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

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# 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): June 3, 2019**

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

| **Nevada** | **001-36019** | **26-1434750** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(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))

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 |

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. ☐

**Item 7.01 Regulation FD Disclosure.**

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 99.02, 99.03 and 99.04 hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.02, 99.03 and 99.04 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. |
|---|---|
| 99.01 | Corporate Presentation by the Company for June 2019 (Long Form) |
| 99.02 | Corporate Presentation by the Company for June 2019 (Short Form) |
| 99.03 | Corporate Presentation by the Company for June 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.**

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

Date: June 3, 2019

**EXHIBIT 99.01**

# Investor Presentation

TONIX PHARMACEUTICALS

June 2019

**Version P0185 6-3-19 (Doc 0496)**

# Cautionary Note on Forward-Looking Statements



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.

# Tonix Pharmaceuticals



**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 as well as potential medical counter-measures to improve biodefense

**What we do:**

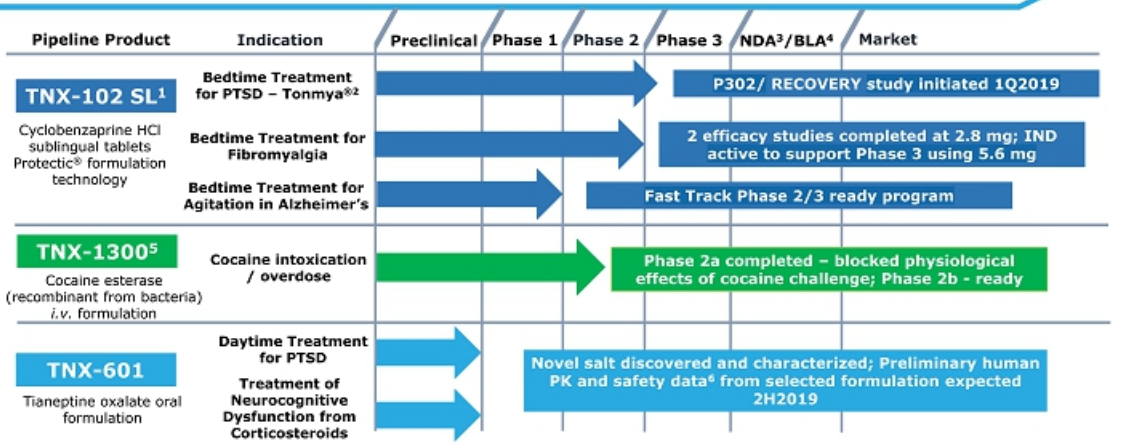
- Target therapeutic areas with high need for improvement
  - Conditions, with no or inadequate treatments
  - Significant patient segments not well served by existing therapies
- Develop innovative treatment options with possibility to be a "game changer"
  - Scientifically unique and innovative
  - Supported by strong scientific rationale
  - Supported by preliminary clinical evidence and published literature
  - Utilize proven regulatory pathway and established clinical endpoint
  - Built on a foundation of proprietary intellectual property

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



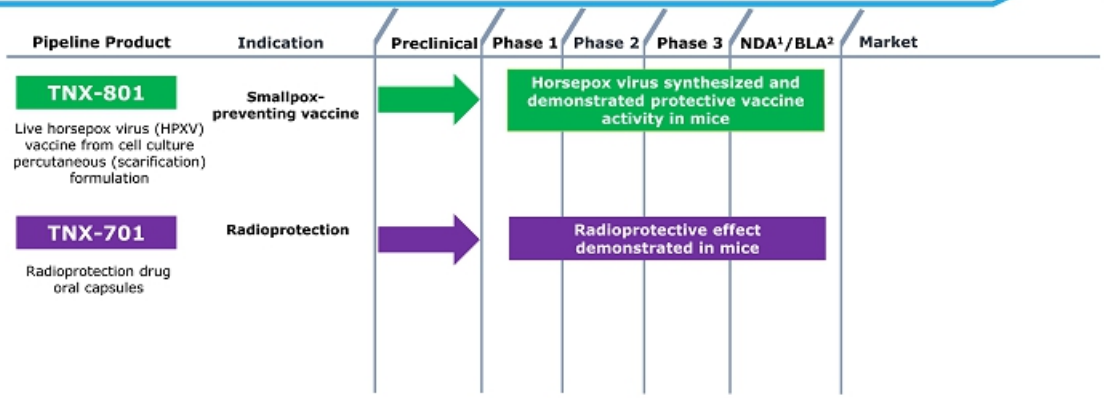



[1] TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication; [2] Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD. [3]NDA- New Drug Application; [4]BLA –Biologic Licensing Application; [5]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; [6]non-Investigational New Drug (IND) study;

# Biodefense Candidates in Development

## Biodefense programs owned outright with no royalties due






¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# Lead Program: TNX-102 SL – Product Concept



**Sleep disturbances are associated with a constellation of disorders**

- Considered co-morbid or a key symptom in these disorders
- Believed to have a role in the onset, progression and severity of these disorders

**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

# TNX-102 SL Proposed Mechanism: Improving Sleep Quality



A unique and innovative approach (improving sleep quality), to potentially address a constellation of disorders in a variety of therapeutic areas where sleep disturbances are co-morbid and believed to have a role in the onset, progression and severity of the disorder.

| Therapeutic Area | Target Indication | Status |
|---|---|---|
| Psychiatry | Posttraumatic stress disorder (PTSD) | Phase 3 |
| Rheumatology | Fibromyalgia (FM) | Phase 3 development with higher dose |
| Psychiatry / Neurology | Agitation in Alzheimer's Disease (AAD) | Phase 2 ready |
| Chronic pain | TBD | Life-cycle opportunity |
| Sleep disorders | TBD | Life-cycle opportunity |

# TNX-102 SL Intellectual Property – U.S. Protection until 2034



| | |
|---|---|
| **Composition of matter (eutectic):**<br>**Protection expected to 2034** | • United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9,636,408 in May 2017, U.S. Patent No. 9,956,188 in May 2018 and U.S. Patent No. 10,117,936 in Nov 2018<br>• Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018<br>• New Zealand Intellectual Property Office (NZIPO) issued New Zealand Patent No. 631152 in May 2017<br>• 37 patent applications pending (2 allowed (U.S. and South Africa)) |
| **Pharmacokinetics (PK):**<br>**Protection expected to 2033** | • JPO issued Japanese Patent No. 6259452 in Dec 2017<br>• NZIPO issued New Zealand Patent No. 631144 in March 2017<br>• Taiwanese Intellectual Property Office issued Taiwanese Patent No. I590820 in July 2017<br>• 21 patent applications pending (1 allowed (Australia)) |
| **Method of use (PTSD) for cyclobenzaprine:**<br>**Protection expected to 2030** | • USPTO issued U.S. Patent 9,918,948 in March 2018<br>• European Patent Office issued European Patent No. 2 501 234B1 in Sept 2017 (validated in 38 countries). Opposition filed in June 2018<br>• 2 patent applications pending |

# Overview of Posttraumatic Stress Disorder (PTSD)



**PSTD 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



**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

# PTSD: U.S. Prevalence and Index Traumas



**PTSD is a chronic response to traumatic event(s)**

- A majority of people will experience a traumatic event at some point in their lifetime[1]
  - 20% of women and 8% of men in the U.S. who experience significant trauma develop PTSD[1]

**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 trauma[2]

- *Twelve month prevalence:* *U.S.* *4.7%* (12 million adults)[2]
  *EU* 2.3% (~10.0 million adults) [3]

**Most common forms of trauma[1]**

- 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 Procela Consultants Ltd, September 2016

# Prevalence of PTSD Among Civilians and Veterans



**4.7%**
Adult population[1]

**19-31%**
Vietnam veterans[2]

**>19%**
Iraq/Afghanistan[3]

**12 million** American adults annually[1]

**Women** more likely to develop than men[1]

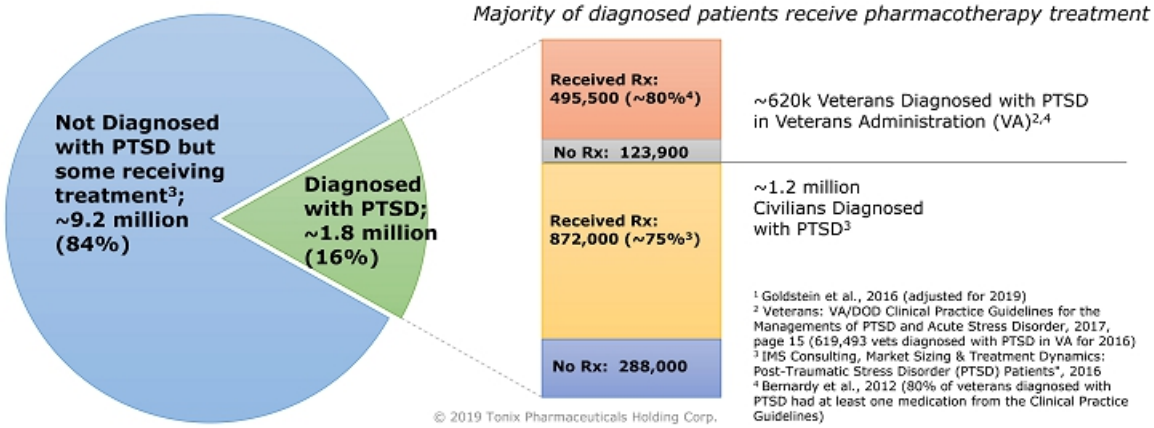
[1]Goldstein et al., 2016 (adjusted for 2019); [2]Norris, *PTSD Res Quar*. 2013; [3]*Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015,* Washington, DC; Among 1.9M separated OEF/OIF/OND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

# PTSD Prevalence and Market Characteristics



**Prevalent Population with PTSD (U.S.)**
**~12 million[1]** (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 PTSD[3]

[1] Goldstein et al., 2016 (adjusted for 2019)
[2] Veterans: VA/DOD Clinical Practice Guidelines for the Managements 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)

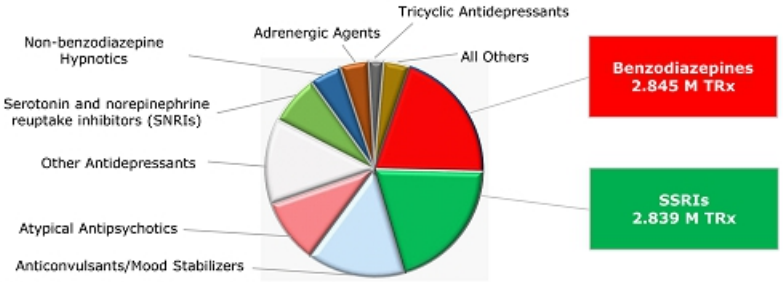
# What Drug Classes are Used to Treat PTSD?



**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

# PTSD: Not Well-Served by Approved Treatments



**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)

**Tonmya 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?



**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 subgroup[2]
  Paroxetine: no sex-related difference in treatment outcomes[3]

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

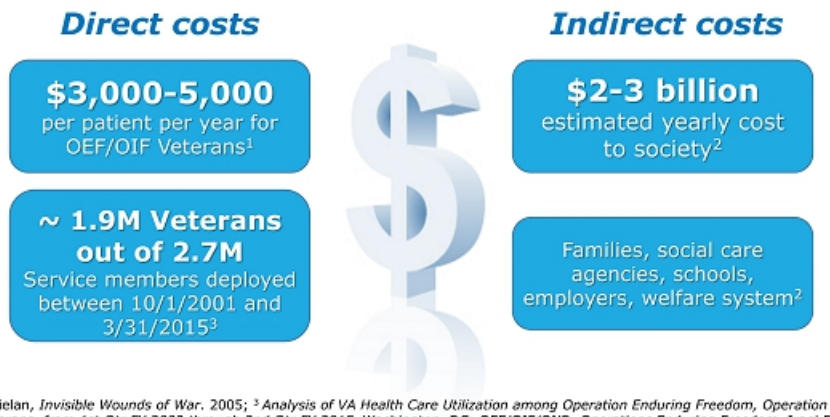
  Sexual dysfunction[2,3]
  Insomnia[2,3]
  SSRI withdrawal syndrome[4]

[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



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




[1] CBO Report 2012; [2] Tanielan, *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.

# Tonmya: a Potential Bedtime Treatment for PTSD



**First investigational new drug to show treatment effect in military-related PTSD in two potential pivotal efficacy studies**

- Phase 2 study (P201/AtEase) showed Tonmya 5.6 mg had a strong signal of treatment effect at Week 12 as measured by CAPS-5[1]
- 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 Tonmya NDA submission
- No serious or unexpected adverse events related to Tonmya were reported

**FDA feedback and acceptance on new Phase 3 study (P302/RECOVERY) received in November 2018[2]**

[1] CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
[2] FDA Meeting Minutes, November 26, 2018

# No Recognized Abuse Potential in Clinical Studies



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

- Cyclobenzaprine interacts with receptors that regulate sleep quality: 5-$HT_{2A,}$ $\alpha_1$-adrenergic and histamine $H_1$ 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

**Tonmya NDA can be filed without drug abuse and dependency assessment studies**

- Discussed at March 9, 2017 meeting with the FDA

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



## 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

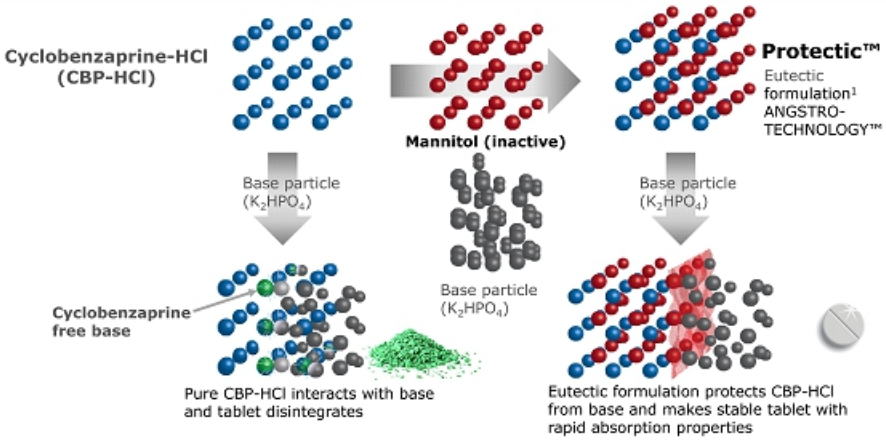
- Active major metabolite, norCBP[1]
  - Long half-life (~72 hours)
  - Less selective for target receptors (5-$HT_{2A}$, $\alpha_1$-adrenergic, histamine $H_1$)
  - More selective for norepinephrine transporter and muscarinic $M_1$

## 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






[1] U.S. Patent issued May 2, 2017

# Tonmya: Hypothesized Novel Mechanism Targets Sleep Quality for Recovery from PTSD



## 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)

## Tonmya targets sleep quality[3]

- The active ingredient in Tonmya, cyclobenzaprine, interacts with receptors that regulate sleep quality: strongly binds and potently blocks 5-$HT_{2A}$, $\alpha_1$-adrenergic and histamine $H_1$ receptors, permissive to sleep-dependent recovery processes

[1]Straus 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. [2]Murkar ALA, De Koninck J. Consolidative mechanisms of emotional processing in REM sleep and PTSD. Sleep Med Rev. 2018; 41:173-184.
[3]Daugherty et al., Abstract 728, Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015, Toronto Ontario, Canada

# Proposed Mechanism of Action of Tonmya in the Treatment of PTSD:

## Focus on Nocturnal 5-$HT_{2A}$ Receptor Blockade in REM



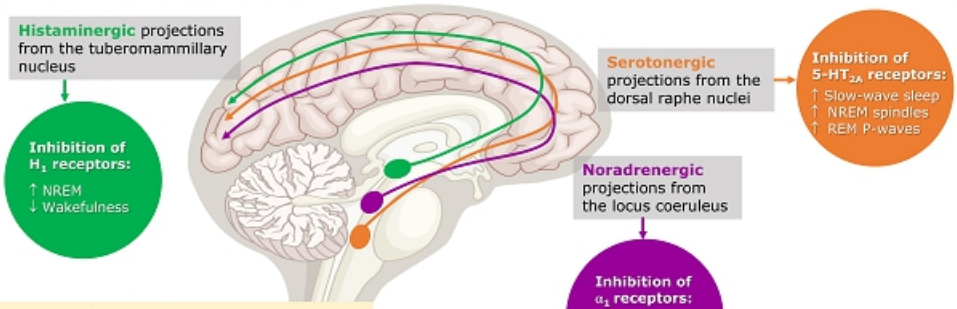
- Generally, serotonin (5-HT) activity promotes the awake state and inhibits REM sleep; whereas once in REM sleep, the 5-HT system is normally quiescent
- Extinction learning is critical to recovery from trauma, and such new learning is consolidated (moving from labile short term to established long 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 consolidation[3]
- 5-HT activation of pontine brainstem region richly expressing 5-$HT_{2A}$ receptors inhibits P-wave generation during REM[4]
- 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 Psych: CNNI. 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 Tonmya 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 $\alpha_1$ receptors, and histaminergic $H_1$ receptors

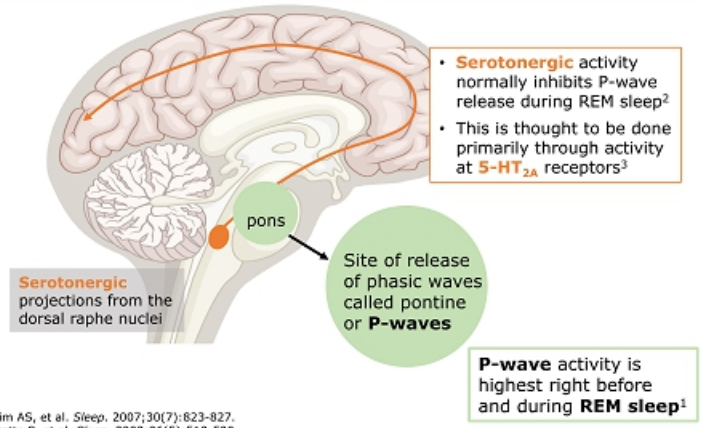



The overall proposed effects of Tonmya on sleep leads to increased sleep-dependent consolidation of extinction memories, facilitating recovery from PTSD

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

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





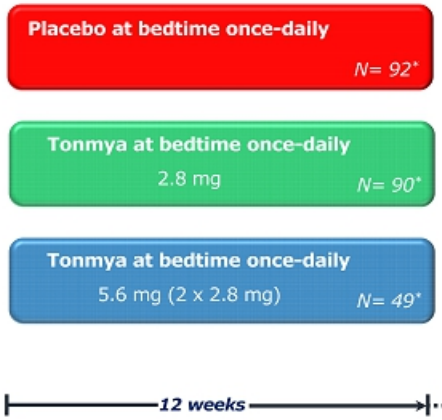

- Increased P-wave activity during REM sleep is critical for fear extinction memory consolidation in rats[4]
- By blocking 5-$HT_{2A}$ receptors, cyclobenzaprine may sustain P-wave activity during REM sleep
- This blockade may lead to better quality of REM sleep with increased fear extinction consolidation 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-HT2A/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; 2008.
4. Datta S, et al. *J Neurosci*. 2013;33(10):4561-4569.

