17(9):744

⁸Settel E. *Am Pract Dig Treat.* 1957 8(10):1584.

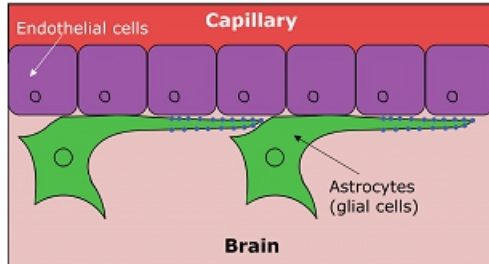


Protective Barriers in the Central and Peripheral Nervous Systems

Glial cells are cells that reside in the central nervous system and can provide protective barriers between the central and peripheral nervous systems^{1,2}

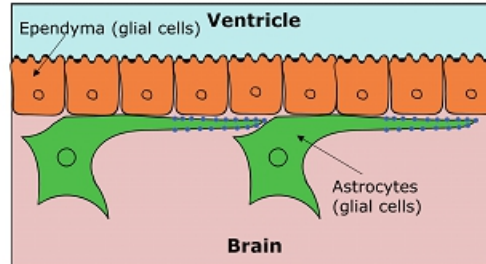
Blood–Brain Barrier:

supplies nutrients to the brain and filters toxins¹



Cerebrospinal Fluid (CSF)–Brain Barrier/Glymphatic System:

extracts toxins from the brain²



1. Ballabh P, et al. *Neurobiol Dis.* 2004;16(1):1-13.

2. Jessen NA, et al. *Neurochem Res.* 2015;40(12):2583-2599.

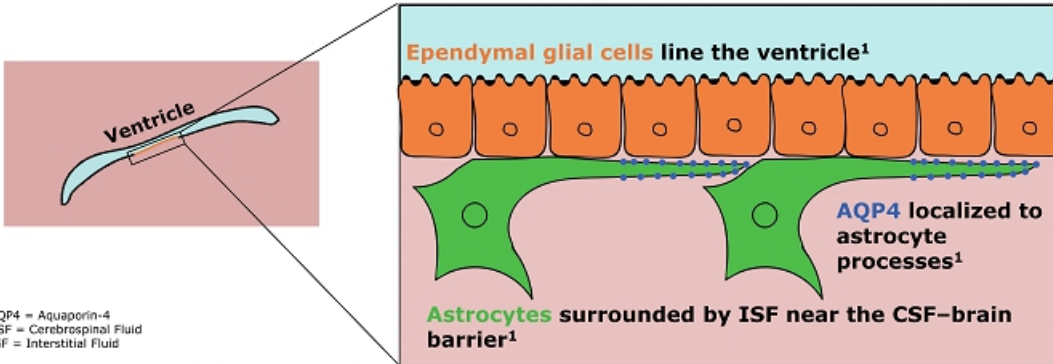
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During Wakefulness, Proteins Linked to Neuronal Death and Neurodegeneration Accumulate in the Brain's Extracellular Space

68

The pathways of interchanging CSF and ISF depend on aquaporin-4 (AQP4) water channels on astrocytes¹



AQP4 = Aquaporin-4
CSF = Cerebrospinal Fluid
ISF = Interstitial Fluid

1. Papadopoulos MC, et al. *Nat Rev Neurosci.* 2013;14(4):265-277.

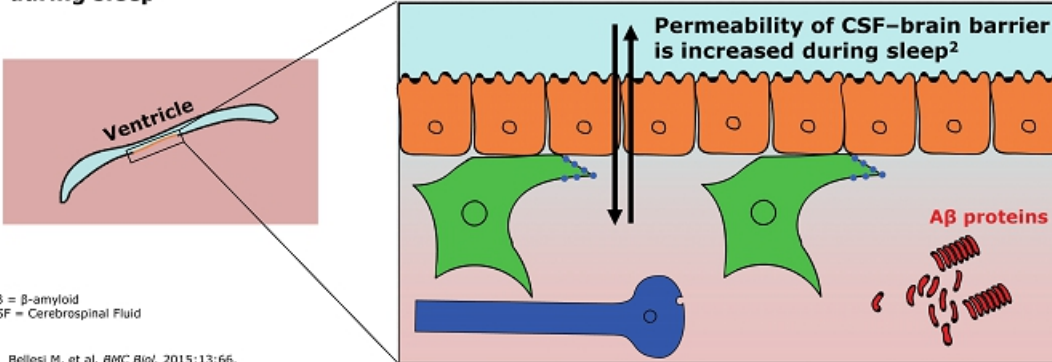
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During Sleep, the CSF–Brain Barrier Is More Permeable, Allowing Debris to Clear

69

Extracellular volume increases during sleep² Astrocytes change shape, promoting fluid exchange¹



A β = β -amyloid
CSF = Cerebrospinal Fluid

1. Bellesi M, et al. *BMC Biol.* 2015;13:66.
2. Xie L, et al. *Science.* 2013;342(6156):373-377.

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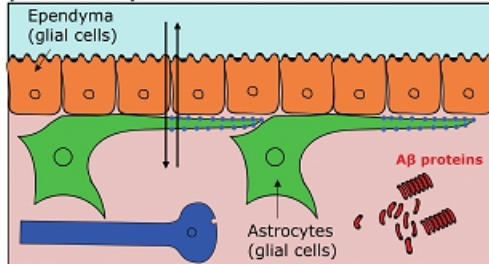
Sleep-Wake Cycles Alter Permeability of the CSF-Brain Barrier

70

Fluid exchange at the CSF-brain barrier allows for clearance of toxic proteins called β -amyloids ($A\beta$).¹ Glial cells in the brain work to facilitate this fluid exchange.² Sleep-wake cycles alter glial cell morphology, which may affect fluid exchange at the CSF-brain barrier.³

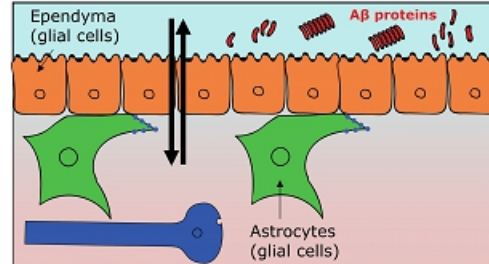
Wakefulness:

Fluid exchange is reduced due to limited permeability of the CSF-brain barrier¹



Sleep:

Fluid exchange is increased due to greater permeability of the CSF-brain barrier¹



1. Xie L, et al. *Science*. 2013;342(6156):373-377.
2. Papadopoulos MC, et al. *Nat Rev Neurosci*. 2013;14(4):265-277.
3. Bellesi M, et al. *BMC Biol*. 2015;13:66.

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Competitive landscape

- 5HT_{2A} Antagonists/inverse agonists
 - Nelotanserin (Axovant)
- Atypical Antipsychotics (also have 5HT_{2A} antagonism)
 - Rexulti® brexpiprazole (Otsuka/Lundbeck)
 - Lumateperone (Intra-Cellular)
- Dextromethorphan – believed to act as SSRI, glutamate/NMDA and sigma-1 receptor modulators
 - Deudextromethorphan (Avanir/Otsuka) - deuterated version of Nuedexta®
 - Dextromethorphan/bupropion (Axsome Therapeutics)

TNX-102 SL uniquely designed for bedtime dosing and transmucosal absorption

- Maximize drug exposure during sleep → improving sleep quality
- Other 5-HT_{2A} antagonists not designed for bedtime sublingual dosing

NDA approval can rely on reference listed drug (AMRIX) safety information



TNX-102 SL: Potential Treatment for Alcohol Use Disorder (AUD)

72

AUD is a chronic relapsing brain disease

- Characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using

Sleep disturbance is extremely common in alcohol recovery¹

- Significantly impacts daytime cognition, mood, and ability to participate in alcohol treatment, and is associated with increased risk of relapse

Prevalence

- An estimated 36 million adults in the U.S. have AUD²

Three FDA-approved medications

- Remains an unmet need due to compliance and safety issues

Pre-IND meeting with the FDA completed in October 2019

- Discussed 505(b)(2) development plan for TNX-102 SL as a treatment for AUD
- FDA official meeting minutes confirm plan to submit IND application in 1Q 2020 for a Phase 2 Proof of Concept Study

¹Arnedt et al, J Addict Dis. 2007 ; 26(4): 41-54

²Grant et al, JAMA Psychiatry 2015; 72(8): 757-766; www.census.gov



CNS Candidates in Clinical Development

Psychiatry, Pain and Addiction

TNX-102 SL and TNX-601 owned outright with no royalties due

73

Pipeline Product	Indication	Phase 1	Phase 2	Phase 3	NDA ³ /BLA ⁴	Market
TNX-102 SL¹ Cyclobenzaprine HCl sublingual tablets Protectic [®] formulation technology	<i>Bedtime Treatment for PTSD – Tonmya²</i>	→			Interim analysis results expected 1Q 2020 Topline data expected 2Q 2020	
	<i>Bedtime Treatment for Fibromyalgia</i>	→			Interim analysis results expected 2H 2020	
	Bedtime Treatment for Agitation in Alzheimer's	→				
	Bedtime Treatment for Alcohol Use Disorder (AUD) ⁵	→				
TNX-1300⁶ Cocaine esterase (recombinant from bacteria) i.v. formulation	Cocaine intoxication / overdose	→				
TNX-601 CR⁷ Tianeptine oxalate oral controlled release formulation	Daytime Treatment for PTSD	→				
	Daytime Treatment for Major Depressive Disorder (MDD)	→				
	Neurocognitive Dysfunction from Corticosteroids	→				

¹ TNX-102 SL (cyclobenzaprine HCl) sublingual tablets is an investigational new drug and has not been approved for any indication; ² Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD; ³ NDA- New Drug Application; ⁴ BLA - Biologic Licensing Application; ⁵ Pre-Investigational New Drug (IND) meeting completed in October with FDA. Upon receiving FDA clearance of an IND application, TNX-102 SL for AUD will be Phase 2 ready as it is expected to qualify for the 505(b)(2) pathway for approval; ⁶ TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, i.v. solution) is an investigational new biologic and has not been approved for any indication; ⁷ TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 study for formulation development was recently completed outside of the U.S.

Pipeline Product	Indication(s)	Category
TNX-1600 Triple reuptake inhibitor ²	Daytime Treatment for PTSD	Psychiatry
TNX-1500³ Anti-CD154 monoclonal antibody	Prevention and treatment of organ transplant rejection Treatment for autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis	Transplant Autoimmunity
TNX-1700 rTFF2 ⁴	Treatment for gastric and pancreatic cancers	Oncology
TNX-801³ Live horsepox virus (HPXV) vaccine from cell culture	Smallpox-preventing vaccine	Biodefense
TNX-701³ Radioprotection drug oral capsules	Protection from radiation injury	Biodefense

¹ (Experimental new medicines and biologics, not approved for any indication)

² (2S,4R,5R)-5-(((2-aminobenzo[d]thiazol-6-yl)methyl)amino)-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol) is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine)

³ Programs owned outright with no royalties due

⁴ recombinant Trefol Family Factor 2



TNX-1300* for the Treatment of Cocaine Intoxication

Recombinant protein that degrades cocaine in the bloodstream¹

- Double-mutant cocaine esterase

Phase 2 study completed by Rickett Benckiser (TNX-1300 was formerly RBP-8000)²

- Volunteer cocaine abusers received cocaine 50 mg *i.v.* infusion over 10 minutes
- TNX-1300 given one minute after completion of cocaine infusion
 - Rapidly reversed the physiologic effects of cocaine; cocaine plasma exposures dropped by 90% within two minutes
 - Well tolerated with the most frequently reported adverse events being gastrointestinal disorders (including dry mouth, nausea); nervous systems disorders (including headache, dizziness) and skin and subcutaneous tissue disorders (including hyperhidrosis, dermatitis)

**TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, i.v. solution) is an investigational new biologic and has not been approved for any indication.*

¹ Gao D et al, *Mol Pharmacol.* 2009, 75(2):318-23.

² Nasser AF et al, *J Addict Dis.*, 2014;33(4):289-302.



Produced through rDNA technology in non-disease-producing strain of *E. coli*.

- Cocaine Esterase (CocE) was identified in bacteria (*Rhodococcus*) that use cocaine as its sole source of carbon and nitrogen and that grow in soil surrounding coca plants¹
- The gene encoding CocE was identified and the protein was extensively characterized¹⁻³
- CocE catalyzes the breakdown of cocaine into metabolite ecgonine methyl ester and benzoic acid
- Wild-type CocE is unstable at body temperature, so targeted mutations were introduced in the CocE gene and resulted in the T172R/G173Q Double-Mutant CocE, which is active for approximately 6 hours at body temperature⁴

¹ Bresler MM et al, Appl Environ Microbiol. 2000. 66(3):904-8.

² Larsen NA et al, Nat Struct Biol. 2002. 9(1):17-21.

³ Turner JM et al, Biochemistry. 2002. 41(41):12297-307.

⁴ Gao D et al, Mol Pharmacol. 2009. 75(2):318-23.



About Cocaine and Cocaine Intoxication

77

Cocaine: an illegal recreational drug taken for its pleasurable effects and associated euphoria.

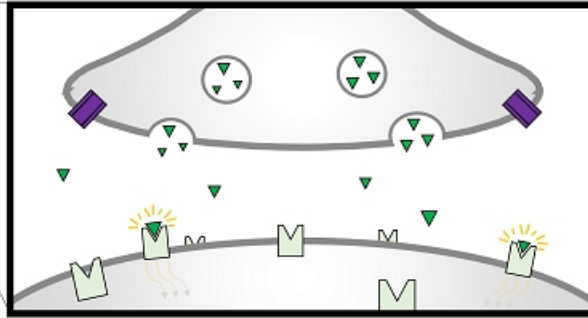
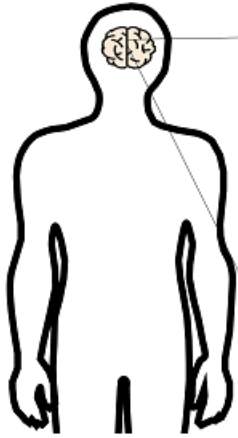
- Cocaine blocks the reuptake of the neurotransmitter dopamine (DA) in the CNS
 - Results in accumulation of DA within the synapse and amplifies DA signaling
 - Creates positive feeling but with intense use of cocaine, results in cocaine craving
 - High potential for abuse/addiction (dependence), and *risk of cocaine intoxication.*

Cocaine intoxication: deleterious effects on the body, especially cardiovascular system.