# Phase 2 P201/AtEase[1] Study in Military-Related PTSD






- 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-5[2] ≥ 29
- Primary Efficacy Analysis:
  - Difference in CAPS-5 score change from baseline between Tonmya 2.8 mg and placebo at Week 12
- Key Secondary Measures:
  - PROMIS Sleep Disturbance, CGI-I, SDS

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

# P201/AtEase Study



**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 ≥ 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/HONOR[1] Study –Evidence of Efficacy at Week 4
## Discontinued Due to High Placebo Response at Week 12



### General study characteristics:

Randomized, double-blind, placebo-controlled, adaptive design, planned 550 military-related PTSD participants with baseline CAPS-5[2] ≥ 33 in approximately 40 U.S. sites

**Tonmya 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-5[2]:

- Mean change from baseline at Week 12 (Tonmya 5.6 mg vs. placebo)

### Unblinded interim analysis at 274 randomized participants (mITT* 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

[1]ClinicalTrials.gov Identifier: NCT03062540
[2]CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
*Modified intent-to-treat

# P301/HONOR Study- Primary Analysis in mITT Population



| Visit | Placebo N=127 | | TNX-102 SL 5.6 mg N=125 | | |
|---|---|---|---|---|---|
| Statistic | CAPS-5 Value | MCFB | CAPS-5 Value | MCFB | Difference |
| 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

# Differences Between P201/AtEase and P301/HONOR Studies Design



| Categories | P201 | P301 |
|---|---|---|
| No. of US Sites Randomizing ≥ 1 | 24 | 43 |
| No. of Treatment Arms | 3 | 2 |
| Baseline Entry CAPS-5 Threshold | ≥ 29 | ≥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 ≥ 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

# P201/AtEase and P301/HONOR Demographics and Characteristics



| 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 |

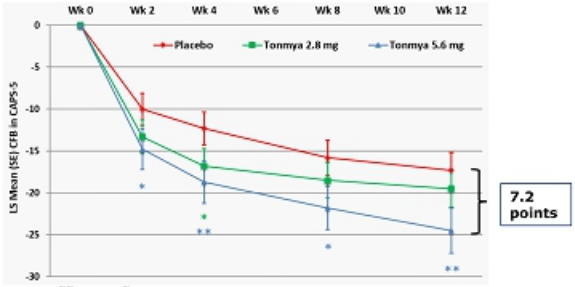
**The striking difference between P201 and P301 was time since trauma**

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

# Tonmya Phase 2 Dose-Effect in Military-Related PTSD[1]

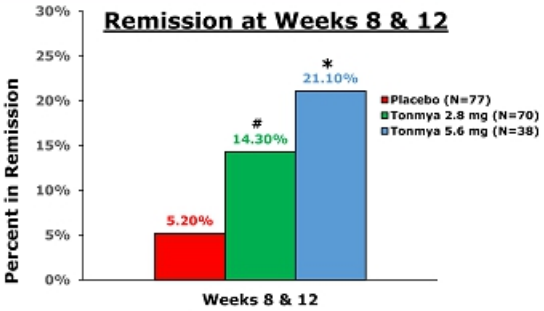


## PTSD Symptoms (CAPS-5[2] Score)




** p<0.01, * p<0.025, Tonmya 5.6 mg group with placebo, MMRM with multiple imputation (MI); *p=0.018, Tonmya 2.8 mg group with placebo, MMRM with MI

## Remission at Weeks 8 & 12



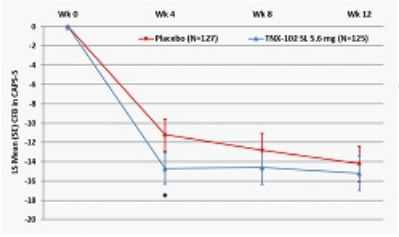

Remission = Loss of Diagnosis and CAPS-5 < 11
Asterisk and hashmark represent pairwise comparisons between Tonmya and Placebo; #p=0.08, Odds Ratio 3.01 (0.89, 10.18)
*p=0.02, Odds Ratio 4.60 (1.27, 16.66); logistic regression

[1] Completed Phase 2 P201/AtEase study: Retrospective analysis of Tonmya 5.6 mg on CAPS-5 ≥33 (high-moderate) subgroup. Primary analysis of P201/AtEase, based on Tonmya 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 (mITT) and ≤9 Years Time Since Trauma Subgroups

## Phase 3 P301/HONOR Study[1]

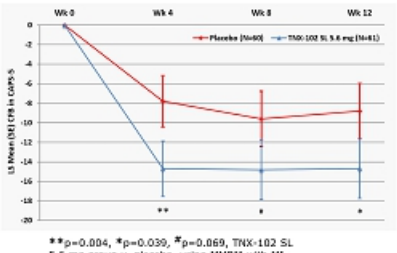
### Modified intent to treat (mITT) population




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

~50% mITT Population

### *Time Since Trauma (TST) ≤9 yrs*

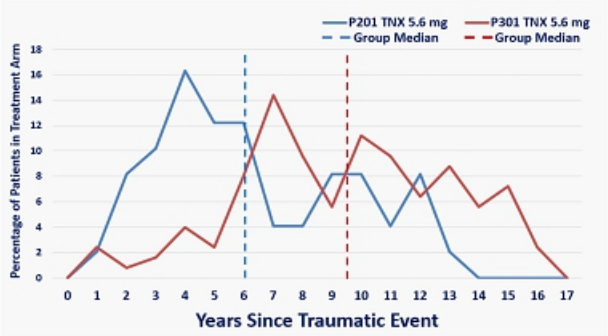



**p=0.004, *p=0.039, *p=0.069, TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

[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 (Tonmya 5.6 mg Groups)






**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 Tonmya 5.6 mg in TST Subgroups in P301[1]




| 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 | 13 | 18 |
| TNX-5.6 mg 'N' | 14 | 17 | 16 | 12 | 22 | 10 | 17 | 18 |

MCFB=mean change from baseline; 'N'=number of participants in group; PBO=placebo; TST=time since trauma



- 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)

[1]*Time 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/1d0c4055b2863fc74e1ef45f9ddaf42b.pdf

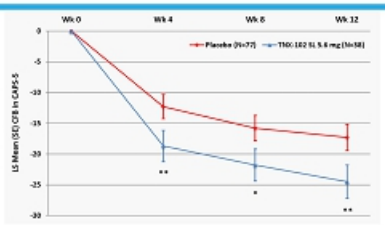
# PTSD Treatment Response to Tonmya in Phase 2 and Phase 3 Studies: Retrospective Analyses of P201 Entry CAPS-5 ≥33 and P301 ≤9 Years Since Trauma Subgroups



## Change in CAPS-5 over course of treatment with Tonmya

CAPS-5 is a structured interview assessing PTSD severity

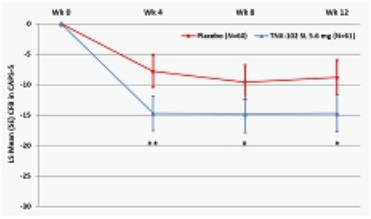
- Required primary endpoint for PTSD drug approval




**P201 Baseline CAPS-5 ≥33 *(majority TST[1] ≤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)

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




**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

[1]*Time since trauma;*
[2]*Majority 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 Phase 2 and Phase 3 Studies:
## Retrospective Analyses of P201 Entry CAPS-5 ≥33 and P301 ≤9 Years Since Trauma Subgroups

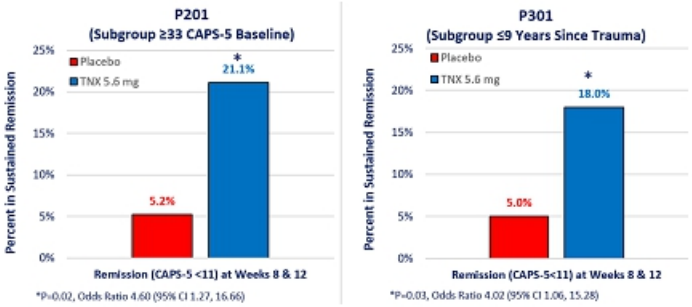


**Remission is a clinical state that is essentially asymptomatic**

**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 P201[1]**




*[1]Majority 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)

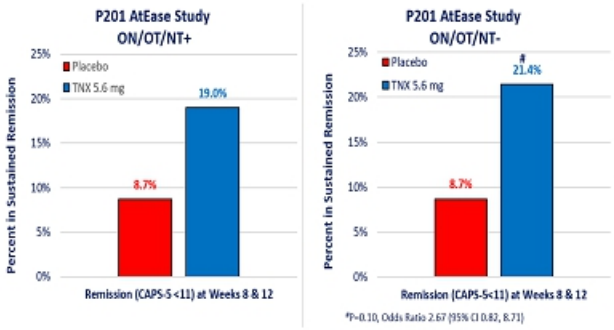


**Oral numbness (ON), oral tingling (OT) and noticeable taste (NT) are local administration site reactions that are potentially unblinding**

- 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



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

| | | | 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 | |
| | Measure | 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

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



| | | P301 mITT | | | | P301 ≤9 Year Subgroup | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | PBO (N=127) v. TNX 5.6 mg (N=125) | | | | PBO (N=60) v. TNX 5.6 mg (N=61) | | | |
| | | Week 4 | | Week 12 | | Week 4 | | Week 12 | |
| | Analysis | LSMD | p-value | LSMD | p-value | LSMD | p-value | LSMD | p-value |
| CGI-I | MMRM | -0.3 | 0.015 | -0.1 | 0.403 | -0.6 | 0.002 | -0.5 | 0.021 |
| PGIC | MMRM | -0.2 | 0.238 | -0.3 | 0.020 | -0.4 | 0.045 | -0.6 | 0.007 |
| SDS | MMRM | -0.2 | 0.785 | -1.6 | 0.101 | -1.8 | 0.167 | -4.3 | 0.007 |
| PROMIS SD | MMRM | -3.1 | 0.015 | -2.7 | 0.082 | -4.5 | 0.029 | -5.0 | 0.042 |

**Key secondary endpoints showed strong treatment effects**

- CGI-I, PGIC and PROMIS SD were pre-specified secondary analyses
- Supports CAPS-5 results and similar to Phase 2 P201 Study results

CGI-I=Clinical Global Impressions – Improvement scale
PGIC, Patient Global Impression of Change scale
PROMIS SD=Patient-Reported Outcome Measures Information System Sleep Disturbance
SDS=Sheehan Disability Scale
LSMD = Least Squares Mean Difference

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



| Category of Adverse Reaction<br>Preferred Term | P201<br>Placebo (N=94) | P201<br>TNX 2.8 mg (N=93) | P201<br>TNX 5.6 mg (N=50) | P301<br>Placebo (N=134) | P301<br>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*# | | | | | |
| Hypoaesthesia 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 Tonmya**

- 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

# Time Since Trauma – Review of Published Studies

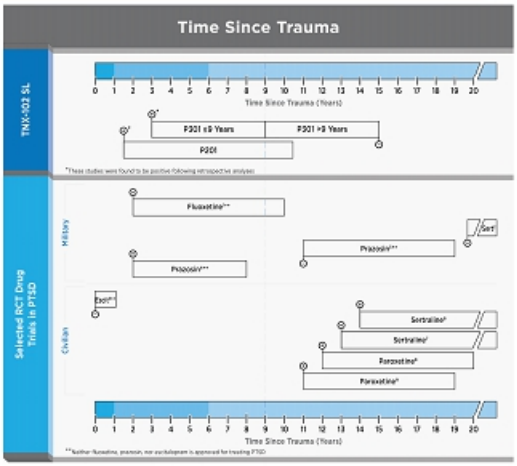


**Published studies of prazosin suggested effects in military-PTSD prior to 9 years**

- 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




Escit=escitalopram



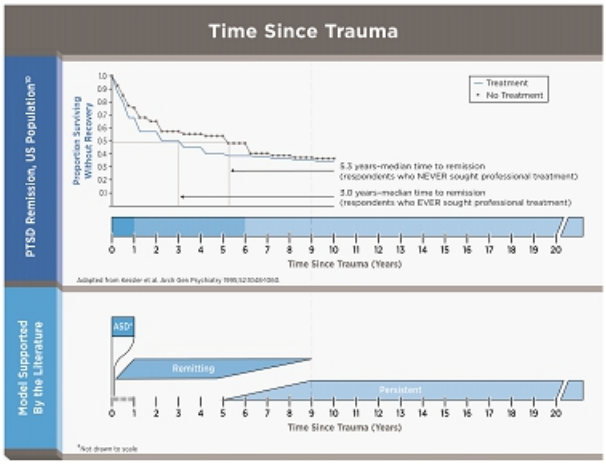
[1]Martenyi et al. *J Clin Psychiatry* 2002;63:199-206.
[2]Friedman et al. *J Clin Psychiatry* 2007;68:711-720.
[3]Raskind et al. *NEJM* 2018;378:507-517.
[4]Raskind et al. *Am J Psychiatry* 2013;170:1003-1010.
[5]Shalev et al. *Arch Gen Psychiatry* 2012;69:166-176.
[6]Davidson et al. *Arch Gen Psychiatry* 2001;58:485-492.
[7]Brady et al. *JAMA* 2000;283:1837-1844.
[8]Marshall et al. *Am J Psychiatry* 2001;158:1982-1988.
[9]Tucker et al. *J Clin Psychiatry* 2001;62:860-868.

# Time Since Trauma – Remitting and Persistent Phases of PTSD



**Kessler et al[1] 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 studies[2-6]




[1]Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.
[2]Armenta et al. *BMC Psychiatry* 2018;18:48.
[3]Galatzer-Levy et al. *PLOS ONE* 2013;8:e70084.
[4]Perkonigg et al. *Am J Psychiatry* 2005;162:1320-1327.
[5]Santiago et al. *PLOS ONE* 2013;8:e59236.
[6]Davidson & Connor. *Eur Neuropsychopharmacol* 2001;11(5upp3):S148-S149.

# Response to Tonmya for Female Participants in P301/HONOR Study[1]



**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 Tonmya 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 Tonmya 5.6 mg likely in mixed civilian and military PTSD population to be studied in upcoming 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 Tonmya for Non-Combat Traumas in P301/HONOR Study in ≤9 Years Time Since Trauma Subgroup[1]



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

**To determine the therapeutic effects of Tonmya 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, Tonmya 5.6 mg N=10):**

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

**Non-combat traumas treated with Tonmya 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 Tonmya**

[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

# Summary of Clinical Experience with Tonmya/ TNX-102 SL in PTSD



**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 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 subgroup of P301 may be enriched for "Remitting Phase" of PTSD[1-4]**

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

**Results from retrospective analyses lead to improved Phase 3 study design**

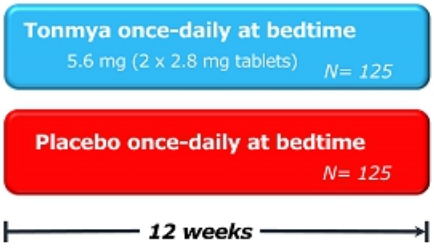
[1]Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.
[2]Armenta et al. *BMC Psychiatry* 2018;18:48.
[3]Galatzer-Levy et al. *PLOS ONE* 2013;8:e70084.
[4]Perkonigg et al. *Am J Psychiatry* 2005;162:1320-1327.