- Common symptoms include tachyarrhythmias and elevated blood pressure, either of which can be life-threatening.
- Known or suspected cocaine intoxication cases are sent immediately to the emergency department, preferably by ambulance in case cardiac arrest occurs during transit.



Cocaine Mechanism of Action (MOA)



▼ Dopamine

M Dopamine receptor

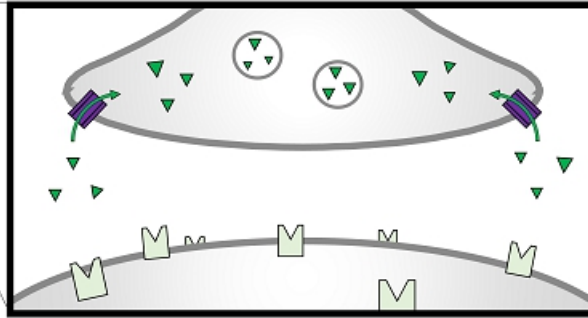
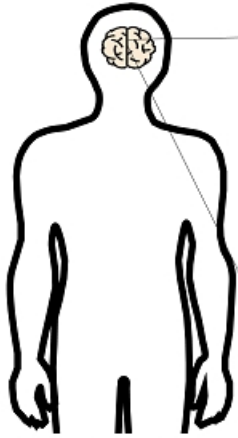
■ Dopamine transporter

When **dopamine** is released into the synapse, it stimulates **dopamine receptors** and triggers feelings of reward.^{1,2}

1. Benowitz NL. *Pharmacol Toxicol*. 1993.
2. Stahl SM, 4th ed. New York, NY: Cambridge University Press; 2013.



Cocaine MOA



▼ Dopamine

⌋ Dopamine receptor

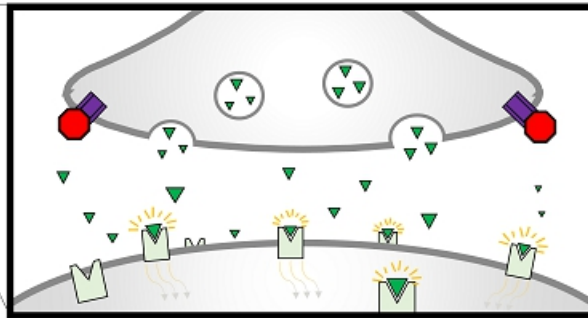
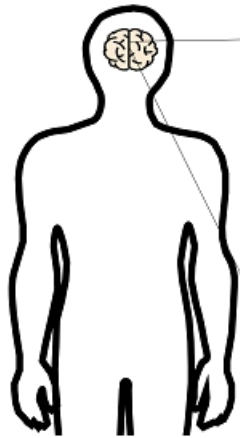
■ Dopamine transporter

Subsequently, dopamine is removed from the synapse and recycled by **dopamine transporters**.^{1,2}

1. Benowitz NL. *Pharmacol Toxicol*. 1993.
2. Stahl SM. 4th ed. New York, NY: Cambridge University Press; 2013.



Cocaine MOA



▼ Dopamine

□ Dopamine receptor

▭ Dopamine transporter

● Cocaine

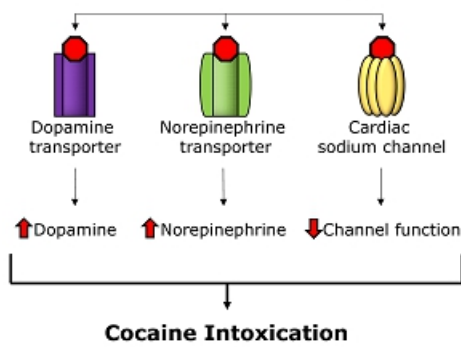
Cocaine blocks **dopamine transporters**, leading to an accumulation of **dopamine** in the synapse and excessive stimulation of **dopamine receptors**.^{1,2}

1. Benowitz NL. *Pharmacol Toxicol*. 1993.
2. Stahl SM, 4th ed. New York, NY: Cambridge University Press; 2013.

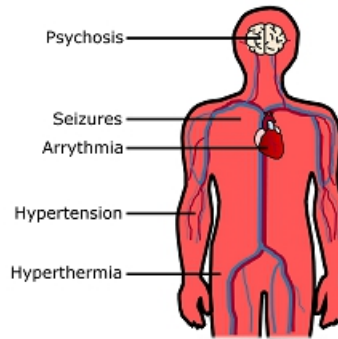


Cocaine Intoxication is the Result of Cocaine's Activity at Multiple Targets

In addition to dopamine transporters, cocaine also blocks other targets¹



The effects of cocaine intoxication include¹:



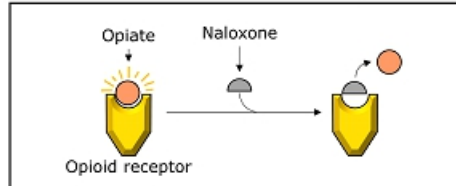
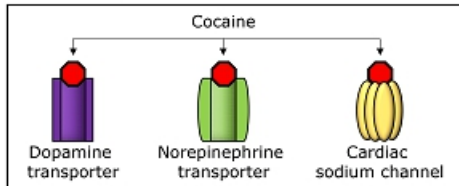
¹. Brim et al. *Mol Pharmacol*. 2011.



Pharmacotherapies for Cocaine Intoxication Have Not Been Effective

Treatments for opiates not effective for cocaine:

	Cocaine	Opiates
MOA of Toxicity	Complex; mediated by multiple targets with distinct biological functions ¹	Simple; mediated by opioid receptors ²
Pharmacology	Antagonist ¹	Agonists ²
Pharmacotherapy	No FDA-approved medication exists¹	Naloxone ²

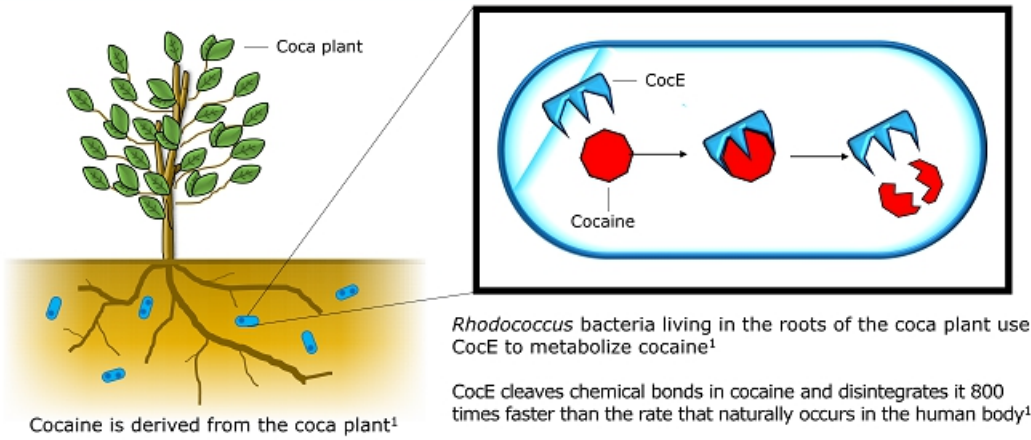


1. Brim et al. *Mol Pharmacol*. 2011.
2. Melichar et al. *Eur J Pharmacol*. 2003.
3. Narasimhan et al. *Future Medicinal Chemistry*. 2012.



TNX-1300 (Cocaine Esterase or CocE) Is a Fast-acting Cocaine Antidote

83



1. Narasimhan D et al. *Future Med Chem.* 2012.

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Pharmacotherapies for Cocaine Intoxication Have Not Been Effective

- While simple pharmacological agents such as naloxone (Narcan[®]) are effective for the treatment of opiate intoxication¹, a similar approach to treat cocaine intoxication is hampered by cocaine's complex mechanism of action, or MOA²
- Another key difference between opiates and cocaine is that opiates are agonists at opiate receptors¹, while cocaine acts as an antagonist at its key targets.² Compounds that compete with an inhibitor such as cocaine are likely to be inhibitors themselves.³
- Despite years of research, pharmacotherapies designed to prevent cocaine from binding to its target molecules have not been effective^{2,3}

References

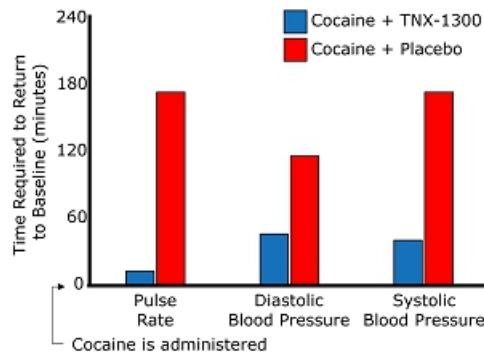
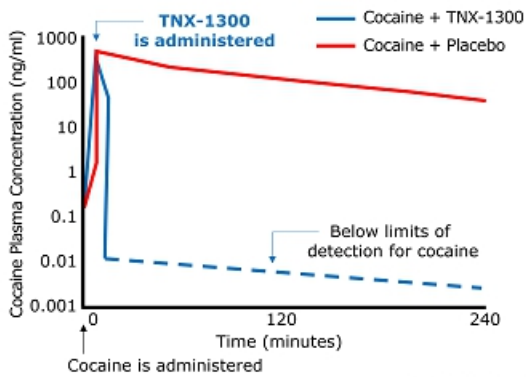
1. Melichar JK, Nutt DJ, Malizia AL. Naloxone displacement at opioid receptor sites measured in vivo in the human brain. *European Journal of Pharmacology*. 2003; 459(2-3):217-219.
 2. Brim RL, Noon KR, Collins GT, Nichols J, Narasimhan D, Sunahara RK, Woods JH. The ability of bacterial cocaine esterase to hydrolyze cocaine metabolites and their simultaneous quantification using high-performance liquid chromatography-tandem mass spectrometry. *Molecular Pharmacology*. 2011; 80:1119-1127.
 3. Narasimhan D, Woods JH, Sunahara RK. Bacterial cocaine esterase: a protein-based therapy for cocaine overdose and addiction. *Future Medicinal Chemistry*. 2012; 4(2):137-150.
-



TNX-1300 (CocE) Accelerates Recovery From Cocaine Intoxication in Humans

TNX-1300 cleaves cocaine in humans and removes it from the blood circulation¹ (N=29)

TNX-1300 accelerates recovery from cocaine intoxication without inducing serious side effects¹



1. Nasser A et al. J Addict Dis. 2014.

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Note: Figures are for illustrative purposes



The Prevalence of Cocaine Usage and Overdose (U.S.)

Cocaine Usage in the U.S.

5.07 million individuals estimated to have used cocaine in past year¹

- 2.2 million “current” (i.e. users in the past month) of cocaine (2017)²
- 966,000 had cocaine use disorder in past year (2017)²

Prevalence of Cocaine Overdose

Based on Drug Abuse Warning Network (DAWN) last compiled in 2011^{3,4}

505,224 emergency department visits for cocaine (2011)	
➔ 270,677 (53%) treated and released	Less likely to be treated aggressively
➔ 167,570 (33%) were admitted to the same hospital	More likely to be treated
➔ 60,609 (14%) visits involving drug detox services	Treated to reverse toxicity

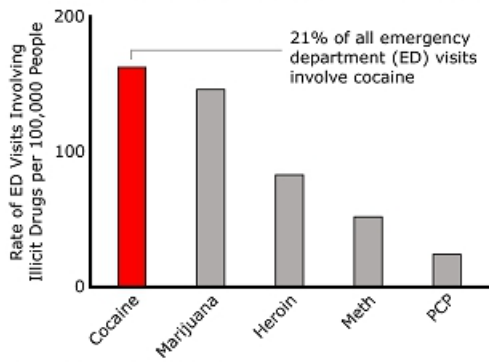
¹ Annual Surveillance Report of Drug-Related Risks and Outcomes, United States CDC National Center for Injury Prevention and Control, 2018
² Substance Abuse and Mental Health Services Administration. (2018). Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53).

³ Substance Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
⁴ Drug Abuse Warning Network, 2011: Selected Tables of National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA, 2013.

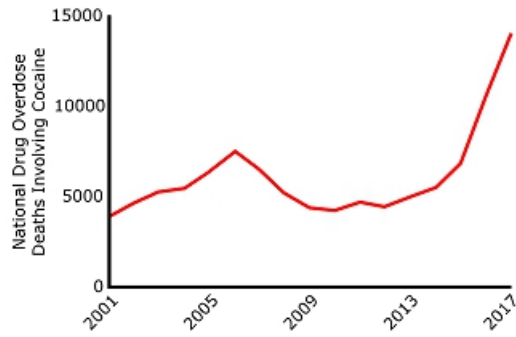


Cocaine Intoxication Is a Growing Problem in the U.S.

Cocaine is involved in more emergency department (ED) visits than any other illicit substance¹



Drug overdose deaths involving cocaine have increased dramatically in recent years²



1. CBHSQ. DAWN 2011. Rockville, MD: SAMHSA; 2013.
2. NIDA. Overdose death rates. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>.

Note: Figures are for illustrative purposes



Current Standard of Care

- Patients present with acute agitation, hyperthermia, tachycardia, arrhythmias, and hypertension
- Potential life-threatening sequelae of myocardial infarction, cerebrovascular accident, rhabdomyolysis, respiratory failure, and seizures
- Patients are currently managed only by supportive care for the adverse effects of cocaine intoxication on the cardiovascular and central nervous systems

Potential Benefit of TNX-1300

- By reversing the cause of cocaine intoxication (rather than treating the symptoms), TNX-1300 may offer significant advantages to the current standard of care for cocaine intoxication.
 - Rapid diminution in circulating cocaine
 - Significantly reduce time and resources required for other detox services
 - Reduces the risk of morbidity and mortality



Value of TNX-1300 to Tonix

Features of the Acquired Asset:

- Full rights to the IP and to develop and commercialize TNX-1300 worldwide
- An inventory of investigational drug product
- Clinical trial results from previous Phase 2 study in which TNX-1300 at 100 mg or 200 mg i.v. doses was well tolerated and interrupted cocaine effects after cocaine 50 mg i.v. challenge

Development Plan:

- Re-qualify the drug substance for Good Manufacturing Practice (GMP) purposes
- Conduct non-clinical studies in reproductive toxicology
- Initiate a Phase 2 study in Emergency Room cocaine intoxication

Exclusivity:

- Expected patent protection through 2029
- As a biologic and new molecular entity, TNX-1300 is eligible for 12 years of U.S. market exclusivity upon approval by the FDA.