# New Phase 3 P302/RECOVERY Study – Initiated 1Q 2019



## General study characteristics:

- Randomized, double-blind, placebo-controlled study with baseline CAPS-5[1] ≥ 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




## Primary endpoint:

- CAPS-5[1] mean change from baseline at Week 4 (Tonmya 5.6 mg vs. placebo)

## Key Secondary endpoints include:

- CAPS-5 mean change from baseline at Week 12 (Tonmya 5.6 mg vs. placebo)
- Change from baseline Clinical Global Impression – Severity scale
- Change from baseline Sheehan Disability Scale total score

**Potential pivotal efficacy study to support NDA approval**

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

# Late-Stage PTSD Drug Candidates



## Tonmya

- Phase 3 development focused on military-related and civilian PTSD; showed activity in treatment of military-related PTSD in large multi-center trials

## MDMA-assisted psychotherapy

- Indication – "drug assisted psychotherapy"
- Breakthrough therapy that is Phase 3-ready; showed activity in a Phase 2 study of PTSD; enrolling in Phase 3 study

## Other drugs currently (or recently) in Phase 2 development

- Rexulti® (brexpiprazole) - Otsuka/Lundbeck; atypical antipsychotic; positive clinical results from Phase 2 study reported in November 2018 for brexpiprazole, when used in combination with an approved PTSD medication, sertraline, but not as monotherapy
- NYX-783 - Aptinyx; NMDA receptor modulator (enrolling for 8-week Phase 2 study of 144 patients using 50 mg either once daily or once weekly)
- BNC-201 – Bionomics; nicotinic receptor modulator (program planned to resume after reformulation)

# Commercialization Options



**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



**Active ingredient, cyclobenzaprine, interacts with 3 receptors**

- Antagonist at 5-$HT_{2A}$ receptors
  - Similar activity to trazodone and Nuplazid® (pimivanserin)
- Antagonist at $\alpha_1$-adrenergic receptor
  - Similar activity to prazosin
- Antagonist at histamine $H_1$ receptors
  - Similar activity to Benadryl® (diphenhydramine) and hydroxyzine

**Multi-functional activity suggests potential for other indications**

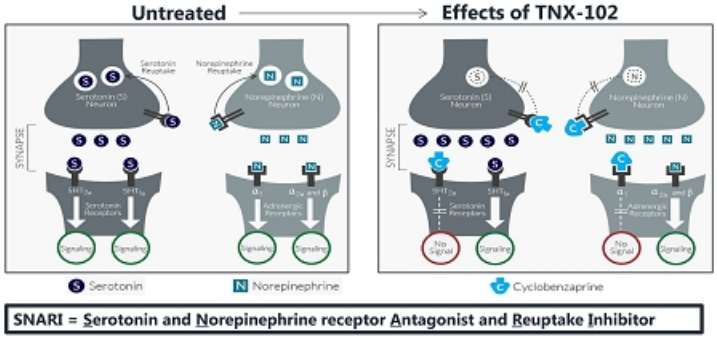
- TNX-102 SL was developed for the management of fibromyalgia (Phase 3)
- Sleep quality is a problem in other conditions

# 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 $\alpha_1$ receptors



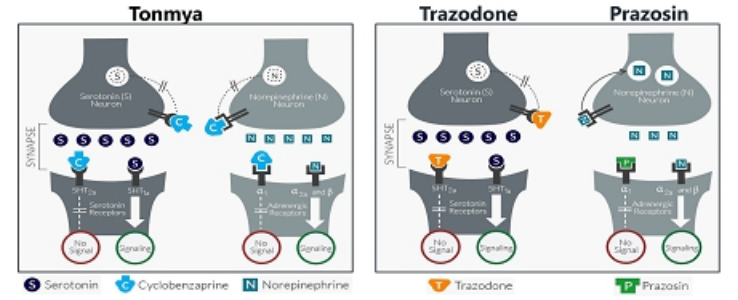

**SNARI = Serotonin and Norepinephrine receptor Antagonist and Reuptake Inhibitor**

# Comparison of Tonmya with Drugs Used Off-Label in PTSD



**Trazodone (disordered sleep), prazosin (night terrors)**

- Trazodone inhibits serotonin $5HT_{2A}$ receptors and serotonin reuptake (SARI)
- Prazosin blocks norepinephrine $\alpha_1$ receptors




*SARI – Serotonin Receptor Antagonist & Reuptake Inhibitor (Stahl SM, CNS Spectrums, 2009;14:536).*

# Opportunities to Expand to Other Indications



**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
- Anxiety Disorders

**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*

# TNX-102 SL – Bedtime Treatment for Multiple Potential Indications



## Management of Fibromyalgia (FM) – chronic pain condition

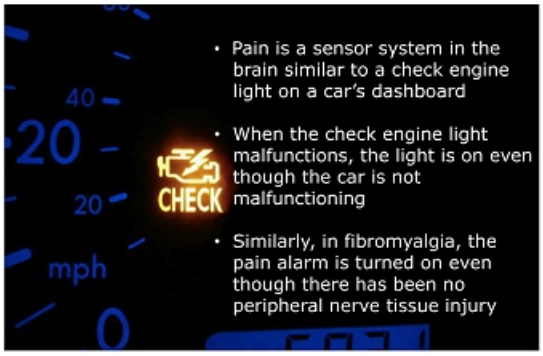
- TNX-102 SL 2.8 mg (half the dose being developed for PTSD) studied in Phase 2/3 trials– did not separate from placebo on primary endpoint: average pain improvement (responder analysis)
- Retrospective analysis showed average pain improvement (secondary endpoint) after 12 weeks of treatment showed statistical 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

- Fast Track designation granted July 2018
- Received Phase 2/potential pivotal efficacy study protocol comments from FDA in October 2018

# Fibromyalgia is a Chronic, Debilitating Disorder that Imposes a Significant Societal and Economic Burden






*Volkswagen Check Engine (Photograph). (2011, October 14). Wikipedia*

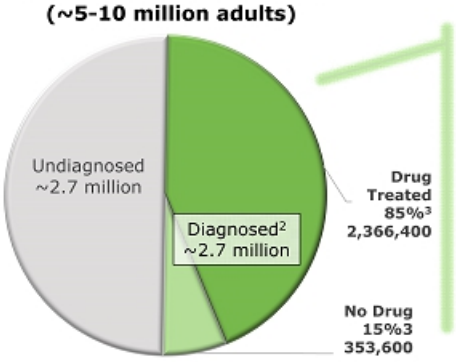
- Fibromyalgia is considered a neurobiological disorder characterized by[1]: chronic widespread pain, non restorative sleep, fatigue, diminished cognition
- Believed to result from inappropriate pain signaling in central nervous system in the absence of peripheral injury[1]
- Causes significant impairment in all areas of life[2]
  - 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 year[3]
  - Annual direct medical costs are twice those for non-fibromyalgia individuals[4]

[1] Phillips 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.

# Fibromyalgia: Market Characteristics



**U.S. Prevalence Rate 2-4%[1]**
**(~5-10 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/patient[3]
- Rotation through therapy common: average ~5 drugs/year[3]
- Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[4,5]

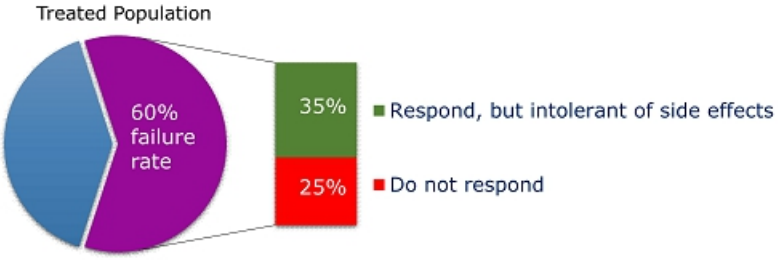
**Unmet Need**
- Majority of patients do not respond or cannot tolerate therapy[6]

1. American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
2. Vincent et al., 2013; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population
3. Robinson, et al., 2012; 85% received drug treatment
4. Vincent et al, Arthritis Care Res 2013;65:786
5. Product sales derived from IMS MIDAS; IMS NDTI 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 Sustained Benefit from the Three FDA-Approved Drugs[1]



- 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



- Currently-approved medications may have side effects that limit long-term use[1]
  - 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 simultaneously[2]
  - The typical patient has tried six different medications[3]
- Substantial off-label use of narcotic painkillers and prescription sleep aids[3]
  - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment[4]
- 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 for Fibromyalgia: Summary of a completed Phase 3 F301 study



**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
- 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-F Function Domain, Daily Sleep Quality Diary, PROMIS Sleep Disturbance

**Efficacy results:**

- mITT population: 425 (81.9%) of 519 patients
- The primary analysis was not statistically significant. However, retrospective analysis showed average pain improvement (secondary endpoint) after 12 weeks of treatment showed statistical significance ($P<0.05$, MMRM)
- Significant improvements observed in sleep quality, patient global impression of change and fibromyalgia-specific measures (secondary analyses).

# TNX-102 SL for Fibromyalgia: F301 Study Results and Program Updates



**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:
  - hypoaesthesia (tongue or oral numbness)
  - glossodynia (burning sensation or other tongue discomfort)
  - oral paraesthesias (tingling sensations)
  - abnormal product taste (bitter or noticeable taste)
- The severity and incidence of oral AE are similar to those reported in our PTSD studies using TNX-102 SL 5.6 mg.

**Conclusion:**

- The promising results and highly relevant efficacy findings support further investigation of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) as a chronic treatment for FM.

**Program updates:**

- Clear guidance and support received from FDA* to advance the FM program. The long-term safety exposure data from the PTSD program may support the fibromyalgia NDA*.
- 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

# What is Agitation in Alzheimer's Disease?



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

- Includes emotional lability, restlessness, irritability and aggression[1]

**Link between disturbed sleep and agitation in Alzheimer's[1-3]**

- 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 2050[4]

[1]Rose, K.et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias*, *30*:78
[2]Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association*, *18*, 396.
[3]Canevelli, M., et al. (2016). *Frontiers in medicine*, *3*.
[4]The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: https://www.alz.org/facts/

# Consequences of Agitation in Alzheimer's Disease



**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 States[1]

[1]The 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



**FDA designated Fast Track development program**

**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



## FDA confirmed no additional study was needed prior to IND submission

- Pre-IND meeting established open dialogue with the FDA on pivotal clinical study design and efficacy endpoints to support product registration

## 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 (sNDA[1]) may be leveraged from the PTSD/FM development program and supported by Initial NDA approval for PTSD/FM

[1]Supplemental New Drug Application

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



## 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 progression[1]

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

# Scientific Rationale for Developing TNX-102 SL for Agitation in Alzheimer's Disease



**Connection between Sleep Disturbance and Agitation**

- Agitation in Alzheimer's Disease is associated with sleep disturbance[1,2]
- Evidence that improving sleep could improve agitation[3]

**Supported by Potential Mechanism of Action**

- TNX-102 is a multifunctional agent including antagonism of 5-$HT_{2A}$, $\alpha_1$-adrenergic and histamine $H_1$ receptors
- Certain 5-$HT_{2A}$ antagonists have shown clinical efficacy against agitation in dementia including trazodone[4,5], and mirtazapine[6]
- The $\alpha_1$-adrenergic antagonist prazosin has shown efficacy in the treatment of agitation in dementia[7]
- The histamine $H_1$ antagonist hydroxyzine had historical use in treating agitation in dementia[8]

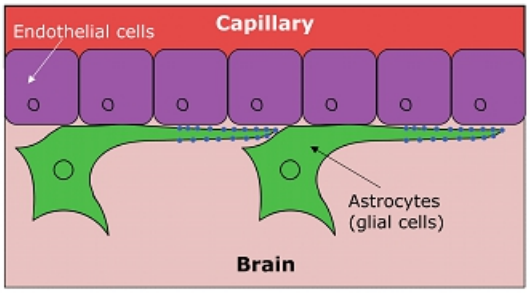
[1]Bachmen, D. and Rabins, P. Annu Rev Med. 2006;57:499.
[2]Rose, K et al. Am J Alzheimers Dis Other Demen. 2015 30(1):78.
[3]Figueiro MG Sleep Med. 2014 15(12):1554-64.
[4]Lebert F. et al. Dement Geriatr Cogn Disord. 2004:17(4):355.
[5]Sulzer DL et al.Am J Geriatr Psychiatry. 1997 5(1):60.
[6]Cakir S. et el., Neuropsychiatr Dis Treat. 2008 4(5):963.
[7]Wang, LY et al., Am J Geriatr Psychiatry. 2009 17(9):744
[8]Settel E. Am Pract Dig Treat. 1957 8(10):1584.

# Protective Barriers in the Central and Peripheral Nervous Systems

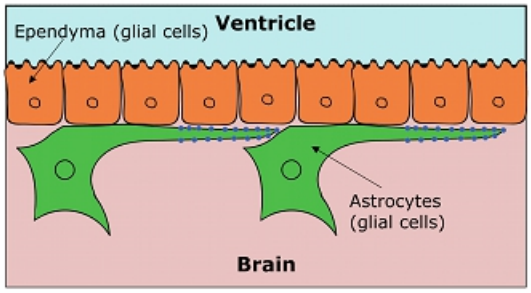


**Glial cells** are cells that reside in the central nervous system and can provide protective barriers between the central and peripheral nervous systems[1,2]

**Blood–Brain Barrier:**
supplies nutrients to the brain and filters toxins[1]




**Cerebrospinal Fluid (CSF)–Brain Barrier/Glymphatic System:**
extracts toxins from the brain[2]

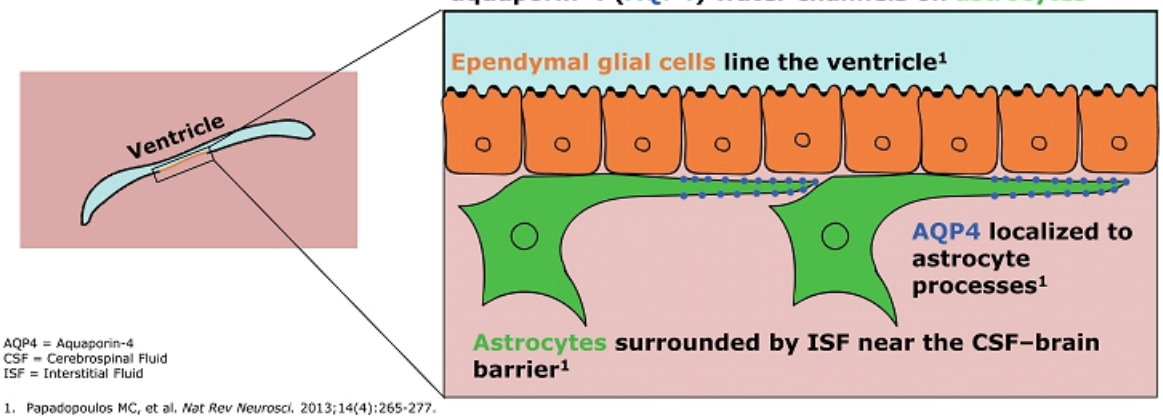



1. Ballabh P, et al. *Neurobiol Dis.* 2004;16(1):1-13.
2. Jessen NA, et al. *Neurochem Res.* 2015;40(12):2583-2599.

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



**The pathways of interchanging CSF and ISF depend on aquaporin-4 (AQP4) water channels on astrocytes[1]**



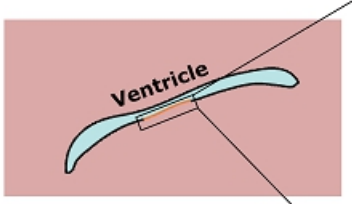

AQP4 = Aquaporin-4
CSF = Cerebrospinal Fluid
ISF = Interstitial Fluid

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

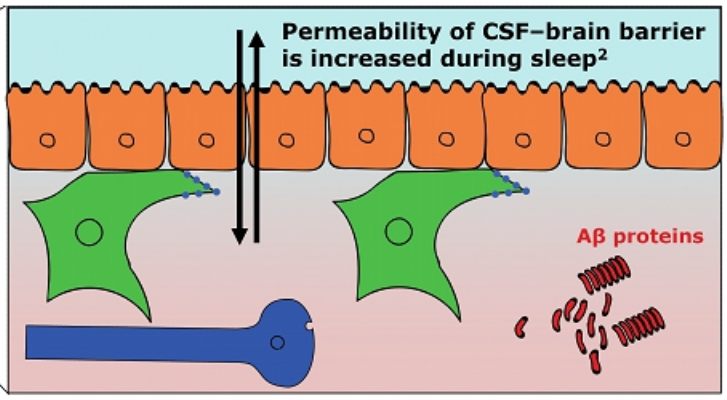
# During Sleep, the CSF–Brain Barrier Is More Permeable, Allowing Debris to Clear



**Extracellular volume increases during sleep[2]**




**Astrocytes change shape, promoting fluid exchange[1]**




Aβ = β-amyloid
CSF = Cerebrospinal Fluid

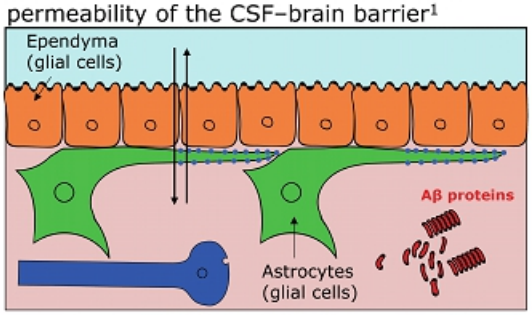
1. Bellesi M, et al. *BMC Biol.* 2015;13:66.
2. Xie L, et al. *Science.* 2013;342(6156):373-377.

# Sleep–Wake Cycles Alter Permeability of the CSF–Brain Barrier

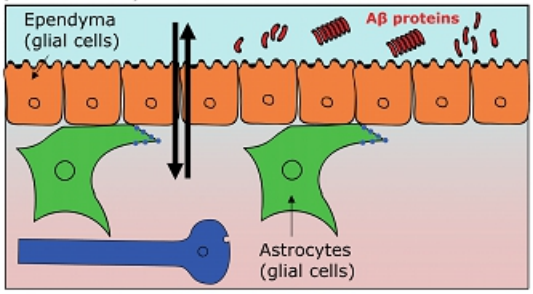


Fluid exchange at the CSF–brain barrier allows for clearance of toxic proteins called β–amyloids (Aβ).[1] Glial cells in the brain work to facilitate this fluid exchange.[2] Sleep–wake cycles alter glial cell morphology, which may affect fluid exchange at the CSF–brain barrier.[3]

**Wakefulness:**
Fluid exchange is reduced due to limited permeability of the CSF–brain barrier[1]




**Sleep:**
Fluid exchange is increased due to greater permeability of the CSF–brain barrier[1]




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.

# Agitation in Alzheimer's – Competitive Landscape of Select Drugs in Development



## Competitive landscape

- $5HT_{2A}$ Antagonists/inverse agonists
  - Nelotanserin (Axovant)
- Atypical Antipsychotics (also have $5HT_{2A}$ antagonism)
  - Rexulti® brexpiprazole (Otsuka/Lundbeck)
  - Lumateperone (Intra-Cellular)
- Dextromethorphans – 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

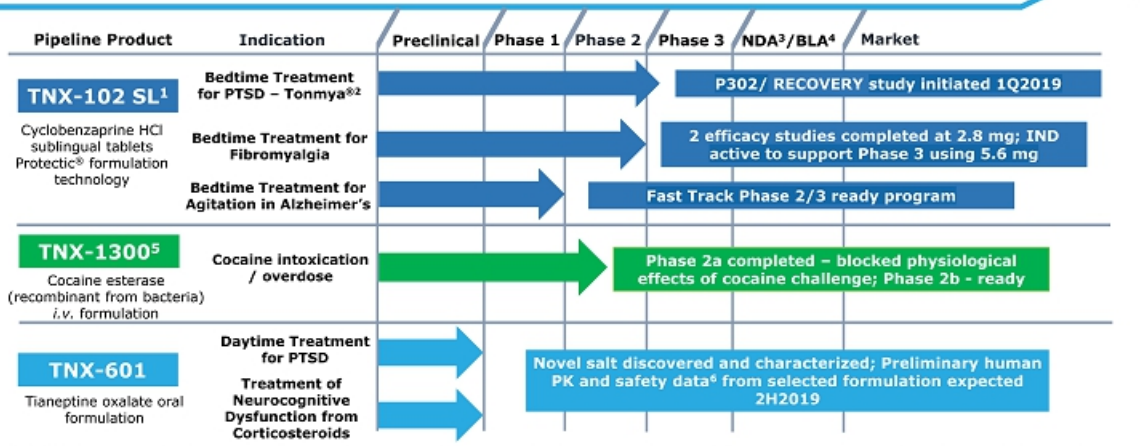
## NDA approval can rely on reference listed drug (AMRIX) safety information

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



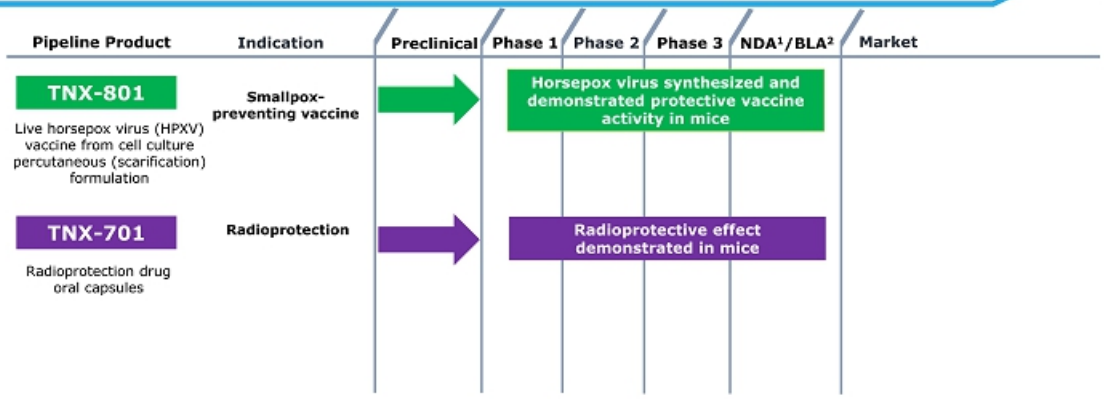



[1] TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication; [2] Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD. [3]NDA- New Drug Application; [4]BLA –Biologic Licensing Application; [5]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; [6]non-Investigational New Drug (IND) study;

# Biodefense Candidates in Development

## Biodefense programs owned outright with no royalties due






¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# About TNX-1300



**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 plants[1]
- The gene encoding CocE was identified and the protein was extensively characterized[1-3]
- 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 temperature[4]

[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



**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.*

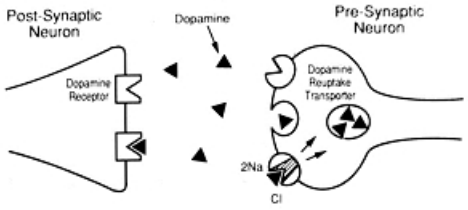
**Cocaine intoxication:** deleterious effects on the body, especially cardiovascular system.

- 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.

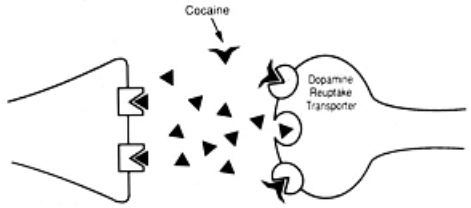
# Cocaine Action



- **Cocaine acts to inhibit the Dopamine Reuptake Transporter**
  - Binds to transporter and blocks reuptake of dopamine from synapse



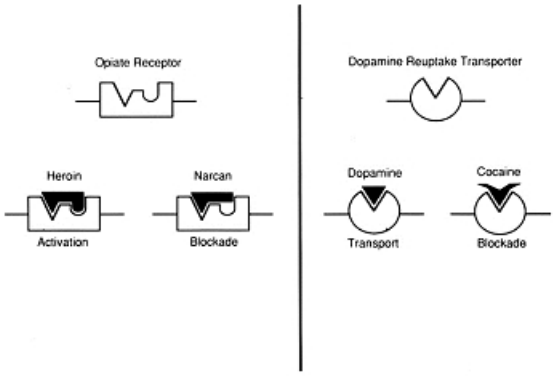

- **No antagonist has been developed for cocaine**
  - Unlike situation for opiates which can be blocked by naloxone ("Narcan") or naltrexone



# Cocaine Action – Lack of "Antidote"

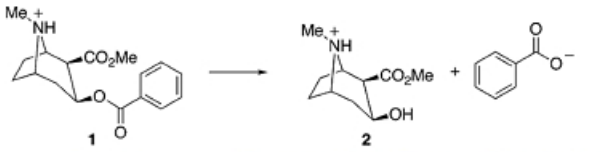


- **Cocaine binding site on Dopamine Reuptake Transporter is too small or simple for a blocker**
  - Antagonists of cocaine binding have the same function as cocaine
- **Naltrexone exploits the complexity of the opiate binding site**
  - Addictive opiates are "agonists", which means their binding and activity can be dissected by antagonists like naloxone



# CocE is a Catalyst that Breaks Cocaine Down into Less Toxic Metabolites[1-4]






Cocaine | Ecgonine Methyl Ester | Benzoic Acid

- Metabolites ecgonine methyl ester and benzoic acid are neither pleasurable nor addictive

[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.

# 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 year[1]

- 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.

# Mortality Due to Cocaine Overdose



**Cocaine is involved in 20% of overdose deaths in the U.S.**

- In 2016, 10,375 deaths due to cocaine overdose[1]
- In 2017, about 13,900 deaths occurred in the U.S. due to cocaine overdose.[2]

**Overdose deaths involving cocaine increased 34% from 2016 to 2017.** [3,4]

[1] Overdose Death Rates - National Institute on Drug Abuse - https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates; accessed May 11, 2019
[2] Kariisa M et al. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. *MMWR Weekly* / May 3, 2019 / 68(17);388–395 - https://www.cdc.gov/mmwr/volumes/68/wr/mm6817a3.htm?s_cid=mm6817a3_w;
[3] Cocaine deaths up in U.S. and opioids are a big part of it. Associated Press. https://www.msn.com/en-us/news/us/cocaine-deaths-up-in-us-and-opioids-are-a-big-part-of-it/ar-AAAOxs8?ocid=se; accessed May 11, 2019
[4] Fottrell, Q. MarketWatch, Fatal drug overdoses involving cocaine and other stimulants have surged by over 52%, May 3, 2019 - https://www.marketwatch.com/story/fatal-drug-overdoses-involving-cocaine-and-other-stimulants-have-surged-by-over-52-2019-05-03; accessed May 11, 2019

# Treatment for Cocaine Intoxication



## Current Standard of Care

- Patients present with acute agitation, hyperthermia, tachycardia, arrhythmias, and hypertension
- Potential life-threatening sequalae 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
- FDA Breakthrough Therapy Designated product
- 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:**

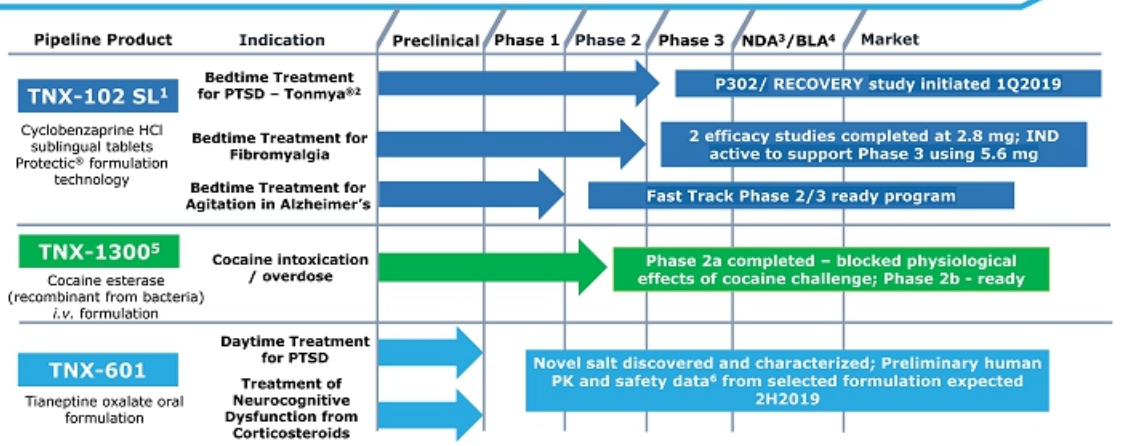
- Brings Tonix into an additional therapeutic area: Addiction Medicine

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



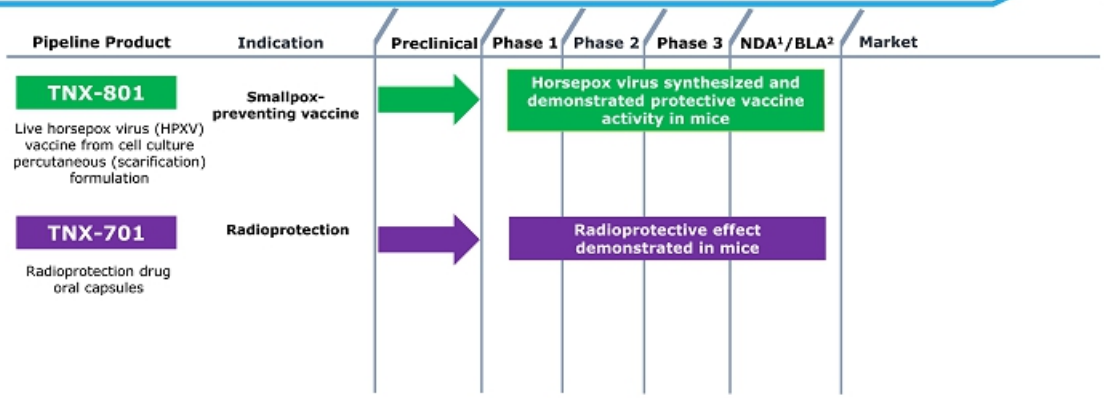



[1] TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication; [2] Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD. [3]NDA- New Drug Application; [4]BLA –Biologic Licensing Application; [5]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; [6]non-Investigational New Drug (IND) study;

# Biodefense Candidates in Development

## Biodefense programs owned outright with no royalties due






¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# TNX-601 (Tianeptine Oxalate): A Potential Clinical Candidate for PTSD



**Pre-IND Candidate**

**Targeting a Condition with Significant Unmet Need**

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

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

- Tianeptine sodium (amorphous), first marketed for depression in France in 1989, is approved as an antidepressant in the EU, Russia, Asia and Latin America; established post-marketing experience
- Identified new oxalate salt with improved pharmaceutical properties ideal for reformulation
- Preliminary human pharmacokinetic and safety data (non-IND study) from selected formulation expected in second half 2019

**Filed patent application on novel salt**

- Issued patent on steroid-induced cognitive impairment and memory loss issues

**Clinical evidence for PTSD**

- Several studies have shown tianeptine to be active in the treatment of PTSD[1-4]

[1] Frančišković 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] Aleksandrovskiĭ IA, et al. Zh Nevrol Psikhiatr 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

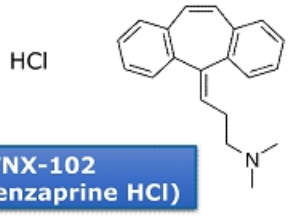
# Structural Comparison: TNX-102 and TNX-601



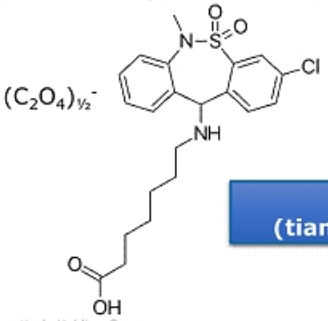
**Cyclobenzaprine and tianeptine share structural similarities with classic tricyclic antidepressants (TCAs) and to each other, but each has unique pharmacological properties**

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

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




**TNX-102 (cyclobenzaprine HCl)**




**TNX-601 (tianeptine oxalate)**

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



**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.

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



## Synthesis[1] from sequence of a 1976 Mongolian isolate[2]

## 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 sources[3-5] 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 genome[6]) to HPXV sequence from the 1976 Mongolian isolate
- Horsepox is now believed to be extinct[5]

[1] Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453 https://doi.org/10.1371/journal.pone.0188453
[2] Tulman 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] Schrick, L. et al. , N Engl J Med 2017; 377:1491-1492, http://www.nejm.org/doi/full/10.1056/NEJMc1707600

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



**ACAM2000 is sold to the U.S. Strategic National Stockpiles[1]**

- 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 humans[2-5]**

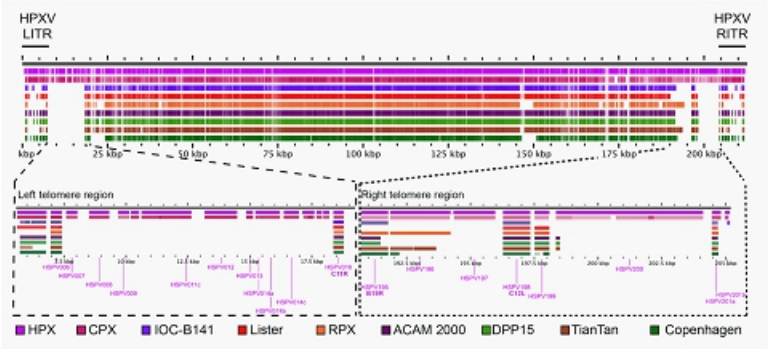
- No known evidence for zoonosis of ACAM2000, but it has not been widely administered