Pipeline Diversification:

- Brings Tonix into an additional therapeutic area: Addiction Medicine



CNS Candidates in Clinical Development

Psychiatry, Pain and Addiction

TNX-102 SL and TNX-601 owned outright with no royalties due

Pipeline Product	Indication	Phase 1	Phase 2	Phase 3	NDA ³ /BLA ⁴	Market
TNX-102 SL¹ Cyclobenzaprine HCl sublingual tablets Protectic [®] formulation technology	<i>Bedtime Treatment for PTSD – Tonmya^{®2}</i>	→			Interim analysis results expected 1Q 2020 Topline data expected 2Q 2020	
	<i>Bedtime Treatment for Fibromyalgia</i>	→			Interim analysis results expected 2H 2020	
	Bedtime Treatment for Agitation in Alzheimer's	→				
	Bedtime Treatment for Alcohol Use Disorder (AUD) ⁵	→				
TNX-1300⁶ Cocaine esterase (recombinant from bacteria) i.v. formulation	Cocaine intoxication / overdose	→				
TNX-601 CR⁷ Tianeptine oxalate oral controlled release formulation	Daytime Treatment for PTSD	→				
	Daytime Treatment for Major Depressive Disorder (MDD)	→				
	Neurocognitive Dysfunction from Corticosteroids	→				

¹ TNX-102 SL (cyclobenzaprine HCl) sublingual tablets is an investigational new drug and has not been approved for any indication; ² Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD; ³ NDA- New Drug Application; ⁴ BLA - Biologic Licensing Application; ⁵ Pre-Investigational New Drug (IND) meeting completed in October with FDA. Upon receiving FDA clearance of an IND application, TNX-102 SL for AUD will be Phase 2 ready as it is expected to qualify for the 505(b)(2) pathway for approval; ⁶ TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, i.v. solution) is an investigational new biologic and has not been approved for any indication; ⁷ TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 study for formulation development was recently completed outside of the U.S.

Pipeline Product	Indication(s)	Category
TNX-1600 Triple reuptake inhibitor ²	Daytime Treatment for PTSD	Psychiatry
TNX-1500³ Anti-CD154 monoclonal antibody	Prevention and treatment of organ transplant rejection Treatment for autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis	Transplant Autoimmunity
TNX-1700 rTFF2 ⁴	Treatment for gastric and pancreatic cancers	Oncology
TNX-801³ Live horsepox virus (HPXV) vaccine from cell culture	Smallpox-preventing vaccine	Biodefense
TNX-701³ Radioprotection drug oral capsules	Protection from radiation injury	Biodefense

¹ (Experimental new medicines and biologics, not approved for any indication)

² (2S,4R,5R)-5-(((2-aminobenzo[d]thiazol-6-yl)methyl)amino)-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol) is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine)

³ Programs owned outright with no royalties due

⁴ recombinant Trefol Family Factor 2



TNX-601 CR* (Tianeptine Oxalate Controlled Release) Tablets

92

Proprietary new controlled release formulation for once-daily dosing

- Suitability for once-daily dosing established in Phase 1 pharmacokinetic study, completed outside of the U.S.
 - Well tolerated in study and the side effects were consistent with the known safety profile of tianeptine sodium
- Tianeptine sodium immediate release is approved and marketed outside of the U.S. for three times a day dosing for the treatment of depression
 - Once-daily dosing for TNX-601 CR believed to be have an adherence advantage over three times a day dosing with tianeptine sodium
- Plan to request pre-IND meeting with FDA in first half 2020
- Plan for first efficacy and safety study ex-U.S.

Proprietary new oxalate salt with improved pharmaceutical properties

- Tianeptine oxalate is crystalline, while tianeptine sodium is amorphous

Issued patents directed to tianeptine and tianeptine oxalate

- **Composition of Matter:** Issued US patent directed to oxalate salt, U.S. Patent No. 10,449,203
- **Method of Use:** Issued European patent directed to methods of treating cognitive impairment associated with corticosteroid treatment, European Patent No. 3246031

*TNX-601 (tianeptine oxalate CR tablets) is in the pre-IND stage in the U.S. and has not been approved for any indication.
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TNX-601 CR: A Potential Daytime Treatment for Depression and PTSD

93

Depression: majority suffering from depression do not have an adequate response to initial antidepressant therapy

- Tianeptine sodium immediate release (IR) tablets for three times a day dosing is approved as an antidepressant in the EU, Russia, Asia and Latin America; first marketed for depression in France in 1989
- Tianeptine sodium is reported to have prominent anti-anxiety effects in depression with a low incidence of sexual side effects
- TNX-601 CR leverages the established efficacy and safety of tianeptine sodium IR as a treatment for depression outside of the U.S.
- Despite multiple approved products for depression in the U.S., there remains significant interest and need for new treatments, particularly for medicines that modulate the glutamatergic system

PTSD: heterogeneous condition, so not all patients are expected to respond to a single medicine

- Distinct mechanism of action from TNX-102 SL – TNX-601 CR modulates the glutamatergic system
- Published studies show tianeptine is active in the treatment of PTSD¹⁻⁴
- Leverages Tonix expertise in PTSD (clinical and regulatory, market analysis, etc.)

¹ Frančičević T, et al. Psychiatr Danub. 2011 Sep;23(3):257-63. PMID: 21963693

² Rumyantseva GM and Stepanov AL. Neurosci Behav Physiol. 2008 Jan;38(1):55-61. PMID: 18097761

³ Aleksandrovskii IA, et al. Zh Nevrol Pskhiatr Im S S Korsakova. 2005;105(11):24-9. PMID: 16329631 [Russian]

⁴ Onder E, et al. Eur Psychiatry. 2006 (3):174-9. PMID: 15964747



Structural Comparison: TNX-102 and TNX-601

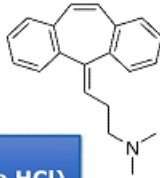
94

Cyclobenzaprine and tianeptine share structural similarities with classic tricyclic antidepressants (TCAs) and to each other, but each has unique pharmacological properties

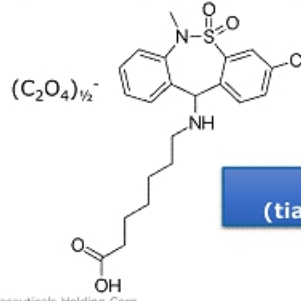
- Tianeptine has a 3-chlorodibenzothiazepine nucleus with an aminoheptanoic side chain

Tianeptine leverages Tonix's expertise in the pharmacology and development of tricyclics

HCl



TNX-102
(cyclobenzaprine HCl)



TNX-601
(tianeptine oxalate)

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TNX-1600¹ (Triple Reuptake Inhibitor): A Potential Daytime Treatment for PTSD

95

Pre-IND
Candidate

Targeting a
Condition with
Significant
Unmet Need

Targeted as a 1st line monotherapy for PTSD: oral formulation for daytime dosing

- ✓ Leverages internal expertise in PTSD (clinical and regulatory experience, market analysis, etc.)
- ✓ Mechanism of Action (MOA) is different from TNX-102 SL or TNX-601

TNX-1600 is a New Chemical Entity, triple-reuptake inhibitor

- Inhibits reuptake of serotonin, norepinephrine and dopamine

Patents and patent applications

- Issued patent directed to composition of matter
- Worldwide exclusive license from Wayne State University

Preclinical evidence for treating PTSD in animal model

- Pre-clinical studies have shown TNX-1600 to be active in an animal model of PTSD²

¹TNX-1600, f.k.a. D-578 or (2S,4R,5R)-5-(((2-aminobenzo[d]thiazol-6-yl)methyl)amino)-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine)

²Dutta, AK, et al., Eur J. Pharmacol. 2019 862:172632



TNX-1500 (monoclonal antibody anti-CD154): A Potential Treatment for Autoimmune Conditions and Organ Transplant Rejection

96

Pre-IND
Candidate

Targeted as a 1st line monotherapy for autoimmunity and add-on therapy for preventing and treating organ transplant rejection

✓ **Mechanism of Action (MOA) is distinct**

- TNX-1500 blocks T cell helper function

New Molecular Entity, biologic

- US Patient Protection and Affordable Care Act provides 12 years of exclusivity for biologics

Patent applications directed to composition of matter

- Expected patent protection through 2039

Targeting a
Condition with
Significant
Unmet Need

Clinical evidence for anti-CD154 mAbs in Systemic Lupus (SLE) and allogeneic kidney transplant

- Several studies have shown TNX-1500 to be active in the treatment of human SLE¹⁻³ and transplant^{4,5}

¹ Huang W, et al. *Arthritis Rheum.* 46(6):1554-62. (2002)

² Boumpas DT, et al. *Arthritis Rheum.* 48:719-27. (2003)

³ Grammer AC, et al. *J Clin Invest.* 112:1506-20. (2003)

⁴ Kawai T, et al. *Nat Med.* 2000;6:114. (2000);

⁵ Koyama I, et al., *Transplantation.* 77(3):460-2. (2004)



About CD40L (CD154)

97

Transiently expressed T cell surface molecule also known as CD40-ligand¹⁻⁴

- Predominantly expressed by T cells
- Interacts with CD40 on B cells and macrophages

Mediates T cell helper function¹⁻⁴

- Activates B cells for humoral (antibody-mediated) immune response
- Activates macrophages and dendritic cell
- Provides T cell help to activated CD8+ T cells

X-linked Hyper-IgM Syndrome – defective CD40L gene⁵⁻⁶

- Lack of T helper function
- Serum antibodies: only IgM, and no IgG or IgE because T cells are required for B cell isotype switching
- If maintained on gamma globulin are otherwise healthy

Member of the TNF α superfamily⁴

- TNF α and RANKL are other family members –drug targets for approved products

¹Lederman, S., et al. *J. Exp. Med.* 175:1091-1101. 1992. PMID: 1348081.

²Lederman, S., et al.; *J. Immunol.* 149:3817-3826. 1992. PMID: 1281189.

³Lederman, S., et al. *J. Immunol.* 152:2163. 1994. PMID: 7907632.

⁴Covey, L.R., et al. *Mol. Immunol.* 31:471-484. 1994. PMID: 7514269.

⁵Ramesh, N., et al. 1993. *Inter Immunology* 5:769-773. PMID: 8103673.

⁶Callard, R.E., et al., *J. Immunol.* 153:3295. 1994. PMID: 7916370.



CD154 is a member of the Tumor Necrosis Factor (TNF α) Super Family¹

- No mAb against CD154 has been licensed anywhere in the world

Other TNF α Super Family members have proven to be targets for antagonist (blocking) mAbs²

- anti-TNF α mAbs for the treatment of certain autoimmune conditions
 - infliximab (Remicade[®])
 - adalimumab (Humira[®])
 - certolizumab pegol (Cimzia[®])
 - golimumab (Simponi[®])
- TNF α antagonist receptor fusion protein
 - Etanercept (Enbrel[®])
- anti-RANKL (CD254) mAb for the treatment of osteoporosis, treatment-induced bone loss, metastases to bone, and giant cell tumor of bone
 - denosumab (Prolia[®] or Xgeva[®])

¹Covey, L.R., et al. *Mol. Immunol.* 31:471-484. 1994. PMID: 7514269.

²Remicade[®] and Simponi[®] are trademarks of Janssen; Humira[®] is a trademark of AbbVie; Cimzia[®] is a trademark of UCB; Enbrel[®] is a trademark of Amgen; and Prolia[®] and Xgeva[®] are trademarks of Amgen.

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Transplantation/Autoimmune treatment development asset

- 3rd generation of monoclonal antibody (mAb) for a class that has had extensive animal and human testing
- Effects on T cell function with lower potential for side effects (e.g. thrombosis via FcγRIIA (CD32A) - dependent pathway)¹
- Patent protection expected through 2039

Transplantation

- Unique effects on facilitating tolerance
- Potential to facilitate xeno-transplants (genetically engineered mini-swine)²

Autoimmune Diseases

- Unique effect at controlling autoimmune conditions³⁻⁵
- Clinical data on related mAbs for systemic lupus erythematosus (SLE)³⁻⁵

Allergy

- Blocks immunoglobulin E (IgE) production

¹Company data

²Längin M, et al., *Nature*. 2018 564(7736):430-433

³Boumpas DT, et al, *Arthritis Rheum*. 48:719-27. (2003)

⁴Huang W, et al. *Arthritis Rheum*. 46(6):1554-62 (2002)

⁵Grammer AC, et al. *J Clin Invest*. 112:1506-20. (2003)

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Facilitates 'transplant tolerance' in multiple preclinical transplant models

- anti-CD154 therapy has a unique activity in controlling the immune response to organ transplants¹⁻³
- Significant need for new treatments with improved activity and tolerability to prevent or treat organ transplant rejection

Human trials of first generation anti-CD154 showed evidence of activity

- Development halted because of increased risk of thrombosis⁴⁻⁶

Potential to enable use of genetically modified, or humanized pig organs – "xenotransplantation." ^{7,8}

- Potential treatment for humans with advanced organ failure or diabetes

¹ Ferrant JL et al., *International Immunol.* (11):1583 (2004)

² O'Neill NA, et al. *Transplantation.* 101(9): 2038 (2017)

³ Zhang T, et al. *Immunotherapy.* 7(8):899 (2015)

⁴ Kawai T, et al. *Nat Med.* 2000;6:114. (2000)

⁵ Koyama I, et al., *Transplantation.* 77(3):460-2. (2004)

⁶ Law and Grewal *Adv Exp Med Biol.* 647:8-36 (2009)

⁷ Långin M, et al. *Nature.* 564(7736):430 (2018)

⁸ Pierson RN 3rd. *J Thorac Cardiovasc Surg.* pii: S0022-5223(19)31024-4. (2019)

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Treats autoimmune conditions in multiple preclinical transplant models

- anti-CD154 therapy has a unique activity in controlling the immune response in autoimmune models¹⁻³
- Significant need for new treatments with improved activity and tolerability to prevent or treat autoimmunity

Human trials of first generation anti-CD154 showed activity

- Clinical trials of hu5c8, in systemic lupus erythematosus (SLE) showed evidence of activity¹⁻³
- Development halted because of increased risk of thrombosis¹⁻³

¹Huang W, et al. *Arthritis Rheum.* 46(6):1554–62. (2002)

²Boumpas DT, et al. *Arthritis Rheum.* 48:719–27. (2003)

³Grammer AC, et al. *J Clin Invest.* 112:1506–20. (2003)



Third Generation anti-CD154: Engineered to Potentially Decrease Risk of Thrombosis

102

First generation anti-CD154 mAbs

- Constant fragment (Fc) domain interacted with FcγRIIA (CD32A), which suggested a mechanism for increased risk of thrombosis^{1,2}

Second generation anti-CD154 mAbs

- Dramatically reduced binding to FcγRIIA^{3,4}, but had other issues, including decreased efficacy^{5,6}

TNX-1500 is a third generation anti-CD154 mAb⁶⁻⁸

- Designed by protein engineering to target CD154 therapeutically, while decreasing FcγRIIA binding and the potential for thrombosis

¹ Inwald DP et al., *Circ Res*. 92(9):1041-8 (2003)

² Robles-Carrillo L et al., *J Immunol*. 185(3):1577-83. (2010)

³ Shock A. et al., *Arthritis Res Ther*. 17:234 (2015)

⁴ Xie et al., *Journal of Immunol*. 192(9):4083 (2014)

⁵ Waters J, *Biocentury*; October 26, (2018)

⁶ Company data

⁷ NCT02273960; *ClinicalTrials.gov*; "Study to Evaluate Safety and Efficacy in Adult Subjects With ITP (ITP)"; results posted April 1, 2019, accessed July 29, 2019)

⁸ Ferrant JL et al., *International Immunol*. (11):1583 (2004) © 2019 Tonix Pharmaceuticals Holding Corp.