**Modern VACV smallpox vaccines are associated with cardiotoxicity[6]**

[1]Nalca, A et al. Drug design, development and Therapy. (2010) 4:71-79
[2]Medaglia MLG, et al. J Virol. (2015) 89:11909 –11925. doi:10.1128/JVI.01833-15.
[3]Trindade,GS. et al. Clinical Infectious Diseases. (2009) 48:e37–40
[4]Leite,JA, et al. Emerging Infectious Diseases. (2005) www.cdc.gov/eid • Vol. 11, No. 12
[5]Medaglia MLG, et al. Emerging Infectious Diseases (2009) www.cdc.gov/eid • Vol. 15, No. 7
[6]Engler RJM et al., PloS ONE (2015) 10(3): e0118283. doi:10.1371/journal.pone.0118283

# HPXV and its Relationship to Other Orthopoxviruses



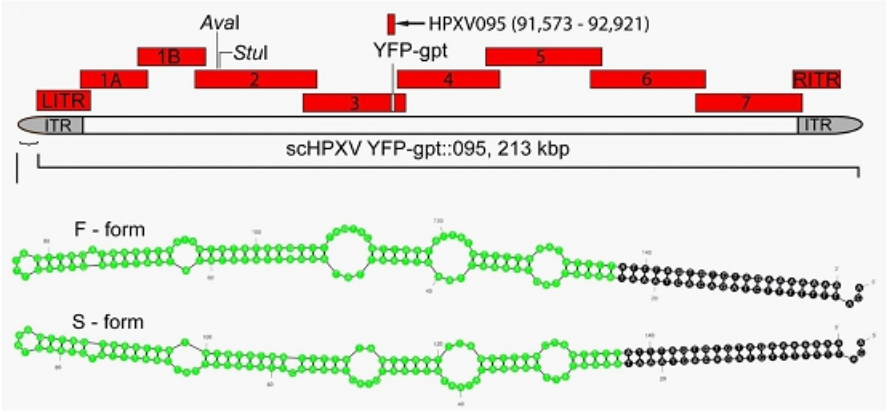



HSPV074 – fragmented homolog of VACV I4L (ribonucleotide reductase)
HSPV200 – 216 kDa protein probably regulates T-cell activation with homologs still present in variola, cowpox, and monkeypox viruses

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

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



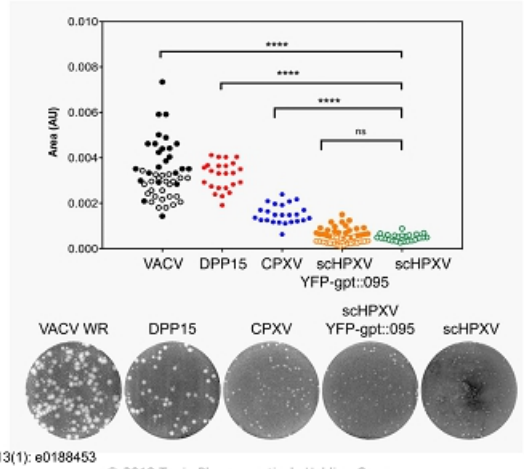



Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

Sequence: GenBank entry DQ792504; DNA: GeneArt

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

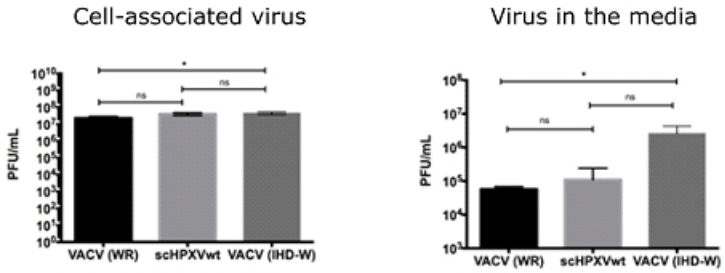





Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

# Production of Cell-Associated and Extracellular Virus

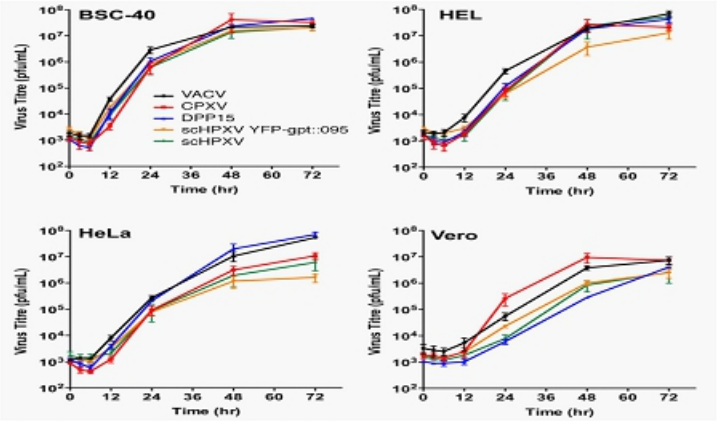





Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

# HPXV Growth Characteristics

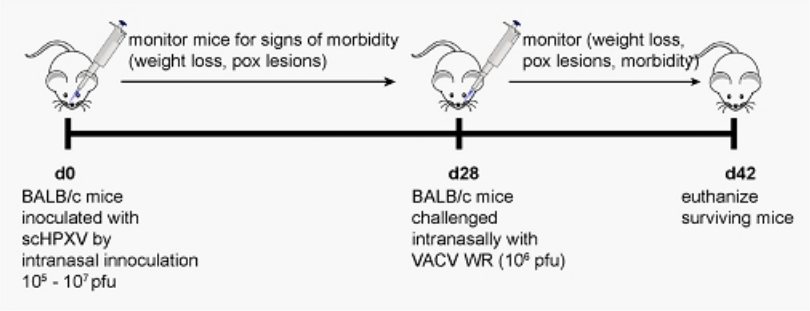





Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

# Testing Vaccine Protective Activity of HPXV in Mice Model

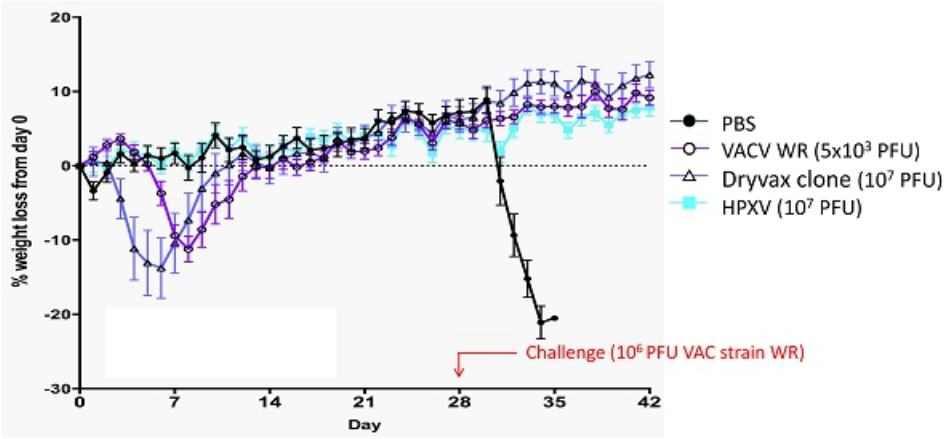





Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

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

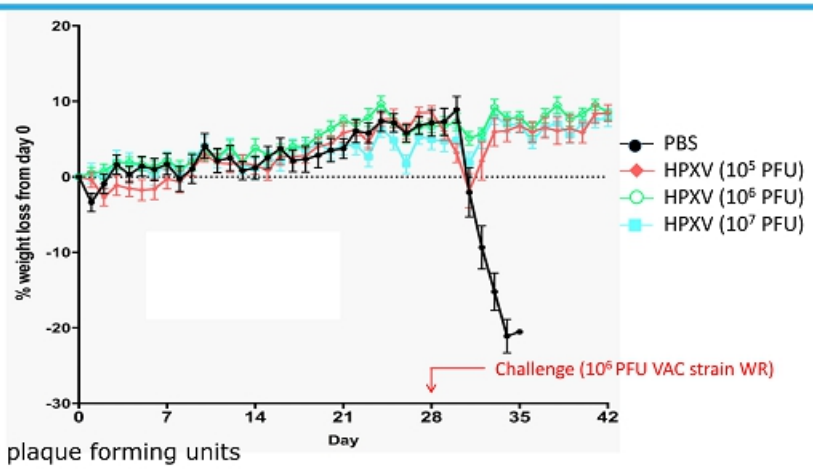





Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453

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



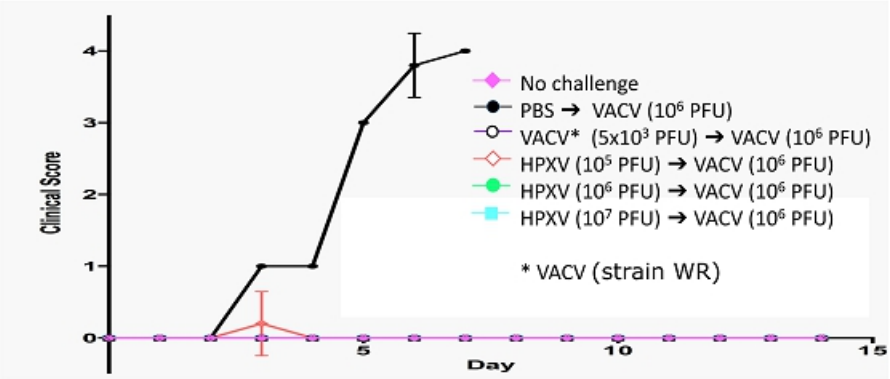



*PFU = plaque forming units

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

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






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

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



**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 cardiotoxicity[1]**

**HPXV has potential for slower proliferation leading to possibly decreased toxicity[2]**

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



**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**

# Current Needs to Vaccinate Against Smallpox



**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 pox[1]**

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

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

# TNX-801: A Potential Medical Countermeasure



## 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

# 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**

# Evidence of Effectiveness for Smallpox Vaccine



**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 sequence[1]**

- 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

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

# ACAM2000[1] – Best Technology of its Time



**Single clone picked from "swarm" of Dryvax®[1]**

- Some rationale for selection[2]

**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 2006[3]

[1]US licensed smallpox preventing vaccine – ACAM2000 is currently marketed, Dryvax has been withdrawn from marketing
[2]Monath, TP et al. Int. J. of Inf. Dis. (2004) 8S2:S31
[3]Tulman, ER. Genome of Horsepox Virus J. Virol. (2006) 80(18) 9244

# Rationale for Developing a Potentially Improved New Smallpox Vaccine



**Toxicity concern of modern vaccinia (VACV) vaccines limit wildly 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%]) vaccinees[1]**

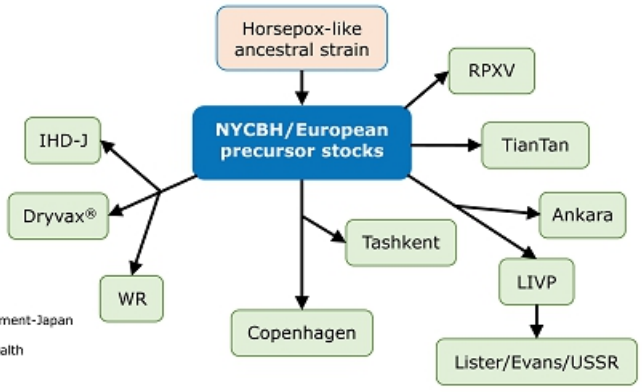
- New onset chest pain, dyspnea and/or palpitations 10.6% of VACV-vaccinees and 2.6% of control immunized (TIV)[2]
- Clinical: 4 probable myo- and 1 suspected peri-carditis (5 cases out of 1081 VACV vaccinees – 0.5%)
- Cardiac specific troponin T (cTnT) elevation in 31 VACV vaccinees (3%)

[1]Engler 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)
[2]TIV = trivalent influenza vaccine - control vaccinees

# Proposed Evolution of Vaccinia Vaccines



Postulated Divergence of Historical Strains of Vaccinia



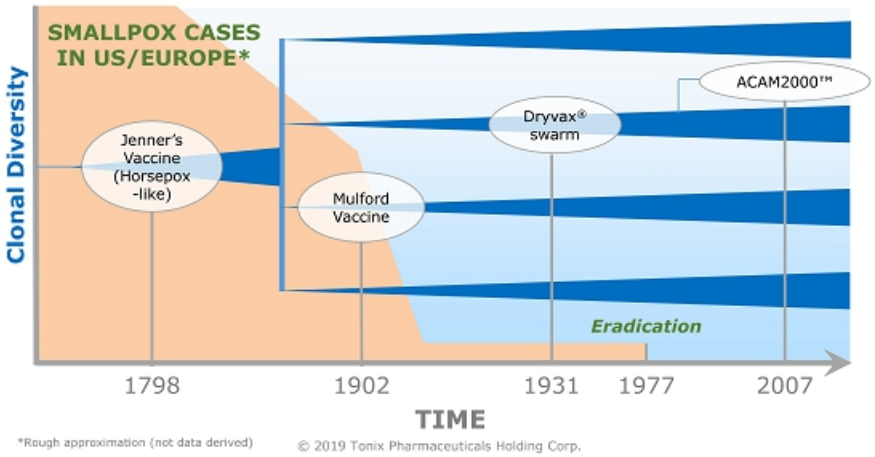

IHD-J=International Health Department-Japan
LIVP=Lister Vaccine Strain
NYCBH=New York City Board of Health
RPXV=Rabbitpox Virus
WR=Western Reserve

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

# Proposed Evolution of Vaccinia Vaccines



**Relationship to Smallpox Incidence and Eradication**




*Rough approximation (not data derived)

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



**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 monkeypox[1]
- MVA has fewer epitopes, and elicits different responses to existing epitopes[2]
  - 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

[1]Golden JW, et al. (2012). PLoS ONE 7(7): e42353. doi:10.1371/journal.pone.0042353
[2]Tscharke, DC et al., J. Exp. Med. 2005 201(1):95

# Possible Smallpox Prevention and Treatment Strategies



## Preventing Vaccine

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

## Post-exposure vaccination[1]

- Jenner's vaccine

## Priming of the immune system

- Imvamune® (MVA) and DNA vaccines[2]

## Pharmacotherapy for infected or exposed individuals

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

## Treatment of disseminated viremia in immunocompromised[3]

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

[1]Described by Jenner as one of his major discoveries
[2]Hooper, JW et al. Smallpox DNA Vaccine Protects Nonhuman Primates Against Lethal Monkeypox. J. Virol. 2004. 78 (9) 4433
[3]Lederman, 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



**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

# Manufacturing and Dosing Requirements



**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



**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



**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**

# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT X · Fusilev (levoleucovorin) for injection · vela

**Gregory Sullivan, MD**
Chief Medical Officer

Columbia University Department of Psychiatry · New York State Psychiatric Institute

**Bradley Saenger, CPA**
Chief Financial Officer

Shire · VERTEX · Steward · pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank · svb SiliconValleyBank · American Capital

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# Milestones – Recently Completed and Upcoming



| | | |
|---|---|---|
| ☑ | July 2018 | Completed P301/HONOR study interim analysis - result did not support study continuation but strengthened new Phase 3 study |
| ☑ | August 2018 | Presentation of P301/HONOR study results at Military Health System Scientific Symposium |
| ☑ | October 2018 | Met with FDA and received preliminary agreement on the design of new Phase 3 study of Tonmya for PTSD (P302/RECOVERY study) |
| ☑ | November 2018 | Received FDA minutes confirming agreement on the design of P302/RECOVERY study |
| ☑ | March 2019 | Met with FDA to discuss new FM Phase 3 study design using TNX-102 SL 5.6 mg |
| ☑ | March 2019 | P302/RECOVERY study initiated |
| ☑ | April 2019 | Received FDA formal minutes with clear guidance and support on new Phase 3 FM study |
| ☑ | May 2019 | In-licensed TNX-1300, BTD product in Phase 2 development for cocaine intoxication |
| ☐ | Second Half 2019 | Preliminary human pharmacokinetic and safety data (non-IND study) from selected TNX-601 (tianeptine oxalate) formulation expected |
| ☐ | First Half 2020 | Topline data from P302/RECOVERY study expected |

# Summary



**Two Phase 3 Programs in indications affecting millions of Americans**

- Tonmya for PTSD: affects 12 million adults in U.S.; currently in Phase 3 with data expected next year; bedtime treatment
- TNX-102 SL for Fibromyalgia: affects between 5-10 million adults in U.S.; ready for Phase 3

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

- TNX-102 SL for Agitation in Alzheimer's Disease: Fast Track designation; ready for Phase 2/3
- TNX-1300 for Cocaine Intoxication: biologic and new molecular entity with Breakthrough Therapy designation; ready for Phase 2

**Pipeline products to improve biodefense and leverage PTSD expertise**

- TNX-801: smallpox-preventing vaccine in preclinical development; demonstrated protective vaccine activity in mice; GMP viral production process in development
- TNX-701: oral radioprotection drug in preclinical development; demonstrated radioprotective effect in mice
- TNX-601: tianeptine oxalate in formulation development for daytime treatment of PTSD

TONIX PHARMACEUTICALS

NASDAQ: TNXP

*Thank you*!

**EXHIBIT 99.02**

# Investor Presentation

TONIX PHARMACEUTICALS

June 2019

**Version P0184 6-3-19 (Doc 0495)**

# Cautionary Note on Forward-Looking Statements



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.

# Tonix Pharmaceuticals



**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 as well as potential medical counter-measures to improve biodefense

**What we do:**

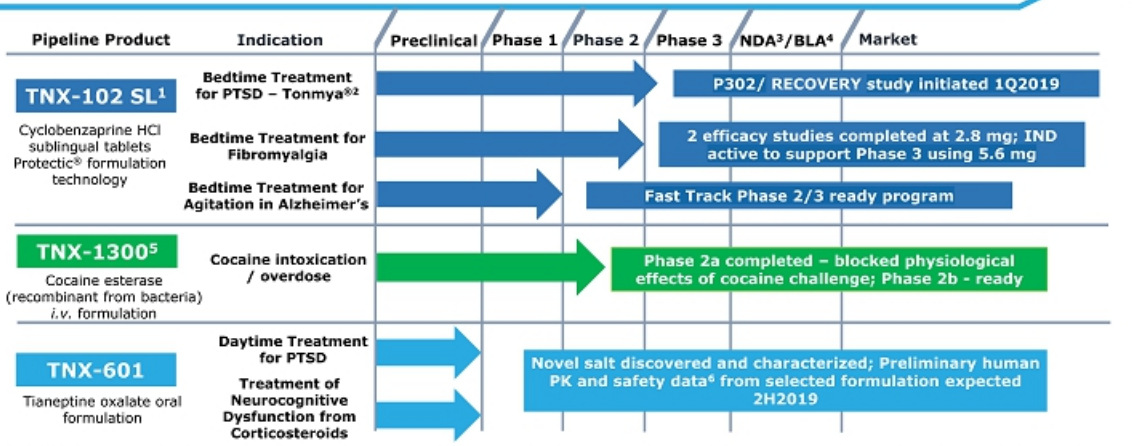
- Target therapeutic areas with high need for improvement
  - Conditions, with no or inadequate treatments
  - Significant patient segments not well served by existing therapies
- Develop innovative treatment options with possibility to be a "game changer"
  - Scientifically unique and innovative
  - Supported by strong scientific rationale
  - Supported by preliminary clinical evidence and published literature
  - Utilize proven regulatory pathway and established clinical endpoint
  - Built on a foundation of proprietary intellectual property

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



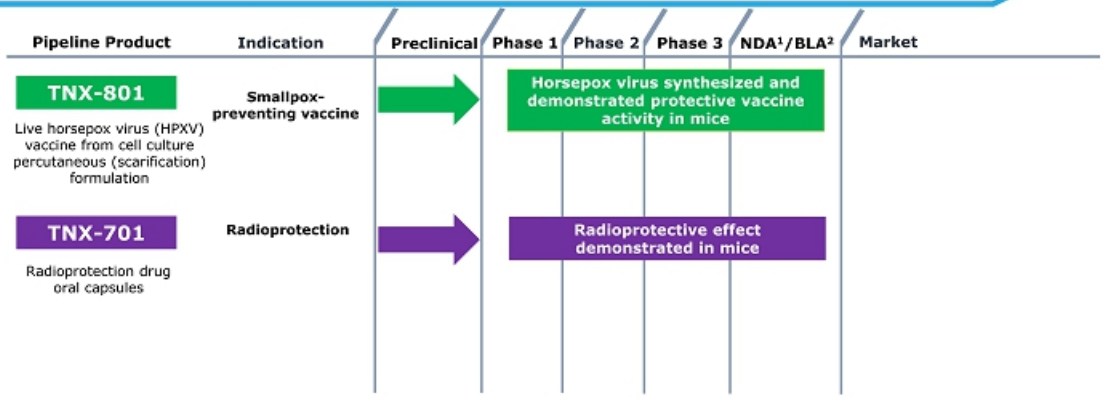



[1] TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication; [2] Tonmya has been conditionally accepted by the U.S. FDA as the proposed trade name for TNX-102 SL for the treatment of PTSD. [3]NDA- New Drug Application; [4]BLA –Biologic Licensing Application; [5]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; [6]non-Investigational New Drug (IND) study;

# Biodefense Candidates in Development

## Biodefense programs owned outright with no royalties due






¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# Lead Program: TNX-102 SL – Product Concept



**Sleep disturbances are associated with a constellation of disorders**

- Considered co-morbid or a key symptom in these disorders
- Believed to have a role in the onset, progression and severity of these disorders

**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

# TNX-102 SL Proposed Mechanism: Improving Sleep Quality



A unique and innovative approach (improving sleep quality), to potentially address a constellation of disorders in a variety of therapeutic areas where sleep disturbances are co-morbid and believed to have a role in the onset, progression and severity of the disorder.

| Therapeutic Area | Target Indication | Status |
|---|---|---|
| Psychiatry | Posttraumatic stress disorder (PTSD) | Phase 3 |
| Rheumatology | Fibromyalgia (FM) | Phase 3 development with higher dose |
| Psychiatry / Neurology | Agitation in Alzheimer's Disease (AAD) | Phase 2 ready |
| Chronic pain | TBD | Life-cycle opportunity |
| Sleep disorders | TBD | Life-cycle opportunity |

# TNX-102 SL Intellectual Property – U.S. Protection until 2034



| | |
|---|---|
| **Composition of matter (eutectic):**<br>**Protection expected to 2034** | • United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9,636,408 in May 2017, U.S. Patent No. 9,956,188 in May 2018 and U.S. Patent No. 10,117,936 in Nov 2018<br>• Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018<br>• New Zealand Intellectual Property Office (NZIPO) issued New Zealand Patent No. 631152 in May 2017<br>• 37 patent applications pending (2 allowed (U.S. and South Africa)) |
| **Pharmacokinetics (PK):**<br>**Protection expected to 2033** | • JPO issued Japanese Patent No. 6259452 in Dec 2017<br>• NZIPO issued New Zealand Patent No. 631144 in March 2017<br>• Taiwanese Intellectual Property Office issued Taiwanese Patent No. I590820 in July 2017<br>• 21 patent applications pending (1 allowed (Australia)) |
| **Method of use (PTSD) for cyclobenzaprine:**<br>**Protection expected to 2030** | • USPTO issued U.S. Patent 9,918,948 in March 2018<br>• European Patent Office issued European Patent No. 2 501 234B1 in Sept 2017 (validated in 38 countries). Opposition filed in June 2018<br>• 2 patent applications pending |

# Prevalence of PTSD Among Civilians and Veterans



**4.7%**
Adult population[1]

**19-31%**
Vietnam veterans[2]

**>19%**
Iraq/Afghanistan[3]

**12 million** American adults annually[1]

**Women** more likely to develop than men[1]

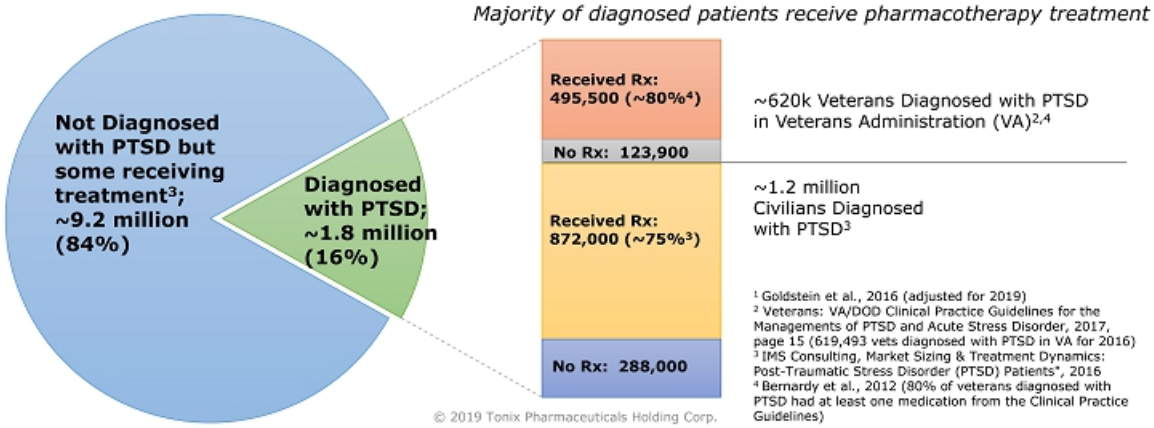
[1]Goldstein et al., 2016 (adjusted for 2019); [2]Norris, *PTSD Res Quar*. 2013; [3]*Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015,* Washington, DC; Among 1.9M separated OEF/OIF/OND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

# PTSD Prevalence and Market Characteristics



**Prevalent Population with PTSD (U.S.)**
**~12 million[1]** (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 PTSD[3]

[1] Goldstein et al., 2016 (adjusted for 2019)
[2] Veterans: VA/DOD Clinical Practice Guidelines for the Managements 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)

# PTSD: Not Well-Served by Approved Treatments



**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)

**Tonmya is being investigated in both military and civilian PTSD and is expected to be indicated as a "treatment for PTSD"**

# Tonmya: a Potential Bedtime Treatment for PTSD



**First investigational new drug to show treatment effect in military-related PTSD in two potential pivotal efficacy studies**

- Phase 2 study (P201/AtEase) showed Tonmya 5.6 mg had a strong signal of treatment effect at Week 12 as measured by CAPS-5[1]
- 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 Tonmya NDA submission
- No serious or unexpected adverse events related to Tonmya were reported

**FDA feedback and acceptance on new Phase 3 study (P302/RECOVERY) received in November 2018[2]**

[1] CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
[2] FDA Meeting Minutes, November 26, 2018

# No Recognized Abuse Potential in Clinical Studies



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

- Cyclobenzaprine interacts with receptors that regulate sleep quality: 5-$HT_{2A,}$ $\alpha_1$-adrenergic and histamine $H_1$ 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 2018) indicates no abuse or dependence concern

**Tonmya NDA can be filed without drug abuse and dependency assessment studies**

- Discussed at March 9, 2017 meeting with the FDA

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



## 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, norCBP[1]
  - Long half-life (~72 hours)
  - Less selective for target receptors (5-$HT_{2A,}$ $\alpha_1$-adrenergic, histamine $H_1$)
  - More selective for norepinephrine transporter and muscarinic $M_1$

## 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)

# Tonmya: Hypothesized Novel Mechanism Targets Sleep Quality for Recovery from PTSD



## 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)

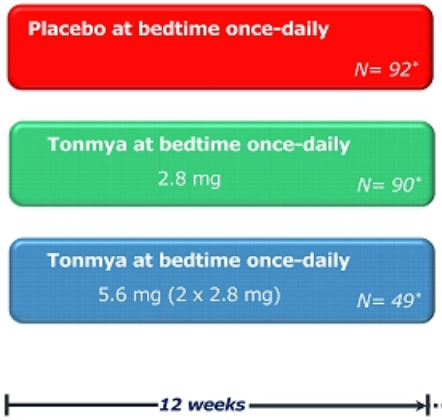
## Tonmya targets sleep quality[3]

- The active ingredient in Tonmya, cyclobenzaprine, interacts with receptors that regulate sleep quality: strongly binds and potently blocks 5-$HT_{2A}$, $\alpha_1$-adrenergic and histamine $H_1$ receptors, permissive to sleep-dependent recovery processes

[1]Straus 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. [2]Murkar ALA, De Koninck J. Consolidative mechanisms of emotional processing in REM sleep and PTSD. Sleep Med Rev. 2018; 41:173-184.
[3]Daugherty et al., Abstract 728, Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015, Toronto Ontario, Canada

# Phase 2 P201/AtEase[1] Study in Military-Related PTSD






- 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-5[2] ≥ 29
- Primary Efficacy Analysis:
  - Difference in CAPS-5 score change from baseline between Tonmya 2.8 mg and placebo at Week 12
- Key Secondary Measures:
  - PROMIS Sleep Disturbance, CGI-I, SDS

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

# P201/AtEase Study



**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 ≥ 33 enrollment criteria for Phase 3

# P301/HONOR[1] Study –Evidence of Efficacy at Week 4
## Discontinued Due to High Placebo Response at Week 12



### General study characteristics:

Randomized, double-blind, placebo-controlled, adaptive design, planned 550 military-related PTSD participants with baseline CAPS-5[2] ≥ 33 in approximately 40 U.S. sites

**Tonmya 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-5[2]:

- Mean change from baseline at Week 12 (Tonmya 5.6 mg vs. placebo)

### Unblinded interim analysis at 274 randomized participants (mITT* 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

[1]ClinicalTrials.gov Identifier: NCT03062540
[2]CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
*Modified intent-to-treat

# P301/HONOR Study Stopped After Interim Analysis (July 2018)



**P301 was a large adequate well-controlled Phase 3 study in military-related PTSD**

- Separation on primary endpoint at Week 12 did not cross pre-specified study continuation threshold at Week 12 (p=0.602)
- No safety or tolerability issue discovered
- Retrospective analyses showed Week 4 CAPS-5 (P=0.019) and CGI-I (P=0.015) scores in Tonmya group had a strong signal of treatment effect

**P301 dataset is complex and rich**

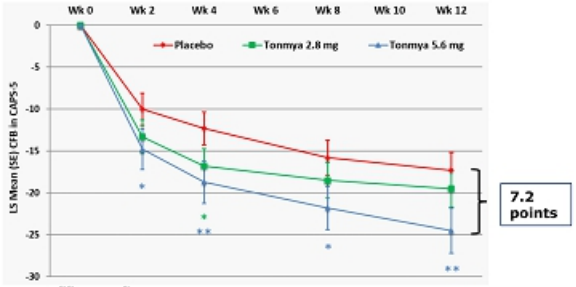
- Retrospective analyses presented at Military Health System Research Symposium (MHSRS) in Kissimmee, FL on August 22, 2018
- Results discussed with the FDA[1] and helped to design the new Phase 3 P302/RECOVERY study with high probability of success

[1]FDA Meeting Minutes (November 26, 2018)

# Tonmya Phase 2 Dose-Effect in Military-Related PTSD[1]

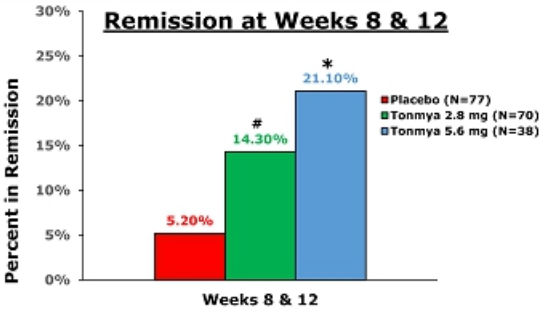


## PTSD Symptoms (CAPS-5[2] Score)




** p<0.01, * p<0.025, Tonmya 5.6 mg group with placebo, MMRM with multiple imputation (MI); *p=0.018, Tonmya 2.8 mg group with placebo, MMRM with MI

## Remission at Weeks 8 & 12



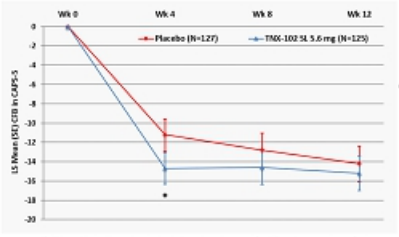

Remission = Loss of Diagnosis and CAPS-5 < 11
Asterisk and hashmark represent pairwise comparisons between Tonmya and Placebo; #p=0.08, Odds Ratio 3.01 (0.89, 10.18)
*p=0.02, Odds Ratio 4.60 (1.27, 16.66); logistic regression

[1] Completed Phase 2 P201/AtEase study: Retrospective analysis of Tonmya 5.6 mg on CAPS-5 ≥33 (high-moderate) subgroup. Primary analysis of P201/AtEase, based on Tonmya 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 (mITT) and ≤9 Years Time Since Trauma Subgroups

## Phase 3 P301/HONOR Study[1]

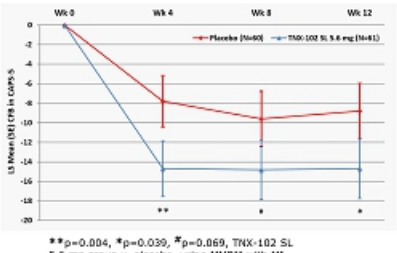
### Modified intent to treat (mITT) population