TNX-1700 (rTFF2): A Potential Treatment for Gastric and Pancreatic Cancers

103

Pre-IND
Candidate

Targeting a
Condition with
Significant
Unmet Need

Targeted as a treatment for Cancer

- ✓ Particularly for gastric and pancreatic cancer
- ✓ Mechanism of Action (MOA) is different from checkpoint inhibitors
- ✓ Potential synergy with anti-PD-1 or anti-PD-L1 monoclonal antibodies

Patents and patent applications directed to rTFF2

- Issued patent licensed from Columbia University

Inventor: Dr. Timothy Wang, MD

- Chief, Division of Digestive and Liver Diseases at Columbia University and Cancer Research Center and Silberberg Professor of Medicine
- Investigated the molecular mechanisms of gastrointestinal carcinogenesis for decades
- Leadership roles in gastroenterology and cancer biology fields

Pre-clinical evidence for inhibiting growth of cancer cells

- Several studies have shown rTFF2 to be active in the treatment of cancer¹⁻²

¹Dubeykovskaya Z, et al. Nat Commun. 2016 7:1-11

²Dubeykovskaya ZA, et al. Cancer Gene Ther. 2019 26(1-2):48-57



TNX-1700 (rTFF2) for Potential Cancer Treatment

104

- **Oncology development program**
 - Recombinant trefoil family factor 2 (rTFF2) has effects on cancer cells and the tumor microenvironment^{1,2}
- **Potential synergy with anti-PD-1/PD-L1 mAbs (Keytruda® and Opdivo®) and/or anti-CTLA-4 (Yervoy®) “Checkpoint Inhibitors”**
 - anti-PD-1 and anti-PDL-1 are breakthrough treatments, but not all patients respond
 - Increasing the response rate to checkpoint inhibitors is an active area of research
 - rTFF2 acts in the tumor microenvironment
- **Novel mechanism for suppressing myeloid-derived suppressor cells, and activating anti-cancer CD8+ T cells**
 - Implications for both cancer prevention and treatment
 - Potential to synergize with other immunotherapy drugs

¹Dubeykovskaya Z, et al. *Nat Commun*. 2016 7:1-11

²Dubeykovskaya ZA, et al. *Cancer Gene Ther*. 2019 26(1-2):48-57



- **Tumor microenvironment sabotages immune T cells**
 - Made up of blood vessels, inflammatory cells, and structural proteins
 - Difficult for cancer-killing immune T cells to penetrate
 - T cells detect and destroy cancer cells
- **Cancer surrounds tumors with a hostile microenvironment**
 - Tumors thrive, while the body's immune forces are not capable of performing their anti-cancer functions
- **Although the tumor microenvironment is known to be highly immunosuppressive, it has not been known precisely how it specifically hampers the function of T cells**



- **TFF2 is a small secreted protein**
 - Encoded by the TFF2 gene in humans
 - Expressed in gastrointestinal mucosa where it functions to protect and repair mucosa
 - TFF2 is also expressed at low levels in splenic memory T cells
 - Upregulated in chronic inflammation
 - Activates the chemokine receptor CXCR4 in cancer cells
 - Blocked by AMD3100 (CXCR4 antagonist) or anti-CXCR4 mAb
- **TFF2 is epigenetically silenced in gastric cancer**
 - Postulated to protect against cancer development through multiple mechanisms
 - Has effects on cancer cells and tumor microenvironment
 - Knockout of the TFF2 gene leads to faster tumor growth



- **Either TFF2 overexpression or adenovirus-delivered rTFF2 markedly suppresses tumor growth^{1,2}**
 - Curtailed the proliferation and expansion of myeloid progenitors that give rise to myeloid derived suppressor cells (MDSCs)
 - Adenovirus over-expression decreased tumor growth in a wild-type mouse model
 - Knockout of the TFF2 gene leads to faster tumor growth
- **Novel mechanism for suppressing myeloid-derived suppressor cells, and activating anti-cancer CD8+ T cells**
 - Implications for both cancer prevention and treatment
 - Potential to synergize with other immunotherapy drugs
- **Modified version of human TFF2 appears to show greater stability and efficacy²**
 - Native TFF2 has a short half-life

¹Dubeykovskaya Z, et al. *Nat Commun*. 2016 7:1-11

²Dubeykovskaya ZA, et al. *Cancer Gene Ther*. 2019 26(1-2):48-57
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TNX-801 (Synthesized Live Horsepox Virus): A Potential Smallpox-Preventing Vaccine

108

Pre-IND Stage

Potential improvement over current biodefense tools against smallpox

- ✓ Leverages Tonix's government affairs effort
- ✓ Collaboration with Professor David Evans and Dr. Ryan Noyce at University of Alberta
- ✓ Demonstrated protective vaccine activity in mice
- ✓ Patent application on novel vaccine submitted

Regulatory strategy

- We intend to meet with FDA to discuss the most efficient and appropriate investigational plan to support the licensure, either:
 - ✓ Application of the "Animal Rule", or
 - ✓ Conducting an active comparator study using ACAM2000
- Good Manufacturing Practice (GMP) viral production process in development

Targeting a Potential Public Health Issue

Material threat medical countermeasure under 21st Century Cures Act

- Qualifies for **Priority Review Voucher (PRV)** upon licensure*
 - ✓ **PRVs have no expiration date, are transferrable and have sold for ~\$125 M**

*BLA/NDA priority 6-month review is expected.

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TNX-801 (Synthesized Live Horsepox Virus): A Potential Smallpox-Preventing Vaccine

109

Synthesis¹ from sequence of a 1976 Mongolian isolate² In mice, TNX-801 behaved like attenuated vaccinia virus

- Vaccinia is the term used to classify the live poxviruses that are used as smallpox vaccines, including ACAM2000, which is the latest smallpox vaccine licensed in the U.S.

How is HPXV related to modern vaccines?

- Multiple sources³⁻⁵ indicate that the smallpox vaccine discovered by Dr. Edward Jenner in the early 19th century was either HPXV or a very similar virus and that vaccinia vaccines are derived from this ancestral strain
- A 1902 U.S. smallpox vaccine was found to be highly similar (99.7% similarity in core genome⁶) to HPXV sequence from the 1976 Mongolian isolate
- Horsepox is now believed to be extinct⁵

¹ Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453 <https://doi.org/10.1371/journal.pone.0188453>

² Tufman et al., Journal of Virology, 2006; 80(18): 9244-9258

³ Qin et al., Journal of Virology, 2011; 85(24):13049-13060

⁴ Medaglia et al., Journal of Virology, 2015; 89(23):11909-11925

⁵ Esparza J. Veterinary Record, 2013; 173: 272-273

⁶ Schriock, L. et al., N Engl J Med 2017; 377:1491-1492, <http://www.nejm.org/doi/full/10.1056/NEJM1707600>



The Currently Licensed Smallpox Vaccine ACAM2000 is a Live Vaccinia Virus (VACV) Vaccine

110

ACAM2000 is sold to the U.S. Strategic National Stockpiles¹

- Sold by Emergent BioSolutions
- Sanofi divested ACAM2000 to Emergent BioSolutions in 2017 for \$97.5 M upfront plus milestones
- ACAM2000 was developed by Acambis which was acquired by Sanofi in 2008 for \$513 M

Vaccinia (VACV) strains have demonstrated potential for zoonotic infections and re-infection of humans²⁻⁵

- No known evidence for zoonosis of ACAM2000, but it has not been widely administered

Modern VACV smallpox vaccines are associated with cardiotoxicity⁶

¹Nalca, A et al. Drug design, development and Therapy. (2010) 4:71-79

²Medaglia MLG, et al. J Virol. (2015) 89:11909 –11925. doi:10.1128/JVI.01833-15.

³Trindade,GS. et al. Clinical Infectious Diseases. (2009) 48:e37-40

⁴Leite,JA, et al. Emerging Infectious Diseases. (2005) www.cdc.gov/eid • Vol. 11, No. 12

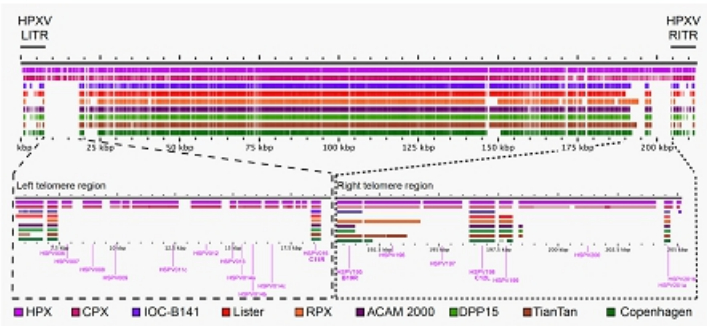
⁵Medaglia MLG, et al. Emerging Infectious Diseases (2009) www.cdc.gov/eid • Vol. 15, No. 7

⁶Engler RJM et al., PloS ONE (2015) 10(3): e0118283. doi:10.1371/journal.pone.0118283

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HPXV and its Relationship to Other Orthopoxviruses



HSPV074 – fragmented homolog of VACV I4L (ribonucleotide reductase)
HSPV200 – 216 kDa protein probably regulates T-cell activation with homologs still present in variola, cowpox, and monkeypox viruses

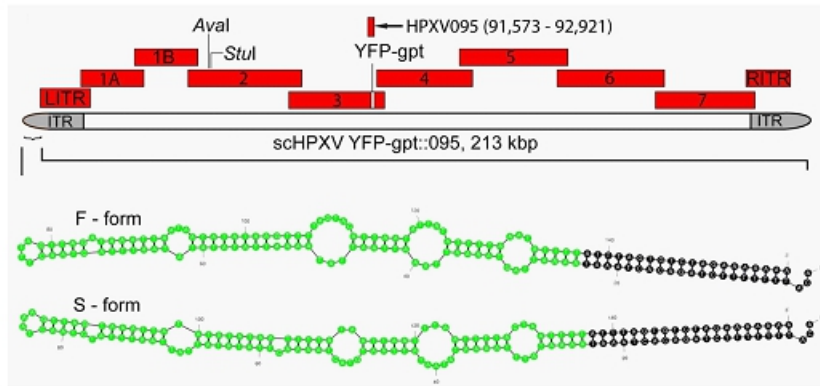
Evans, D. U. of Alberta (2018) with permission

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Genome Assembly (212 kbp) by Synthesis of Fragments and Construction of Telomeres

112



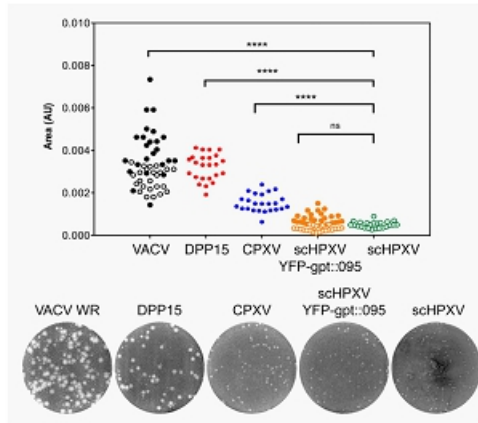
Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

Sequence: GenBank entry DQ792504; DNA: GeneArt

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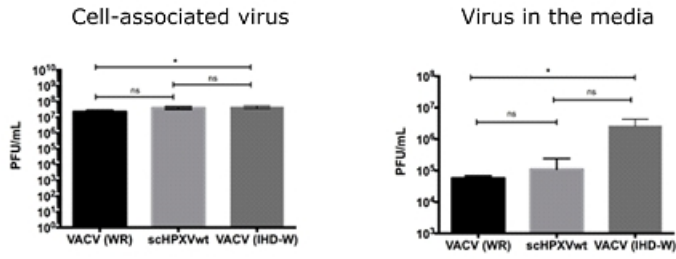


HPXV Produces Small Plaques that are More Like Cowpox Than Vaccinia (VACV)