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

~50% mITT Population

### *Time Since Trauma (TST) ≤9 yrs*

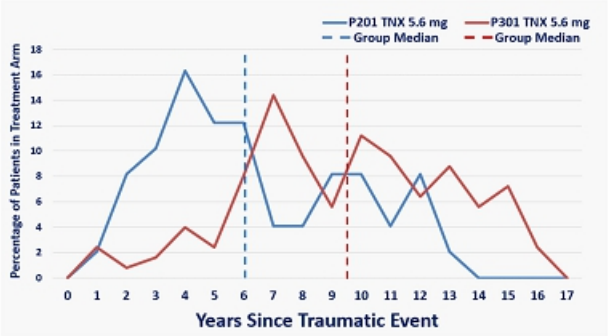



**p=0.004, *p=0.039, *p=0.069, TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

[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 (Tonmya 5.6 mg Groups)






**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 Tonmya 5.6 mg in TST Subgroups in P301[1]




| 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 | 13 | 18 |
| TNX-5.6 mg 'N' | 14 | 17 | 16 | 12 | 22 | 10 | 17 | 18 |

MCFB=mean change from baseline; 'N'=number of participants in group; PBO=placebo; TST=time since trauma



- 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)

[1]*Time 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/1d0c4055b2863fc74e1ef45f9ddaf42b.pdf

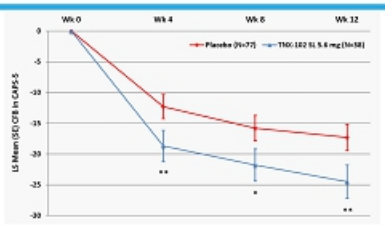
# PTSD Treatment Response to Tonmya in Phase 2 and Phase 3 Studies: Retrospective Analyses of P201 Entry CAPS-5 ≥33 and P301 ≤9 Years Since Trauma Subgroups



## Change in CAPS-5 over course of treatment with Tonmya

CAPS-5 is a structured interview assessing PTSD severity

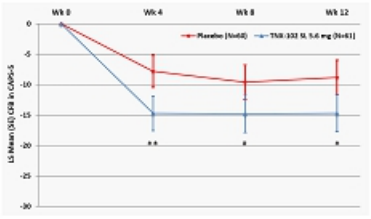
- Required primary endpoint for PTSD drug approval




**P201 Baseline CAPS-5 ≥33 *(majority TST[1] ≤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)

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




**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

*[1]Time since trauma; [2]Majority 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 Phase 2 and Phase 3 Studies:
## Retrospective Analyses of P201 Entry CAPS-5 ≥33 and P301 ≤9 Years Since Trauma Subgroups

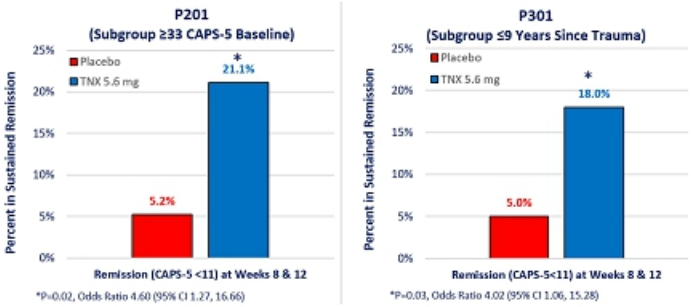


**Remission is a clinical state that is essentially asymptomatic**

**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 P201[1]**




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

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

| | | | 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 | |
| | Measure | 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<br>Preferred Term | P201<br>Placebo (N=94) | P201<br>TNX 2.8 mg (N=93) | P201<br>TNX 5.6 mg (N=50) | P301<br>Placebo (N=134) | P301<br>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*# | | | | | |
| Hypoaesthesia 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 Tonmya**

- 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

# Time Since Trauma – Review of Published Studies

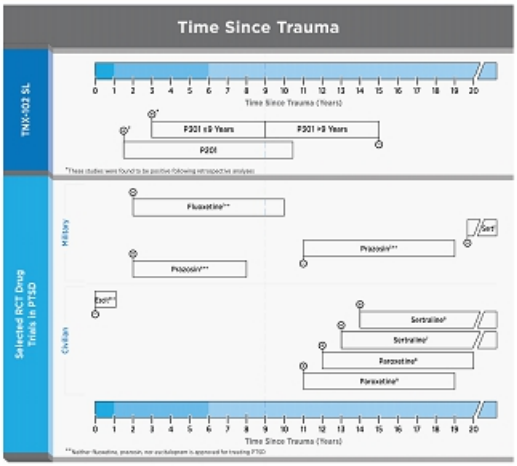


**Published studies of prazosin suggested effects in military-PTSD prior to 9 years**

- 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




Escit=escitalopram



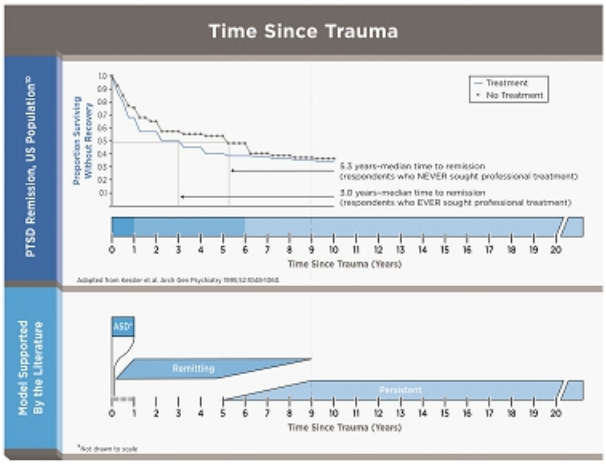
[1]Martenyi et al. *J Clin Psychiatry* 2002;63:199-206.
[2]Friedman et al. *J Clin Psychiatry* 2007;68:711-720.
[3]Raskind et al. *NEJM* 2018;378:507-517.
[4]Raskind et al. *Am J Psychiatry* 2013;170:1003-1010.
[5]Shalev et al. *Arch Gen Psychiatry* 2012;69:166-176.
[6]Davidson et al. *Arch Gen Psychiatry* 2001;58:485-492.
[7]Brady et al. *JAMA* 2000;283:1837-1844.
[8]Marshall et al. *Am J Psychiatry* 2001;158:1982-1988.
[9]Tucker et al. *J Clin Psychiatry* 2001;62:860-868.

# Time Since Trauma – Remitting and Persistent Phases of PTSD



**Kessler et al[1] 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 studies[2-6]




[1]Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.
[2]Armenta et al. *BMC Psychiatry* 2018;18:48.
[3]Galatzer-Levy et al. *PLOS ONE* 2013;8:e70084.
[4]Perkonigg et al. *Am J Psychiatry* 2005;162:1320-1327.
[5]Santiago et al. *PLOS ONE* 2013;8:e59236.
[6]Davidson & Connor. *Eur Neuropsychopharmacol* 2001;11(Supp3):S148-S149.

# Response to Tonmya for Female Participants in P301/HONOR Study[1]



**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 Tonmya 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 Tonmya 5.6 mg likely in mixed civilian and military PTSD population to be studied in upcoming 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 Tonmya for Non-Combat Traumas in P301/HONOR Study in ≤9 Years Time Since Trauma Subgroup[1]



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

**To determine the therapeutic effects of Tonmya 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, Tonmya 5.6 mg N=10):**

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

**Non-combat traumas treated with Tonmya 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 Tonmya**

[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

# Summary of Clinical Experience with Tonmya/ TNX-102 SL in PTSD



**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 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 subgroup of P301 may be enriched for "Remitting Phase" of PTSD[1-4]**

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

**Results from retrospective analyses lead to improved Phase 3 study design**

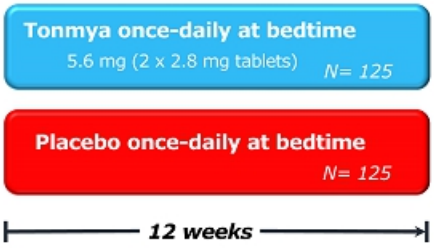
[1]Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060.
[2]Armenta et al. *BMC Psychiatry* 2018;18:48.
[3]Galatzer-Levy et al. *PLOS ONE* 2013;8:e70084.
[4]Perkonigg et al. *Am J Psychiatry* 2005;162:1320-1327.

# New Phase 3 P302/RECOVERY Study – Initiated 1Q 2019



## General study characteristics:

- Randomized, double-blind, placebo-controlled study with baseline CAPS-5[1] ≥ 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




## Primary endpoint:

- CAPS-5[1] mean change from baseline at Week 4 (Tonmya 5.6 mg vs. placebo)

## Key Secondary endpoints include:

- CAPS-5 mean change from baseline at Week 12 (Tonmya 5.6 mg vs. placebo)
- Change from baseline Clinical Global Impression – Severity scale
- Change from baseline Sheehan Disability Scale total score

**Potential pivotal efficacy study to support NDA approval**

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

# Late-Stage PTSD Drug Candidates



## Tonmya

- Phase 3 development focused on military-related and civilian PTSD; showed activity in treatment of military-related PTSD in large multi-center trials

## MDMA-assisted psychotherapy

- Indication – "drug assisted psychotherapy"
- Breakthrough therapy that is Phase 3-ready; showed activity in a Phase 2 study of PTSD; enrolling in Phase 3 study

## Other drugs currently (or recently) in Phase 2 development

- Rexulti® (brexpiprazole) - Otsuka/Lundbeck; atypical antipsychotic; positive clinical results from Phase 2 study reported in November 2018 for brexpiprazole, when used in combination with an approved PTSD medication, sertraline, but not as monotherapy
- NYX-783 - Aptinyx; NMDA receptor modulator (enrolling for 8-week Phase 2 study of 144 patients using 50 mg either once daily or once weekly)
- BNC-201 – Bionomics; nicotinic receptor modulator (program planned to resume after reformulation)

# Opportunities to Expand to Other Indications



**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
- Anxiety Disorders

**Psychiatric Symptoms of Neurological Disorders**
- Agitation in Alzheimer's
- Psychosis in Parkinson's, Alzheimer's and other dementias

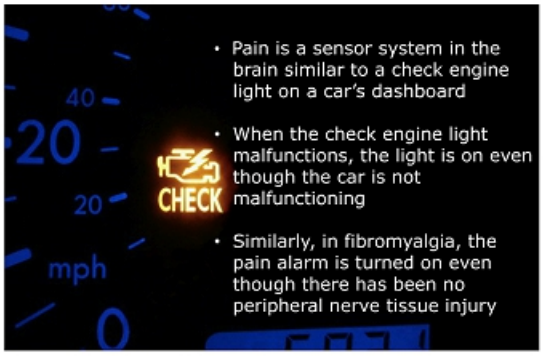
**Chronic Pain States**
- Chronic wide-spread pain (fibromyalgia)
- Osteoarthritis

**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*

# Fibromyalgia is a Chronic, Debilitating Disorder that Imposes a Significant Societal and Economic Burden






*Volkswagen Check Engine (Photograph). (2011, October 14). Wikipedia*

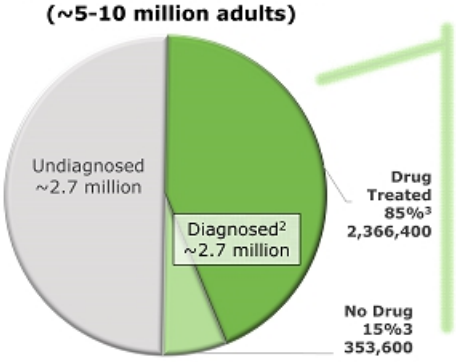
- Fibromyalgia is considered a neurobiological disorder characterized by[1]: chronic widespread pain, non restorative sleep, fatigue, diminished cognition
- Believed to result from inappropriate pain signaling in central nervous system in the absence of peripheral injury[1]
- Causes significant impairment in all areas of life[2]
  - 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 year[3]
  - Annual direct medical costs are twice those for non-fibromyalgia individuals[4]

[1] Phillips 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.

# Fibromyalgia: Market Characteristics



**U.S. Prevalence Rate 2-4%[1]**
**(~5-10 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/patient[3]
- Rotation through therapy common: average ~5 drugs/year[3]
- Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[4,5]

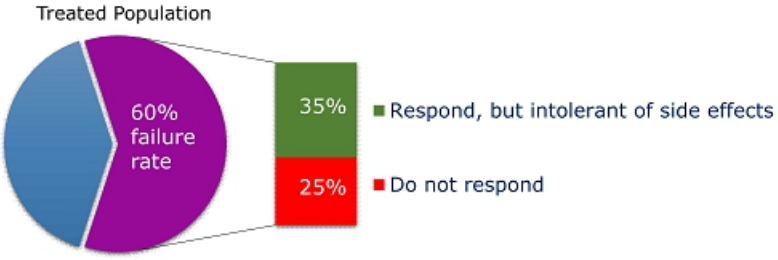
**Unmet Need**
- Majority of patients do not respond or cannot tolerate therapy[6]

1. American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
2. Vincent et al., 2013; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population
3. Robinson, et al., 2012; 85% received drug treatment
4. Vincent et al, Arthritis Care Res 2013;65:786
5. Product sales derived from IMS MIDAS; IMS NDTI 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 Sustained Benefit from the Three FDA-Approved Drugs[1]



- 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



- Currently-approved medications may have side effects that limit long-term use[1]
  - 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 simultaneously[2]
  - The typical patient has tried six different medications[3]
- Substantial off-label use of narcotic painkillers and prescription sleep aids[3]
  - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment[4]
- 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 for Fibromyalgia: Summary of a completed Phase 3 F301 study



**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
- 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-F Function Domain, Daily Sleep Quality Diary, PROMIS Sleep Disturbance

**Efficacy results:**

- mITT population: 425 (81.9%) of 519 patients
- The primary analysis was not statistically significant. However, retrospective analysis showed average pain improvement (secondary endpoint) after 12 weeks of treatment showed statistical significance ($P<0.05$, MMRM)
- Significant improvements observed in sleep quality, patient global impression of change and fibromyalgia-specific measures (secondary analyses).

# TNX-102 SL for Fibromyalgia: F301 Study Results and Program Updates



**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:
  - hypoaesthesia (tongue or oral numbness)
  - glossodynia (burning sensation or other tongue discomfort)
  - oral paraesthesias (tingling sensations)
  - abnormal product taste (bitter or noticeable taste)
- The severity and incidence of oral AE are similar to those reported in our PTSD studies using TNX-102 SL 5.6 mg.

**Conclusion:**

- The promising results and highly relevant efficacy findings support further investigation of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) as a chronic treatment for FM.

**Program updates:**

- Clear guidance and support received from FDA* to advance the FM program. The long-term safety exposure data from the PTSD program may support the fibromyalgia NDA*.
- 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

# TNX-102 SL: Potential Treatment for Agitation in Alzheimer's Disease (AAD)



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

- Includes emotional lability, restlessness, irritability and aggression[1]

**Link between disturbed sleep and agitation in Alzheimer's[1-3]**

- 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 2050[4]

**FDA-designated Fast Track development program**

**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 approval[5]**

[1]Rose, K.et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias, 30*:78
[2]Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association, 18*, 396.
[3]Canevelli, M., et al. (2016). *Frontiers in medicine, 3*.
[4]The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: https://www.alz.org/facts/
[5]FDA comments on final protocol received October 2018

# New Addition to Tonix's Pipeline: TNX-1300* for the Treatment of Cocaine Intoxication

**Recombinant protein that degrades cocaine in the bloodstream[1]**

- Double-mutant cocaine esterase

**In-licensed from Columbia University (Univ. of Kentucky and Univ. of Michigan)**

**Phase 2 study completed by Rickett Benckiser (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 (incl dry mouth, nausea); nervous systems disorders (incl headache, dizziness) and skin and subcutaneous tissue disorders (incl hyperhidrosis, dermatitis)

**TNX-1300 for the treatment of cocaine intoxication has U.S. FDA Breakthrough Therapy designation (BTD)**

**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.

# About TNX-1300



**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 plants[1]
- The gene encoding CocE was identified and the protein was extensively characterized[1-3]
- 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 temperature[4]

[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



**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.*

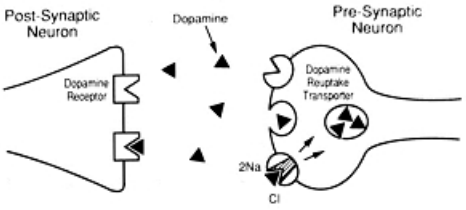
**Cocaine intoxication:** deleterious effects on the body, especially cardiovascular system.

- 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.