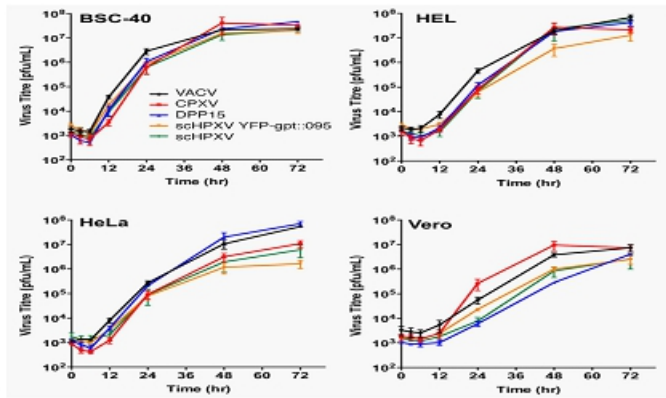
Noyce, RS, Lederman S, Evans DH, PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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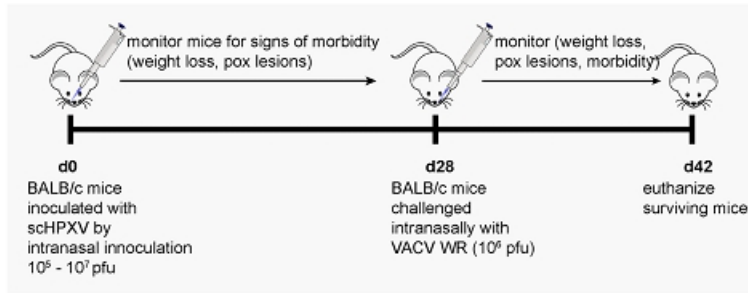
Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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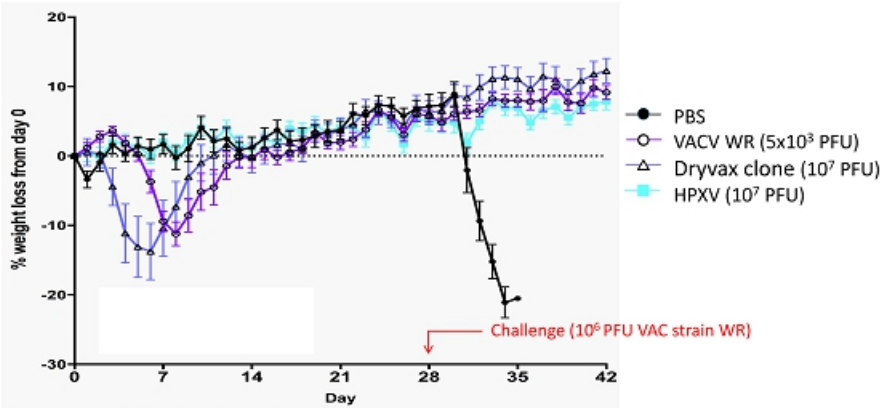
Testing Vaccine Protective Activity of HPXV in Mice Model

116





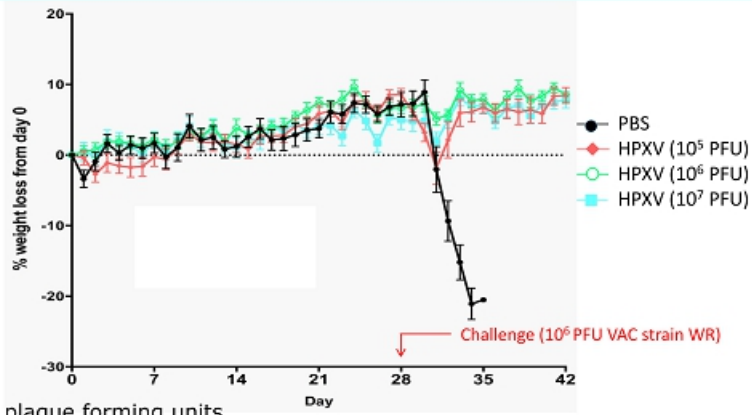
Biological Properties of HPXV: Less Virulent than a Dryvax Clone, but Produces Protective Immunity



Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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HPXV Vaccine Protection Activity Observed As Low As 10^5 PFU*



*PFU = plaque forming units

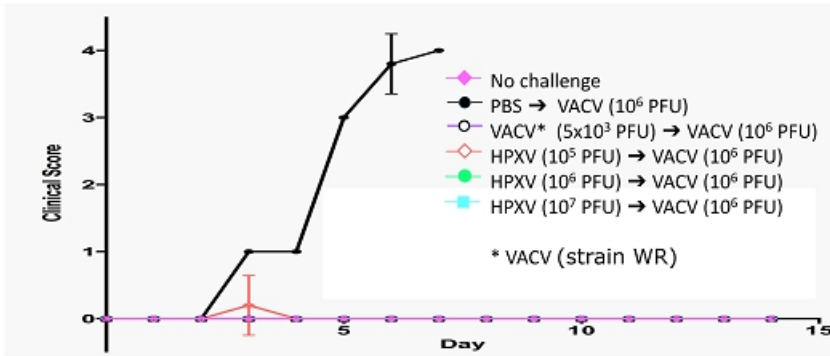
Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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No Overt Clinical Sign Observed in HPXV Vaccinated Mice After VACV Challenge

119



Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
<https://doi.org/10.1371/journal.pone.0188453>

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HPXV or TNX-801– May Have an Improved Safety Profile as a Smallpox Preventing Vaccine

120

Horsepox is caused by HPXV and is characterized by mouth and skin eruptions

HXPV isolate from the 1976 outbreak later sequenced

Modern smallpox vaccines are associated with cardiotoxicity¹

HPXV has potential for slower proliferation leading to possibly decreased toxicity²

¹ Engler RJM et al., PLoS ONE 10(3): e0116283. doi:10.1371/journal.pone.0116283 (2015)

² Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453 <https://doi.org/10.1371/journal.pone.0188453>



An Improved Smallpox-Preventing Vaccine is Important and Necessary for a Potential Public Health Issue

121

Smallpox was eradicated as a result of global public health campaigns

No cases of naturally-occurring smallpox have been reported since 1977

Accidental or intentional transmission of smallpox does not require a natural reservoir

Stockpiles of smallpox-preventing vaccines are currently maintained and refreshed in case of need



Ongoing vaccination of U.S. troops

- Troops in the Global Response Force

Threat of smallpox re-introduction

- Strategic National Stockpile & public health policy

Re-emergence of monkey pox¹

- Believed to resurgent because of vaccinia-naïve populations in Africa
- Multiple U.S. military operations ongoing in Africa

¹Nda- Isaiah, J. Nigeria: Monkey Pox Scourge Spreads to Seven States. All Africa. 12 OCTOBER 2017, [HTTP://ALLAFRICA.COM/STORIES/201710120177.HTML](http://allafrica.com/stories/201710120177.html)



21st Century Cures Act (2016), Section 3086

- Encouraging treatments for agents that present a national security threat

Medical countermeasures are drugs, biologics (vaccines) or devices intended to treat:

- Biological, chemical, radiological, or nuclear agents that present a national security threat
- Public health issues stemming from a naturally occurring emerging disease or a natural disaster

New Priority Review Voucher program for "Material Threat Medical Countermeasures"

- Priority Review Voucher may be transferred or sold

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TNX-801 (Synthesized Live Horsepox Virus): A Smallpox-Preventing Vaccine Candidate

TNX-801 (HPVX)

- Synthesized live horsepox virus
- Shares structural characteristics with vaccinia-based smallpox vaccines
- Unique properties that suggest lower toxicity

Mechanism of Action

Live virus vaccines stimulate cross-reactive immunity

- Protects from possible infection with smallpox virus
- Renders recipient "immune"
- Provides indirect protection to non-immunized population "herd immunity"

Possible advantages of TNX-801

Potential safety improvement over existing vaccines

- Cardiotoxicity limits widespread smallpox vaccination in at-risk population

Exclusivity

- Patent application filed on novel virus composition
- 12 years exclusivity can be anticipated

Eligibility for Priority Review Voucher upon licensure if accepted as medical counter-measure



Given that smallpox is eradicated the only evidence of effectiveness for modern vaccines is from historical use when smallpox was endemic

- Stimulates interest in the evolution of vaccinia

Vaccinia stocks around the world diverged from Jenner's 1798 vaccine

- Evolutionary argument that common progenitor was horsepox or a similar virus

U.S. vaccine from 1902 was found to be 99.7% similar to horsepox in core viral sequence¹

- Strong evidence linking a horsepox-like virus as progenitor to modern vaccinia
- Effectiveness of older vaccines support belief that HPXV will be protective against smallpox

¹Schrick, L. et al (2017) An Early American Smallpox Vaccine Based on Horsepox N Engl J Med 2017; 377:1491



Single clone picked from “swarm” of Dryvax^{®1}

- Some rationale for selection²

Growth in serum free Vero cells

- Eliminates risk of Bovine Spongiform Encephalopathy (BSE)/prion contamination – safety concerns in Wyeth’s Dryvax (grown in calf lymph)

In 2000, the evolutionary connection between vaccinia and horsepox was not understood

- Tulman’s sequence of horsepox was published in 2006³

¹US licensed smallpox preventing vaccine – ACAM2000 is currently marketed, Dryvax has been withdrawn from marketing

²Monath, TP et al. Int. J. of Inf. Dis. (2004) 8S2:S31

³Tulman, ER. Genome of Horsepox Virus J. Virol. (2006) 80(18) 9244



Rationale for Developing a Potentially Improved New Smallpox Vaccine

127

Toxicity concern of modern vaccinia (VACV) vaccines limit widely administration

- Not recommended for use, even in first responders
- U.S. soldiers in the Global Response Force are immunized

Modern VACV vaccination safety studied in 1081 VACV (Dryvax [62.5%] and ACAM2000 [37.5%]) vaccinees¹

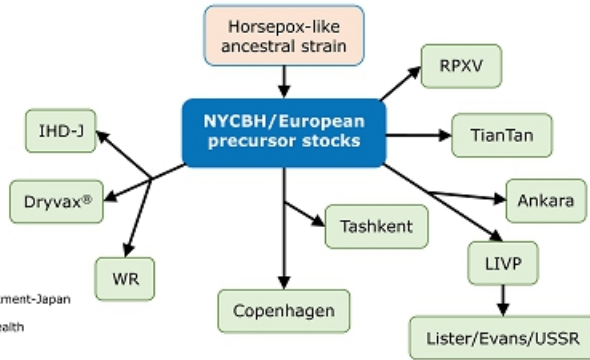
- New onset chest pain, dyspnea and/or palpitations 10.6% of VACV-vaccinees and 2.6% of control immunized (TIV)²
- Clinical: 4 probable myo- and 1 suspected peri-carditis (5 cases out of 1081 VACV vaccinees – 0.5%)
- Cardiac specific troponin T (cTnT) elevation in 31 VACV vaccinees (3%)

¹Engler RJM, et al. (2015) A Prospective Study of the Incidence of Myocarditis/Pericarditis and New Onset Cardiac Symptoms following Smallpox and Influenza Vaccination. PLoS ONE 10(3)

²TIV = trivalent influenza vaccine - control vaccinees



Postulated Divergence of Historical Strains of Vaccinia



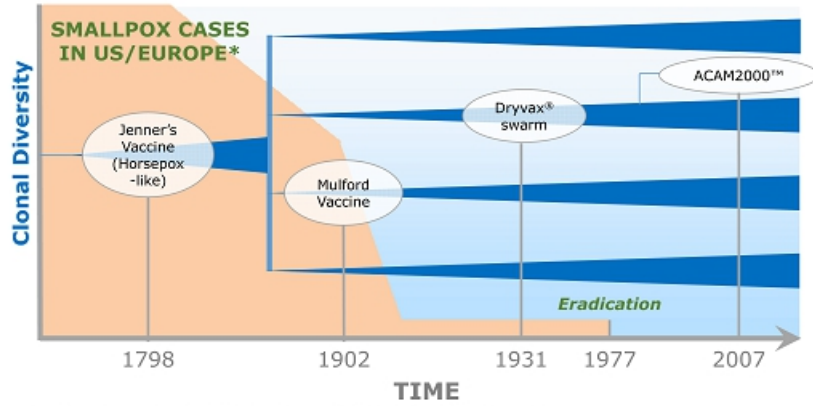
IHD-J=International Health Department-Japan
LIVP=Lister Vaccine Strain
NYCBH=New York City Board of Health
RPXV=Rabbitpox Virus
WR=Western Reserve

Figure Adapted from Qin et al. *Journal of Virology*. 2015;89(3):1809-1824.
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Proposed Evolution of Vaccinia Vaccines

Relationship to Smallpox Incidence and Eradication





What's the Evidence of Effectiveness of Smallpox Vaccines for Preventing Smallpox?

130

Theoretical effectiveness of modern vaccinia vaccines are based on extrapolation from older vaccines

- Newer/modern vaccines were not widely used when smallpox was endemic

MVA (Modified Virus Ankara) which has large deletions also produces different T cell responses

- In non-human primates, MVA is less effective than ACAM2000 in protecting against monkeypox¹
- MVA has fewer epitopes, and elicits different responses to existing epitopes²
 - MVA effectiveness argument is based on the immune response to intracellular mature virus (IMV)
 - Immunity to the other form of virus, extracellular enveloped virus (EEV), is weak because the immunodominant B5 gene is heavily mutated and deleted in MVA

¹Golden JW, et al. (2012). PLoS ONE 7(7): e42353. doi:10.1371/journal.pone.0042353

²Tscharke, DC et al., J. Exp. Med. 2005 201(1):95

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Preventing Vaccine

- Jenner's vaccine, HPXV (upon licensure), Vaccinia

Post-exposure vaccination¹

- Jenner's vaccine

Priming of the immune system

- Imvamune® (MVA) and DNA vaccines²

Pharmacotherapy for infected or exposed individuals

- Arestvyr®/TPOXX® (tecovirimat, formerly ST-246)

Treatment of disseminated viremia in immunocompromised³

- Arestvyr®/TPOXX®, Brincidofovir and vaccinia immune globulin

¹Described by Jenner as one of his major discoveries

²Hooper, JW et al. Smallpox DNA Vaccine Protects Nonhuman Primates Against Lethal Monkeypox. *J. Virol.* 2004. 78 (9) 4433

³Lederman, ER et al, Progressive Vaccinia: Case Description and Laboratory-Guided Therapy With Vaccinia Immune Globulin, ST-246, and CMX001 *JID* 2012. 206:1372



Viral Replication Proficiency is Critical to Human Immunogenicity but May Compromise Safety

132

Pox vaccines with low or no replication appear safer than vaccines replicate fast in human cells

- Canarypox and Imvamune® (Modified Virus Ankara/MVA) appear to have good tolerability
- Relatively safe in immunocompromised hosts
- Rapidly replicating modern vaccinia vaccines (Dryvax® and ACAM2000®) are associated with myocarditis

Replication correlates positively with immunogenicity

- Jenner's vaccine and modern vaccinia engender strong immunity
- Canarypox and MVA appear to be weak immunogens, suitable for priming of the immune system in healthy human being and potentially safe enough to use in immunocompromised people



TNX-801 (HPXV) is expected to have similar scalability for mass production as ACAM2000

- TNX-801 grows well in cell lines – immunity is expected after single administration (immunization)
- Only a small dose (replicating live virus) is required for immunization

MVA is hard to scale up for commercial production

- Requires high dose to engender an immune response (non-replicating virus)
- Cumbersome immunization schedule– two doses, 4 weeks apart, are used typically to prime the immune system (slow growth)

Antivirals

- Relatively expensive to manufacture – requires repeated dosing
- May provide logistical challenges to at risk population over the at risk period



Rationale for Developing a Potentially Improved New Smallpox Vaccine Based on Jenner's Vaccine

134

Vaccination protects against smallpox – both individuals and populations at risk

- Use of Jenner's vaccine resulted in eradication of smallpox

Vaccination can protect AFTER smallpox infection

- Vaccinia can be administered 1-3 days after infection

Vaccination indirectly protects non-immunized people in a population

- "Wetting the forest" or "herd immunity"

Vaccination can be cost effective with safe/low-risk vaccines

- Replication-efficient live virus vaccines can be manufactured and administered for broader use

"The Time is Right"

New synthetic biology technology and new understanding of vaccinia evolution provide an opportunity for a potentially safer vaccine using HPXV



Potential for Use of HPXV as a Vector for Vaccines to Infectious Disease or Cancer

135

Poxviruses like HPXV can be engineered to express foreign genes and are well recognized platforms for vaccine development

- Large packaging capacity for exogenous DNA inserts (i.e. encoding antigens)
- Precise virus-specific control of exogenous gene insert expression
- Lack of persistence or genomic integration in the host
- Strong immunogenicity as a vaccine
- Ability to rapidly generate vector/insert constructs
- Readily manufacture at scale
- Live, replicating vaccine – direct antigen presentation

Potential advantages of HPXV- strong immunogenicity with good tolerability



Financial Overview

136

NASDAQ: TNXP	
Cash and cash equivalents, September 30, 2019	\$10.0 million
Net proceeds from equity offering in 4Q2019	\$8.1 million
Common stock outstanding as of December 17, 2019	8.5 million shares



Management Team



Seth Lederman, MD
President & CEO



Gregory Sullivan, MD
Chief Medical Officer



Bradley Saenger, CPA
Chief Financial Officer



Jessica Morris
Chief Operating Officer





Board of Directors

138

Seth Lederman, MD

Chairman

Adeoye "Oye" Olukotun, MD

Squibb, BMS, Mallinckrodt, Esperion

Margaret Smith Bell

Standard Life Investments, Putnam
Investments, State Street Research

John Rhodes

Chair, NYS Public Service Commission, CEO,
NYS Dept. of Public Service, Booz Allen

Daniel Goodman, MD

Psychiatrist, co-founder Psychogenics

James Treco

First Chicago, Salomon Brothers/Citigroup

Brig. General David Grange (U.S. Army, ret.)

Pharm-Olam, PPD, McCormick Foundation



Milestones – Recently Completed and Upcoming

139

- ✓ March 2019 P302/RECOVERY study initiated
- ✓ April 2019 Received FDA formal minutes with clear guidance and support for new Phase 3 FM study using TNX-102 SL 5.6 mg
- ✓ May 2019 In-licensed TNX-1300, product candidate in Phase 2 development for cocaine intoxication
- ✓ August 2019 In-licensed TNX-1600, product candidate in preclinical development for PTSD
- ✓ August 2019 Entered into research collaboration to study internally-developed TNX-1500
- ✓ September 2019 In-licensed TNX-1700, product candidate in preclinical development for gastric and pancreatic cancers
- ✓ October 2019 Completed long-term exposure studies in participants with PTSD to evaluate tolerability of TNX-102 SL 5.6 mg
- ✓ October 2019 Met with FDA to discuss new program for TNX-102 SL to treat AUD
- ✓ 4th Quarter 2019 Developed a once-daily dosing formulation for TNX-601 CR in PK study
- 1st Quarter 2020 Interim analysis results from Phase 3 P302/RECOVERY study in PTSD expected
- 2nd Quarter 2020 Topline data from Phase 3 P302/RECOVERY study in PTSD expected
- 2nd Half 2020 Interim analysis results from Phase 3 F304/RELIEF study in fibromyalgia expected

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Pipeline Summary – by Select Therapeutic Areas

140

- **Psychiatry/PTSD:**
 - **TNX-102 SL – (sublingual cyclobenzaprine) for PTSD**
 - Phase 3/RECOVERY
 - **TNX-601 – (tianeptine) for depression and PTSD**
 - Phase 1 formulation development study completed
 - **TNX-1600 – (triple reuptake inhibitor) for PTSD**
 - Pre-clinical
- **Pain:**
 - **TNX-102 SL for fibromyalgia**
 - Phase 3/RELIEF
- **Addiction Medicine:**
 - **TNX-1300 – (cocaine esterase) for cocaine intoxication**
 - Mid-Phase 2
 - **TNX-102 SL – (sublingual cyclobenzaprine) for alcohol use disorder (AUD)**
 - Pre-clinical; FDA official meeting minutes confirm plan to submit IND application for a Phase 2 POC study
- **Biodefense:**
 - **TNX-801 – (live horsepox vaccine) – for preventing smallpox**
 - Pre-clinical
 - **TNX-701 – (oral radioprotective agent) – for radioprotection**
 - Pre-clinical



Pipeline Summary – by Phase of Development

141

Two Phase 3 Programs in indications affecting millions of Americans

- TNX-102 SL for PTSD: affects an estimated 12 million adults in U.S.
- TNX-102 SL for Fibromyalgia: affects an estimated 6-12 million adults in U.S.

Two Phase 2 Programs in indications for which there is no FDA-approved drug available

- TNX-1300 for Cocaine Intoxication
- TNX-102 SL for Agitation in Alzheimer’s Disease

Robust pipeline of preclinical and Phase 1 products to improve biodefense, leverage PTSD and internal expertise



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NASDAQ: TNXP

Thank you!

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Investor Presentation

1



December 2019

Version P0212 12-17-19 (Doc 0576)

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Cautionary Note on Forward-Looking Statements

2

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, substantial competition; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and risks related to failure to obtain U.S. Food and Drug Administration clearances or approvals and noncompliance with its regulations. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission (the "SEC") on March 18, 2019, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.



Who we are:

- A clinical stage biopharmaceutical company dedicated to developing innovative treatments for patients and making meaningful contributions to society
- Focusing on small molecules and biologics to treat psychiatric, pain and addiction conditions

What we do:

- Target therapeutic areas with high need for improvement
 - Conditions with no, or inadequate, treatments
 - Significant patient populations not well served by existing therapies
- Develop innovative treatment options with possibility to be a “game changer”
 - Scientifically unique and innovative
 - Strong scientific rationale supported by preliminary clinical evidence and published literature
 - Proven regulatory pathways and established clinical endpoints
 - Built on a foundation of proprietary intellectual property

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CNS Candidates in Clinical Development

Psychiatry, Pain and Addiction

TNX-102 SL and TNX-601 owned outright with no royalties due

4

Pipeline Product	Indication	Phase 1	Phase 2	Phase 3	NDA ³ /BLA ⁴	Market
TNX-102 SL¹ Cyclobenzaprine HCl sublingual tablets Protectic [®] formulation technology	<i>Bedtime Treatment for PTSD – Tonmya^{®2}</i>	→			Interim analysis results expected 1Q 2020 Topline data expected 2Q 2020	
	<i>Bedtime Treatment for Fibromyalgia</i>	→			Interim analysis results expected 2H 2020	
	Bedtime Treatment for Agitation in Alzheimer's	→				
	Bedtime Treatment for Alcohol Use Disorder (AUD) ⁵	→				
TNX-1300⁶ Cocaine esterase (recombinant from bacteria) i.v. formulation	Cocaine intoxication / overdose	→				
TNX-601 CR⁷ Tianeptine oxalate oral controlled release formulation	Daytime Treatment for PTSD	→				
	Daytime Treatment for Major Depressive Disorder (MDD)	→				
	Neurocognitive Dysfunction from Corticosteroids	→				

¹ TNX-102 SL (cyclobenzaprine HCl) sublingual tablets is an investigational new drug and has not been approved for any indication; ² Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD; ³ NDA- New Drug Application; ⁴ BLA - Biologic Licensing Application; ⁵ Pre-Investigational New Drug (IND) meeting completed in October with FDA. Upon receiving FDA clearance of an IND application, TNX-102 SL for AUD will be Phase 2 ready as it is expected to qualify for the 505(b)(2) pathway for approval; ⁶ TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, i.v. solution) is an investigational new biologic and has not been approved for any indication; ⁷ TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 study for formulation development was recently completed outside of the U.S.

Pipeline Product	Indication(s)	Category
TNX-1600 Triple reuptake inhibitor ²	Daytime Treatment for PTSD	Psychiatry
TNX-1500³ Anti-CD154 monoclonal antibody	Prevention and treatment of organ transplant rejection Treatment for autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis	Transplant Autoimmunity
TNX-1700 rTFF2 ⁴	Treatment for gastric and pancreatic cancers	Oncology
TNX-801³ Live horsepox virus (HPXV) vaccine from cell culture	Smallpox-preventing vaccine	Biodefense
TNX-701³ Radioprotection drug oral capsules	Protection from radiation injury	Biodefense

¹ (Experimental new medicines and biologics, not approved for any indication)

² (2S,4R,5R)-5-(((2-aminobenzo[σ]thiazol-6-yl)methyl)amino)-2-[[bis(4-fluorophenyl)methyl]tetrahydro-2H-pyran-4-yl] is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine)

³ Programs owned outright with no royalties due

⁴ recombinant Trefol Family Factor 2



TNX-102 SL Proposed Mechanism: Improving Sleep Quality

6

The focus of TNX-102 SL development is both unique and innovative

- Testing the therapeutic benefit of sleep ('sleep quality')
 - Restorative sleep, in contrast to time spent sleeping ('sleep quantity')
- Targeting clinical conditions for which improved sleep quality may have a therapeutic benefit
 - Reduction in disease-specific symptoms, with sleep improvement as a secondary endpoint

Therapeutic Area	Target Indication	Status
Psychiatry	Posttraumatic stress disorder (PTSD)	Phase 3
Rheumatology	Fibromyalgia (FM)	Phase 3
Psychiatry / Neurology	Agitation in Alzheimer's Disease (AAD)	Phase 2 ready
Addiction	Alcohol Use Disorder (AUD)	Pre-IND
Chronic pain	TBD	Life-cycle opportunity
Sleep disorders	TBD	Life-cycle opportunity



TNX-102 SL Intellectual Property – U.S. Protection expected until 2035

7

Composition of matter (eutectic): Protection expected to 2034/2035

- United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9636408 in May 2017, U.S. Patent No. 9956188 in May 2018, U.S. Patent No. 10117936 in Nov 2018, and U.S. Patent No. 10,357,465 in July 2019
- European Patent Office (EPO) issued Patent No. 2968992 in December 2019
- China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019
- Indonesian Patent Office issued Indonesian Patent No. IDP000055516 in January 2019
- Saudi Arabian Patent Office issued Saudi Patent No. 6088 in September 2018
- Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018
- New Zealand Intellectual Property Office (NZIPO) issued New Zealand Patent No. 631152 in August 2017
- 35 patent applications pending (5 being allowed in U.S, Australia, Europe, Taiwan, South Africa)

Composition of matter (sublingual): Protection expected to 2033

- NZIPO issued New Zealand Patent No. 631144 in March 2017 and Patent No. 726488 in January 2019
- Taiwanese Intellectual Property Office issued Taiwanese Patent No. 1590820 in July 2017 and Patent No. 1642429 in December 2018
- Australian Patent Office issued Australian Patent No. 2013274003 in October 2018
- JPO issued Japanese Patent No. 6259452 in Dec 2017
- 21 patent applications pending

Method of use (PTSD) for cyclobenzaprine: Protection expected to 2030

- Hong Kong Patent Office issued Hong Kong Patent No. HK1176235 in September 2018
- USPTO issued U.S. Patent No. 9918948 in March 2018
- European Patent Office (EPO) issued European Patent No. 2501234B1 in Sept 2017 (validated in 37 countries). In response to an opposition filed in June 2018, EPO's Opposition Division determined in October 2019 that it will uphold this patent.
- 1 patent application pending

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Prevalence of PTSD Among Civilians and Veterans

8



Approximately **12 million** American adults annually¹



Women more likely to develop than men¹

¹ Goldstein et al., 2016 (adjusted for 2019); ² Norris, PTSD Res Quar, 2013;

³ Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015, Washington, DC; Among 1.9M separated OEF/OIF/OND veterans, 1.2M have obtained VA healthcare; 685k evaluated by VA with possible mental disorder, and 379k diagnosed with PTSD.



Unmet Need for Effective and Safe Therapies for Treatment of PTSD

9

No FDA-approved products for PTSD since Pfizer's Zoloft® (sertraline) in 1999 and GSK's Paxil® (paroxetine) in 2001

- Neither has shown efficacy in military-related PTSD
- Side effects relating to sexual dysfunction, sleep disruption and weight gain are commonly reported

PTSD is signature wound of last 25 years of war

- Affects servicemember health and performance, force readiness, and retention
- Believed to be the underlying cause of suicide in many cases
- Male PTSD patients often unresponsive or intolerant of current treatments

Civilian PTSD is more prevalent than military

- Results from physical and sexual assault trauma, vehicular accidents, natural disasters
- Significant cause of morbidity



Potential Therapeutic Advantages of TNX-102 SL

10

TNX-102 SL is believed to treat PTSD by improving sleep *quality*

- The brain naturally processes memories during sleep
- PTSD sufferers' emotionally charged memories disturb sleep and disrupt the natural processing of memories during sleep
- TNX-102 SL is believed to normalize memory processing and facilitate extinction consolidation (breaking the link between "triggers" and PTSD symptoms)

Cyclobenzaprine, active ingredient of TNX-102 SL, is *NEITHER* a benzodiazepine nor a narcotic

- Does **NOT** interact with the same receptors as traditional hypnotic sleep drugs associated with retrograde amnesia and is **NOT** an opiate

TNX-102 SL is non-addictive

- Cyclobenzaprine is the active ingredient of an orally ingested immediate release tablet (Flexeril®), approved 40 years ago; Flexeril's current labeling indicates no abuse and dependence concern at higher doses than TNX-102 SL (15-30 mg/day v. 5.6 mg/day)
- TNX-102 SL NDA can be filed without drug abuse and dependency assessment studies

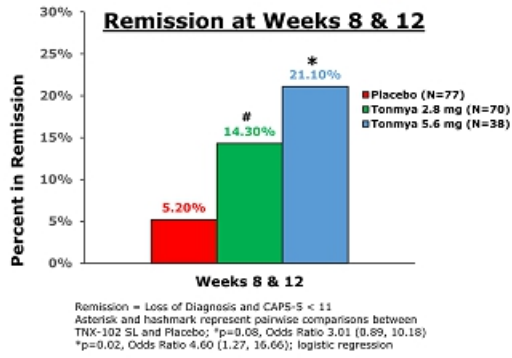
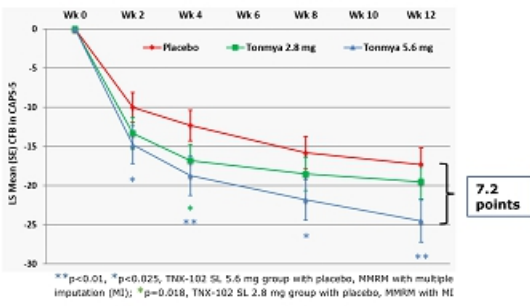
Once-daily sublingual dose taken at bedtime enhances patient adherence and transmucosal absorption aligns bioavailability of drug with sleep cycle

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TNX-102 SL Phase 2 Dose-Effect in Military-Related PTSD¹

PTSD Symptoms (CAPS-5² Score)



¹ Completed Phase 2 P201/MEase study; Retrospective analysis of TNX-102 SL 5.6 mg on CAPS-5 ≥33 (high-moderate) subgroup. Primary analysis of P201/MEase, based on TNX-102 SL 2.8 mg in participants with entry CAPS-5 ≥29 (moderate PTSD severity), was not statistically significant.
² CAPS-5 = Clinician administered PTSD Scale for DSM-5



Primary Outcome (CAPS-5) in Phase 3 Study: mITT and ≤ 9 Years Time Since Trauma Subgroup

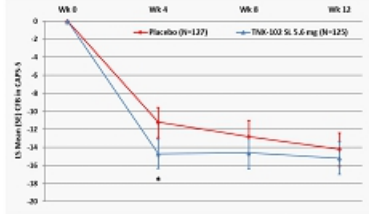
Phase 3 P301/HONOR Study¹

PTSD Symptoms (CAPS-5 Score)

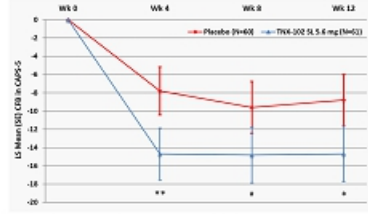
PTSD Symptoms (CAPS-5 Score)

Modified intent to treat (mITT) population

Time Since Trauma (TST) ≤ 9 yrs



~50% mITT Population



*p=0.019, TNX-102 SL 5.6 mg group v. placebo, using mixed model repeated measures (MMRM) with multiple imputation (MI)

**p=0.004, *p=0.069, *p=0.039, TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

¹ Phase 3 P301/HONOR study: stopped in July 2018. Separation on primary endpoint did not cross pre-specified study continuation threshold at Week 12 in the interim analysis at ~50% randomization; no safety or tolerability issues discovered.



Adverse Events (AEs) in P201/AtEase and P301/HONOR Studies

Category of Adverse Reaction Preferred Term	P201			P301	
	Placebo (N=94)	TNX 2.8 mg (N=93)	TNX 5.6 mg (N=50)	Placebo (N=134)	TNX 5.6 mg (N=134)
Systemic Adverse Events**					
Somnolence	6.4%	11.8%	16.0%	9.0%	15.7%
Dry mouth	10.6%	4.3%	16.0%		
Headache	4.3%	5.4%	12.0%		
Insomnia	8.5%	7.5%	6.0%		
Sedation	1.1%	2.2%	12.0%		
Local Administration Site Reactions**					
Hypoesthesia oral	2.1%	38.7%	36.0%	1.5%	37.3%
Paraesthesia oral	3.2%	16.1%	4.0%	0.7%	9.7%
Glossodynia	1.1%	3.2%	6.0%		
Product Taste Abnormal				3.0%	11.9%

*only adverse events (AEs) are listed that are at a rate of ≥ 5% in any TNX-treated group

**no values in a row for either study means the AE in the active group(s) in that study was at a rate of <5%

No serious or unexpected AEs in P201 or P301 related to TNX-102 SL

- Systemic AEs comparable between studies and also consistent with those described in approved oral cyclobenzaprine product labeling
- Severity and incidence of oral hypoesthesia (oral numbness) are not dose related and similar in both studies



TNX-102 SL for PTSD: Phase 3 P302/RECOVERY Study Expecting Interim Analysis Results in 1Q 2020

14

General study characteristics:

- Randomized, double-blind, placebo-controlled study with baseline CAPS-5¹ ≥ 33 in approximately 30 U.S. sites
- Enrollment restricted to study participants with PTSD who experienced an index trauma ≤ 9 years from the date of screening
- Both civilian and military-related PTSD to be included

TNX-102 SL once-daily at bedtime
5.6 mg (2 x 2.8 mg tablets) *N= 125*

Placebo once-daily at bedtime
N= 125

12 weeks

Potential pivotal efficacy study to support NDA approval

Primary endpoint:

- CAPS-5¹ mean change from baseline at Week 12 (TNX-102 SL 5.6 mg vs. placebo)

Key Secondary endpoints include:

- Change from baseline Clinical Global Impression – Severity scale
- Change from baseline Sheehan Disability Scale total score

Interim analysis results expected 1Q 2020

Topline data expected 2Q 2020

¹CAPS-5 = Clinician-Administered PTSD Scale for DSM-5

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Opportunities to Expand to Other Indications

15

Role of sleep disturbance more established in common psychiatric and neurological/pain disorders

- Recognized as a core symptom of many of these disorders
- Traditional sleep medications, which increase sleep quantity, may not provide benefit (benzodiazepines in major depression) or are contraindicated (benzodiazepines in PTSD)

Psychiatric Disorders

- Stress Disorders (PTSD)
- Mood Disorders (MDD)
- Anxiety Disorders
- Addiction (Alcohol Use Disorder)

Psychiatric Symptoms of Neurological Disorders

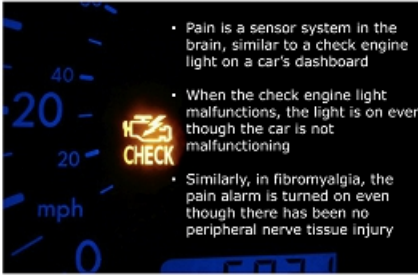
- Agitation in Alzheimer's
- Psychosis in Parkinson's, Alzheimer's and other dementias

Chronic Pain States

- Chronic wide-spread pain (fibromyalgia)
- Osteoarthritis

Growing recognition that there are many disorders where sleep disturbances may have a role in the pathophysiology (cardiovascular, metabolic, neurologic)

- Homeostatic role of sleep quality *in several disorders*



Volkanoglu Check Engine [Photograph]. (2011, October 14). Wikipedia

- Pain is a sensor system in the brain, similar to a check engine light on a car's dashboard
- When the check engine light malfunctions, the light is on even though the car is not malfunctioning
- Similarly, in fibromyalgia, the pain alarm is turned on even though there has been no peripheral nerve tissue injury

- Fibromyalgia is considered a neurobiological disorder characterized by¹: chronic widespread pain, non-restorative sleep, fatigue, diminished cognition
- Believed to result from inappropriate pain signaling in central nervous system in the absence of peripheral injury¹
- An estimated 6-12 million adults in the U.S. have fibromyalgia²
- Causes significant impairment in all areas of life³
 - Lower levels of health-related quality of life – reduced daily functioning
 - Interference with work (loss of productivity, disability)
- Fewer than half of those treated for fibromyalgia receive complete relief from the three FDA-approved drugs⁴
- Inflicts substantial strain on the healthcare system
 - Average patient has 20 physician office visits per year⁵
 - Annual direct medical costs are twice those of non-fibromyalgia individuals⁶

¹ Phillips K & Clauw DJ, Best Pract Res Clin Rheumatol 2011;25:141.

² American Chronic Pain Association (www.theacpa.org, 2019)

³ Schaefer et al., Pain Pract, 2015.

⁴ The three drugs with FDA approval for the treatment of fibromyalgia:

Pregabalin (Lyrica), Duloxetine (Cymbalta), Milnacipran (Savella)

⁵ Robinson et al., Pain Medicine 2013;14:3400.

⁶ White et al., J Occupational Environ Med 2006;50:13.



Large Need for New Fibromyalgia Therapies that Provide Broad Symptom Improvement with Better Tolerability

17

- Currently-approved medications may have side effects that limit long-term use¹
 - Many patients skip doses or discontinue altogether within months of treatment initiation
- Medication-related side effects may be similar to fibromyalgia symptoms
- High rates of discontinuation, switching and augmentation
 - Attempts to treat multiple symptoms and/or avoid intolerable side effects
 - Average of 2-3 medications used simultaneously²
 - Typical patient has tried six different medications³
- Substantial off-label use of narcotic painkillers and prescription sleep aids³
 - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment⁴
- TNX-102 SL is a non-opioid, centrally-acting analgesic that could provide a new therapeutic option for fibromyalgia patients

¹ Nuesch et al, Ann Rheum Dis 2013;72:955-62.

² Robinson RL et al, Pain Medicine 2012;13:1366.

³ Patient Trends: Fibromyalgia[®], Decision Resources, 2011.

⁴ Berger A, Dukes E, Martin S, Edelsberg J, Oster G, Int J Clin Pract, 2007; 61(9):1498-1508.



TNX-102 SL 2.8 mg for Fibromyalgia: Summary of Completed Phase 3 AFFIRM Study (F301) and Results

18

General study characteristics:

- Randomized, 12-week, double-blind, placebo-controlled Phase 3 study of TNX-102 SL 2.8 mg (half the dose being developed for PTSD) taken daily at bedtime (n=519)
- Patients had to satisfy the 2010 ACR Preliminary Diagnostic Classification Criteria
- **Primary endpoint:** Weekly average pain improvement as a 30% responder analysis
- **Secondary endpoints:** PGIC, FIQ-R Symptom Domain, FIQ-R Function Domain, Daily Sleep Quality Diary, PROMIS Sleep Disturbance

Efficacy results:

- Completers: 425 (81.9%) of 519 patients in Intent-to-Treat population
- The primary analysis (responder analysis) was not statistically significant (P=0.095). However, the pre-specified secondary analysis of average pain improvement after 12 weeks of treatment showed P<0.001, mixed model repeated measures (MMRM)
- Significant improvements observed in sleep quality, patient global impression of change and fibromyalgia-specific measures (secondary analyses)

PGIC = Patient Global Impression of Pain
FIQ-R = Fibromyalgia Impact Questionnaire - Revised
MMRM = mixed model repeated measures

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Phase 3 AFFIRM (F301) Study Results:

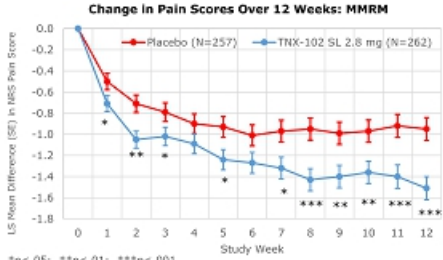
Mean Pain Analyzed by Mixed Model Repeated Measures (MMRM), with and without Multiple Imputation

Pre-specified secondary analysis of AFFIRM:

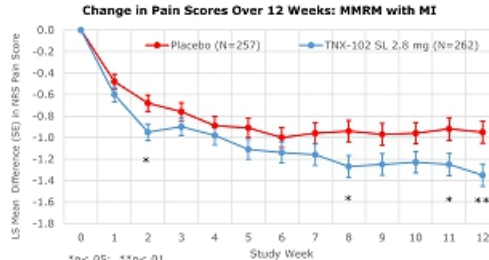
- Mean Pain Analysis, MMRM
- TNX-102 SL N=262; Placebo N=257
- Difference in LS Mean (SE): -0.6 (0.15); 95% CI (-0.8, -0.3); p<0.001

Retrospective analysis of AFFIRM:

- Mean Pain Analysis, MMRM with MI*
- TNX-102 SL N=262; Placebo N=257
- Difference in LS Mean (SE): -0.4 (0.14); 95% CI (-0.7, -0.1); p = 0.005
- Tonix intends to use MMRM with MI in calculating the primary endpoint for the new RELIEF (F304) study, in line with current FDA statistical guidance on handling of missing data



*p<.05; **p<.01; ***p<.001



*p<.05; **p<.01

*As will be the case for the RELIEF F304 primary analysis, all discontinuations due to Adverse Event and Lack of Efficacy are imputed using MI based on baseline values; all other discontinuations assumed to be Missing at Random and are imputed with MI using weekly data of subjects.
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TNX-102 SL 2.8 mg for Fibromyalgia: F301 Study Results and Program Updates

20

Safety results:

- Good tolerability and low rates of systemic AEs.
- The most common AEs were generally mild and transient events related to the sublingual administration of the study drug:
 - hypoesthesia (tongue or oral numbness)
 - glossodynia (burning sensation or other tongue discomfort)
 - oral paresthesias (tingling sensations)
 - abnormal product taste (bitter or noticeable taste)
- The severity and incidence of oral AEs are similar to those reported in our PTSD studies using TNX-102 SL 5.6 mg.

Conclusion:

- The results and efficacy findings support further investigation of TNX-102 SL at double the dose, 5.6 mg (2 x 2.8 mg tablets), as a chronic treatment for FM.

Program updates:

- Clear guidance received from FDA* to advance the FM program. The long-term safety exposure data from the PTSD program is expected to support the fibromyalgia NDA*.
- TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) daily at bedtime will be studied in new Phase 3 study to support product registration.

*March 2019 FDA meeting minutes

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TNX-102 SL 5.6 mg for Fibromyalgia: New Phase 3 RELIEF Study Initiated

General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia in approximately 40 U.S. sites (N=470)
- 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria for Inclusion
- Adaptive Design: one planned unblinded interim analysis based on 50% of randomized participants¹

TNX-102 SL once-daily at bedtime

5.6 mg (2 x 2.8 mg tablets)²

N= ~235

Placebo once-daily at bedtime

N= ~235

14 weeks

Primary endpoint (Week 14):

- Daily diary pain severity score change (TNX-102 SL 5.6 mg vs. placebo) from Baseline in the weekly average by numerical rating scale (NRS) analyzed by mixed model repeated measures analysis with multiple imputation (MMRM with MI)

Key Secondary endpoints (Week 14) include:

- Patient Global Impression of Change (PGIC): Proportion of patients with a rating of "very much improved" or "much improved"
- Fibromyalgia Impact Questionnaire – Revised (FIQR): Symptoms Domain
- FIQR Function Domain
- PROMIS^{*} Sleep Disturbance instrument T-score
- PROMIS Fatigue instrument T-score
- Daily diary sleep quality NRS (weekly average) score

Interim analysis results expected 2H 2020

Topline results expected 1H 2021 based on currently-planned sample size

Potential pivotal efficacy study to support NDA approval

¹Pending agreement with FDA

²Two week run in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose *PROMIS = Patient Reported Outcome Measurement Information System
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TNX-102 SL: Potential Treatment for Agitation in Alzheimer's Disease (AAD)

22

Agitation is one of the most distressing and debilitating of the behavioral complications of Alzheimer's disease

- Includes emotional lability, restlessness, irritability and aggression¹

Link between disturbed sleep and agitation in Alzheimer's¹⁻³

- Agitation is commonly diurnal ("sundowning")

Prevalence

- Agitation is likely to affect more than half of the 5.3 million Americans who currently suffer from moderate to severe Alzheimer's disease; expected to nearly triple by 2050⁴

Significant unmet need with no FDA approved drugs for the treatment of AAD

Proposed Phase 2 IND study can potentially serve as a pivotal efficacy study to support NDA approval⁵

¹Rose, K. et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias*, 30:78

²Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association*, 16, 396.

³Canevelli, M., et al. (2016). *Frontiers in medicine*, 3.

⁴The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: <https://www.alz.org/facts/>

⁵FDA comments on final protocol received October 2018



TNX-102 SL: Potential Treatment for Alcohol Use Disorder (AUD)

23

AUD is a chronic relapsing brain disease

- Characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using

Sleep disturbance is extremely common in alcohol recovery¹

- Significantly impacts daytime cognition, mood, and ability to participate in alcohol treatment, and is associated with increased risk of relapse

Prevalence

- An estimated 36 million adults in the U.S. have AUD²

Three FDA-approved medications

- Remains an unmet need due to compliance and safety issues

Pre-IND meeting with the FDA completed in October 2019

- Discussed 505(b)(2) development plan for TNX-102 SL as a treatment for AUD
- FDA official meeting minutes confirm plan to submit IND application in 1Q 2020 for a Phase 2 Proof of Concept Study

¹Arnedt et al, J Addict Dis. 2007 ; 26(4): 41-54

²Grant et al, JAMA Psychiatry 2015; 72(8): 757-766; www.census.gov

Recombinant protein that degrades cocaine in the bloodstream¹

- Double-mutant cocaine esterase (CocE)
- CocE was identified in bacteria (*Rhodococcus*) that use cocaine as its sole source of carbon and nitrogen and that grow in soil surrounding coca plants²
- CocE catalyzes the breakdown of cocaine into metabolites ecgonine methyl ester and benzoic acid

Phase 2 study completed by Rickett Benckiser (TNX-1300 was formerly RBP-8000)³

- Volunteer cocaine abusers received cocaine 50 mg *i.v.* infusion over 10 minutes
- TNX-1300 given one minute after completion of cocaine infusion
 - Rapidly reversed the physiologic effects of cocaine; cocaine plasma exposures dropped by 90% within two minutes
 - Well tolerated with the most frequently reported adverse events being gastrointestinal disorders (including dry mouth, nausea); nervous systems disorders (including headache, dizziness) and skin and subcutaneous tissue disorders (including hyperhidrosis, dermatitis)

⁴TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, *i.v.* solution) is an investigational new biologic and has not been approved for any indication.

¹ Gao D et al, *Mol Pharmacol*. 2009. 75(2):318-23.

² Bresler MM et al, *Appl Environ Microbiol*. 2000. 66(3):904-8.

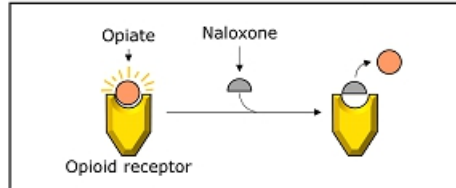
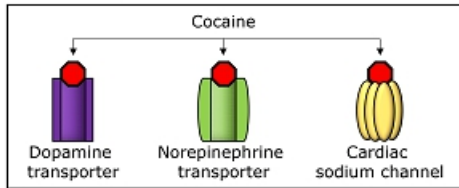
³ Nasser AF et al, *J Addict Dis*. 2014;33(4):289-302.



Pharmacotherapies for Cocaine Intoxication Have Not Been Effective

Treatments for opiates not effective for cocaine:

	Cocaine	Opiates
MOA of Toxicity	Complex; mediated by multiple targets with distinct biological functions ¹	Simple; mediated by opioid receptors ²
Pharmacology	Antagonist ¹	Agonists ²
Pharmacotherapy	No FDA-approved medication exists¹	Naloxone ²

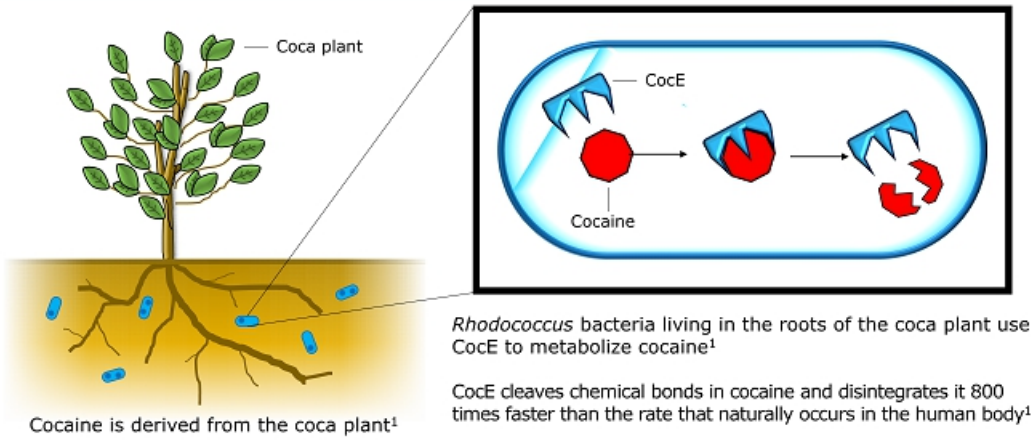


1. Brim et al. *Mol Pharmacol*. 2011.
2. Melichar et al. *Eur J Pharmacol*. 2003.
3. Narasimhan et al. *Future Medicinal Chemistry*. 2012.



TNX-1300 (Cocaine Esterase or CocE) Is a Fast-acting Cocaine Antidote

26



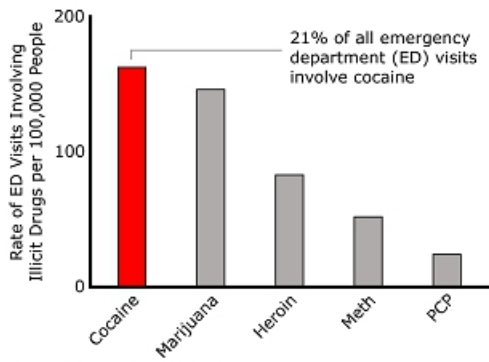
1. Narasimhan D et al. *Future Med Chem.* 2012.

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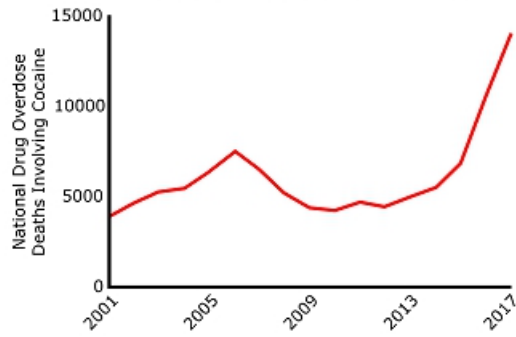


Cocaine Intoxication Is a Growing Problem in the U.S.

Cocaine is involved in more emergency department (ED) visits than any other illicit substance¹



Drug overdose deaths involving cocaine have increased dramatically in recent years²



1. CBHSQ. DAWN 2011. Rockville, MD: SAMHSA; 2013.
2. NIDA. Overdose death rates.
<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>.

Note: Figures are for illustrative purposes



TNX-601 CR* (Tianeptine Oxalate Controlled Release) Tablets

28

Proprietary new controlled release formulation for once-daily dosing

- Suitability for once-daily dosing established in Phase 1 pharmacokinetic study, completed outside of the U.S.
 - Well tolerated in study and the side effects were consistent with the known safety profile of tianeptine sodium
- Tianeptine sodium immediate release is approved and marketed outside of the U.S. for three times a day dosing for the treatment of depression
 - Once-daily dosing for TNX-601 CR believed to be have an adherence advantage over three times a day dosing with tianeptine sodium
- Plan to request pre-IND meeting with FDA in first half 2020
- Plan for first efficacy and safety study ex-U.S.

Proprietary new oxalate salt with improved pharmaceutical properties

- Tianeptine oxalate is crystalline, while tianeptine sodium is amorphous

Issued patents directed to tianeptine and tianeptine oxalate

- **Composition of Matter:** Issued US patent directed to oxalate salt, U.S. Patent No. 10,449,203
- **Method of Use:** Issued European patent directed to methods of treating cognitive impairment associated with corticosteroid treatment, European Patent No. 3246031

*TNX-601 (tianeptine oxalate CR tablets) is in the pre-IND stage in the U.S. and has not been approved for any indication.
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TNX-601 CR: A Potential Daytime Treatment for Depression and PTSD

29

Depression: majority suffering from depression do not have an adequate response to initial antidepressant therapy

- Tianeptine sodium immediate release (IR) tablets for three times a day dosing is approved as an antidepressant in the EU, Russia, Asia and Latin America; first marketed for depression in France in 1989
- Tianeptine sodium is reported to have prominent anti-anxiety effects in depression with a low incidence of sexual side effects
- TNX-601 CR leverages the established efficacy and safety of tianeptine sodium IR as a treatment for depression outside of the U.S.
- Despite multiple approved products for depression in the U.S., there remains significant interest and need for new treatments, particularly for medicines that modulate the glutamatergic system

PTSD: heterogeneous condition, so not all patients are expected to respond to a single medicine

- Distinct mechanism of action from TNX-102 SL – TNX-601 CR modulates the glutamatergic system
- Published studies show tianeptine is active in the treatment of PTSD¹⁻⁴
- Leverages Tonix expertise in PTSD (clinical and regulatory, market analysis, etc.)

¹ Frančičević T, et al. Psychiatr Danub. 2011 Sep;23(3):257-63. PMID: 21963693

² Rumyantseva GM and Stepanov AL. Neurosci Behav Physiol. 2008 Jan;38(1):55-61. PMID: 18097761

³ Aleksandrovskii IA, et al. Zh Nevrol Pskhiatr Im S S Korsakova. 2005;105(11):24-9. PMID: 16329631 [Russian]

⁴ Onder E, et al. Eur Psychiatry. 2006 (3):174-9. PMID: 15964747



Financial Overview

30

NASDAQ: TNXP	
Cash and cash equivalents, September 30, 2019	\$10.0 million
Net proceeds from equity offering in 4Q2019	\$8.1 million
Common stock outstanding as of December 17, 2019	8.5 million shares



Management Team



Seth Lederman, MD
President & CEO



Gregory Sullivan, MD
Chief Medical Officer



Bradley Saenger, CPA
Chief Financial Officer



Jessica Morris
Chief Operating Officer





Milestones – Recently Completed and Upcoming

32

- ✓ March 2019 P302/RECOVERY study initiated
- ✓ April 2019 Received FDA formal minutes with clear guidance and support for new Phase 3 FM study using TNX-102 SL 5.6 mg
- ✓ May 2019 In-licensed TNX-1300, product candidate in Phase 2 development for cocaine intoxication
- ✓ August 2019 In-licensed TNX-1600, product candidate in preclinical development for PTSD
- ✓ August 2019 Entered into research collaboration to study internally-developed TNX-1500
- ✓ September 2019 In-licensed TNX-1700, product candidate in preclinical development for gastric and pancreatic cancers
- ✓ October 2019 Completed long-term exposure studies in participants with PTSD to evaluate tolerability of TNX-102 SL 5.6 mg
- ✓ October 2019 Met with FDA to discuss new program for TNX-102 SL to treat AUD
- ✓ 4th Quarter 2019 Developed a once-daily dosing formulation for TNX-601 CR in PK study
- 1st Quarter 2020 Interim analysis results from Phase 3 P302/RECOVERY study in PTSD expected
- 2nd Quarter 2020 Topline data from Phase 3 P302/RECOVERY study in PTSD expected
- 2nd Half 2020 Interim analysis results from Phase 3 F304/RELIEF study in fibromyalgia expected

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Pipeline Summary – by Select Therapeutic Areas

33

- **Psychiatry/PTSD:**
 - **TNX-102 SL – (sublingual cyclobenzaprine) for PTSD**
 - Phase 3/RECOVERY
 - **TNX-601 – (tianeptine) for depression and PTSD**
 - Phase 1 formulation development study completed
 - **TNX-1600 – (triple reuptake inhibitor) for PTSD**
 - Pre-clinical
- **Pain:**
 - **TNX-102 SL for fibromyalgia**
 - Phase 3/RELIEF
- **Addiction Medicine:**
 - **TNX-1300 – (cocaine esterase) for cocaine intoxication**
 - Mid-Phase 2
 - **TNX-102 SL – (sublingual cyclobenzaprine) for alcohol use disorder (AUD)**
 - Pre-clinical; FDA official meeting minutes confirm plan to submit IND application for a Phase 2 POC study
- **Biodefense:**
 - **TNX-801 – (live horsepox vaccine) – for preventing smallpox**
 - Pre-clinical
 - **TNX-701 – (oral radioprotective agent) – for radioprotection**
 - Pre-clinical



Pipeline Summary – by Phase of Development

34

Two Phase 3 Programs in indications affecting millions of Americans

- TNX-102 SL for PTSD: affects an estimated 12 million adults in U.S.
- TNX-102 SL for Fibromyalgia: affects an estimated 6-12 million adults in U.S.

Two Phase 2 Programs in indications for which there is no FDA-approved drug available

- TNX-1300 for Cocaine Intoxication
- TNX-102 SL for Agitation in Alzheimer’s Disease

Robust pipeline of preclinical and Phase 1 products to improve biodefense, leverage PTSD and internal expertise



Thank you!