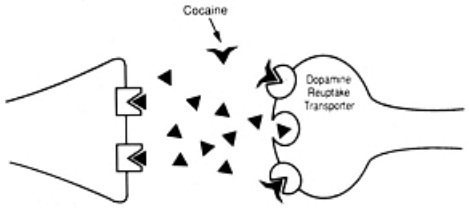
# Cocaine Action



- **Cocaine acts to inhibit the Dopamine Reuptake Transporter**
  - Binds to transporter and blocks reuptake of dopamine from synapse



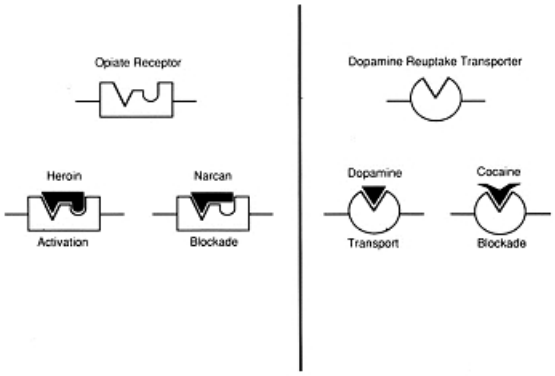

- **No antagonist has been developed for cocaine**
  - Unlike situation for opiates which can be blocked by naloxone ("Narcan") or naltrexone



# Cocaine Action – Lack of "Antidote"

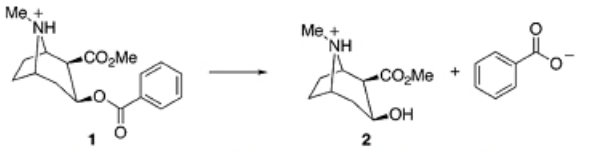


- **Cocaine binding site on Dopamine Reuptake Transporter is too small or simple for a blocker**
  - Antagonists of cocaine binding have the same function as cocaine
- **Naltrexone exploits the complexity of the opiate binding site**
  - Addictive opiates are "agonists", which means their binding and activity can be dissected by antagonists like naloxone



# CocE is a Catalyst that Breaks Cocaine Down into Less Toxic Metabolites[1-4]






Cocaine | Ecgonine Methyl Ester | Benzoic Acid

- Metabolites ecgonine methyl ester and benzoic acid are neither pleasurable nor addictive

[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.

# 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 year[1]

- 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.

# Mortality Due to Cocaine Overdose



**Cocaine is involved in 20% of overdose deaths in the U.S.**

- In 2016, 10,375 deaths due to cocaine overdose[1]
- In 2017, about 13,900 deaths occurred in the U.S. due to cocaine overdose.[2]

**Overdose deaths involving cocaine increased 34% from 2016 to 2017.** [3,4]

[1] Overdose Death Rates - National Institute on Drug Abuse - https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates; accessed May 11, 2019
[2] Kariisa M et al. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. *MMWR Weekly* / May 3, 2019 / 68(17);388–395 - https://www.cdc.gov/mmwr/volumes/68/wr/mm6817a3.htm?s_cid=mm6817a3_w;
[3] Cocaine deaths up in U.S. and opioids are a big part of it. Associated Press. https://www.msn.com/en-us/news/us/cocaine-deaths-up-in-us-and-opioids-are-a-big-part-of-it/ar-AAAOxs8?ocid=se; accessed May 11, 2019
[4] Fottrell, Q. MarketWatch, Fatal drug overdoses involving cocaine and other stimulants have surged by over 52%, May 3, 2019 - https://www.marketwatch.com/story/fatal-drug-overdoses-involving-cocaine-and-other-stimulants-have-surged-by-over-52-2019-05-03; accessed May 11, 2019

# Treatment for Cocaine Intoxication



## Current Standard of Care

- Patients present with acute agitation, hyperthermia, tachycardia, arrhythmias, and hypertension
- Potential life-threatening sequalae 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
- FDA Breakthrough Therapy Designated product
- 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:**

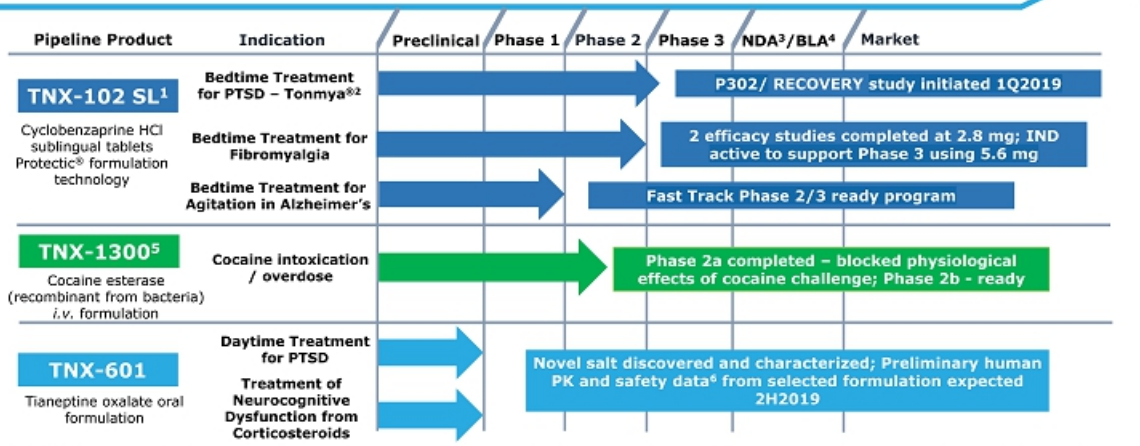
- Brings Tonix into an additional therapeutic area: Addiction Medicine

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



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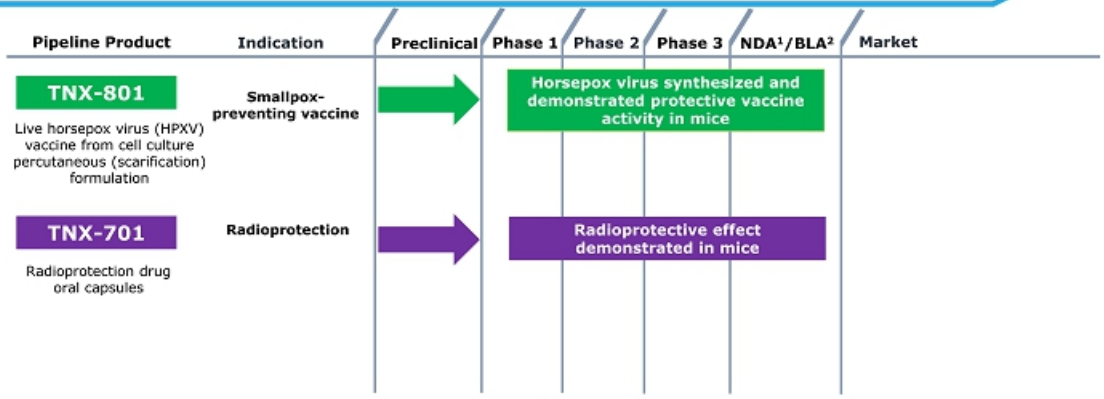
# Biodefense Candidates in Development

## Biodefense programs owned outright with no royalties due






¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# TNX-601 (Tianeptine Oxalate): A Potential Clinical Candidate for PTSD



**Pre-IND Candidate**

**Targeting a Condition with Significant Unmet Need**

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

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

- Tianeptine sodium (amorphous), first marketed for depression in France in 1989, is approved as an antidepressant in the EU, Russia, Asia and Latin America; established post-marketing experience
- Identified new oxalate salt with improved pharmaceutical properties ideal for reformulation
- Preliminary human pharmacokinetic and safety data (non-IND study) from selected formulation expected in second half 2019

**Filed patent application on novel salt**

- Issued patent on steroid-induced cognitive impairment and memory loss issues

**Clinical evidence for PTSD**

- Several studies have shown tianeptine to be active in the treatment of PTSD[1-4]

[1] Frančišković 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] Aleksandrovskiĭ IA, et al. Zh Nevrol Psikhiatr 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

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



**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.

# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT X · Fusilev (levoleucovorin) for injection · vela

**Gregory Sullivan, MD**
Chief Medical Officer

Columbia University Department of Psychiatry · New York State Psychiatric Institute

**Bradley Saenger, CPA**
Chief Financial Officer

Shire · VERTEX · Steward · pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank · svb SiliconValleyBank · American Capital

# Board of Directors



| | |
|---|---|
| **Seth Lederman, MD**<br>Chairman | **Gen. David Grange (U.S. Army, ret.)**<br>Pharm-Olam, PPD, McCormick Foundation |
| **Margaret Smith Bell**<br>Standard Life Investments, Putnam Investments, State Street Research | **Adeoye "Oye" Olukotun, MD**<br>Squibb, BMS, Mallinckrodt, Esperion |
| **Daniel Goodman, MD**<br>Psychiatrist, co-founder Psychogenics | **John Rhodes**<br>Chair, NYS Public Service Commission, CEO, NYS Dept. of Public Service, Booz Allen |
| **Patrick Grace**<br>(qp) global family offices, Grace Institute Foundation, WR Grace, Chemed | **James Treco**<br>First Chicago, Salomon Brothers/Citigroup |

# Milestones – Recently Completed and Upcoming



| | |
|---|---|
| ☑ July 2018 | Completed P301/HONOR study interim analysis - result did not support study continuation but strengthened new Phase 3 study |
| ☑ August 2018 | Presentation of P301/HONOR study results at Military Health System Scientific Symposium |
| ☑ October 2018 | Met with FDA and received preliminary agreement on the design of new Phase 3 study of Tonmya for PTSD (P302/RECOVERY study) |
| ☑ November 2018 | Received FDA minutes confirming agreement on the design of P302/RECOVERY study |
| ☑ March 2019 | Met with FDA to discuss new FM Phase 3 study design using TNX-102 SL 5.6 mg |
| ☑ March 2019 | P302/RECOVERY study initiated |
| ☑ April 2019 | Received FDA formal minutes with clear guidance and support on new Phase 3 FM study |
| ☑ May 2019 | In-licensed TNX-1300, BTD product in Phase 2 development for cocaine intoxication |
| ❑ Second Half 2019 | Preliminary human pharmacokinetic and safety data (non-IND study) from selected TNX-601 (tianeptine oxalate) formulation expected |
| ❑ First Half 2020 | Topline data from P302/RECOVERY study expected |

# Summary



**Two Phase 3 Programs in indications affecting millions of Americans**

- Tonmya for PTSD: affects 12 million adults in U.S.; currently in Phase 3 with data expected next year; bedtime treatment
- TNX-102 SL for Fibromyalgia: affects between 5-10 million adults in U.S.; ready for Phase 3

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

- TNX-102 SL for Agitation in Alzheimer's Disease: Fast Track designation; ready for Phase 2/3
- TNX-1300 for Cocaine Intoxication: biologic and new molecular entity with Breakthrough Therapy designation; ready for Phase 2

**Pipeline products to improve biodefense and leverage PTSD expertise**

- TNX-801: smallpox-preventing vaccine in preclinical development; demonstrated protective vaccine activity in mice; GMP viral production process in development
- TNX-701: oral radioprotection drug in preclinical development; demonstrated radioprotective effect in mice
- TNX-601: tianeptine oxalate in formulation development for daytime treatment of PTSD

TONIX PHARMACEUTICALS

NASDAQ: TNXP

*Thank you*!

**EXHIBIT 99.03**

# Investor Presentation



TONIX PHARMACEUTICALS

June 2019

**Version P0183 6-3-19 (Doc 0494)**

# Cautionary Note on Forward-Looking Statements



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.

# Tonix Pharmaceuticals



**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 as well as potential medical counter-measures to improve biodefense

**What we do:**

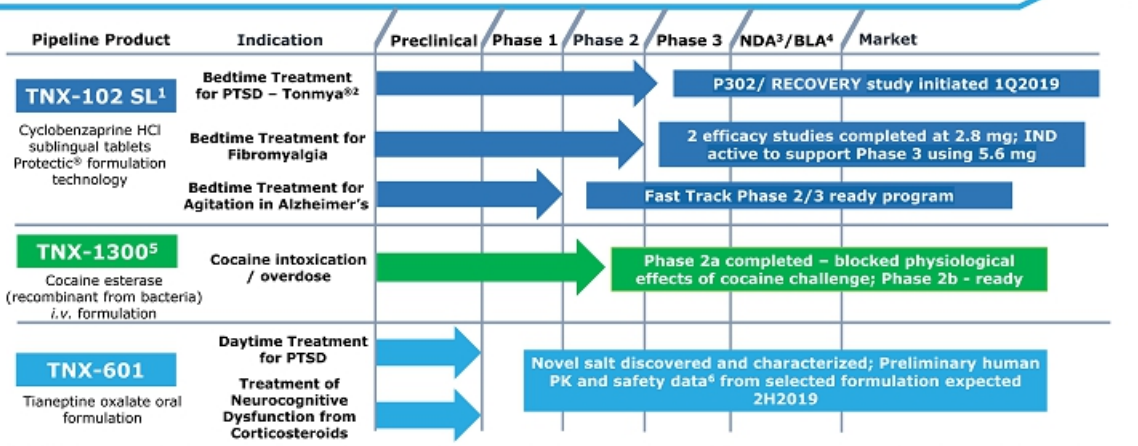
- Target therapeutic areas with high need for improvement
  - Conditions, with no or inadequate treatments
  - Significant patient segments not well served by existing therapies
- Develop innovative treatment options with possibility to be a "game changer"
  - Scientifically unique and innovative
  - Supported by strong scientific rationale
  - Supported by preliminary clinical evidence and published literature
  - Utilize proven regulatory pathway and established clinical endpoint
  - Built on a foundation of proprietary intellectual property

# CNS Candidates in Development

## Psychiatry, Pain and Addiction

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



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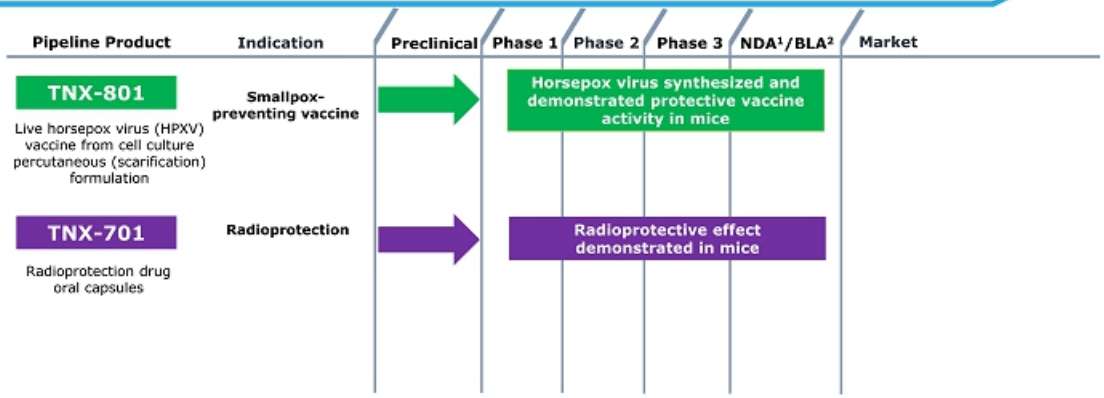



¹NDA- New Drug Application; ²BLA –Biologic Licensing Application

# Lead Program: TNX-102 SL – Product Concept



**Sleep disturbances are associated with a constellation of disorders**

- Considered co-morbid or a key symptom in these disorders
- Believed to have a role in the onset, progression and severity of these disorders

**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

# TNX-102 SL Proposed Mechanism: Improving Sleep Quality



A unique and innovative approach (improving sleep quality), to potentially address a constellation of disorders in a variety of therapeutic areas where sleep disturbances are co-morbid and believed to have a role in the onset, progression and severity of the disorder.

| Therapeutic Area | Target Indication | Status |
|---|---|---|
| Psychiatry | Posttraumatic stress disorder (PTSD) | Phase 3 |
| Rheumatology | Fibromyalgia (FM) | Phase 3 development with higher dose |
| Psychiatry / Neurology | Agitation in Alzheimer's Disease (AAD) | Phase 2 ready |
| Chronic pain | TBD | Life-cycle opportunity |
| Sleep disorders | TBD | Life-cycle opportunity |

# TNX-102 SL Intellectual Property – U.S. Protection until 2034



| | |
|---|---|
| **Composition of matter (eutectic):**<br>**Protection expected to 2034** | • United States Patent and Trademark Office (USPTO) issued U.S. Patent No. 9,636,408 in May 2017, U.S. Patent No. 9,956,188 in May 2018 and U.S. Patent No. 10,117,936 in Nov 2018<br>• Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018<br>• New Zealand Intellectual Property Office (NZIPO) issued New Zealand Patent No. 631152 in May 2017<br>• 37 patent applications pending (2 allowed (U.S. and South Africa)) |
| **Pharmacokinetics (PK):**<br>**Protection expected to 2033** | • JPO issued Japanese Patent No. 6259452 in Dec 2017<br>• NZIPO issued New Zealand Patent No. 631144 in March 2017<br>• Taiwanese Intellectual Property Office issued Taiwanese Patent No. I590820 in July 2017<br>• 21 patent applications pending (1 allowed (Australia)) |
| **Method of use (PTSD) for cyclobenzaprine:**<br>**Protection expected to 2030** | • USPTO issued U.S. Patent 9,918,948 in March 2018<br>• European Patent Office issued European Patent No. 2 501 234B1 in Sept 2017 (validated in 38 countries). Opposition filed in June 2018<br>• 2 patent applications pending |

# Prevalence of PTSD Among Civilians and Veterans



**4.7%**
Adult population[1]

**19-31%**
Vietnam veterans[2]

**>19%**
Iraq/Afghanistan[3]

**12 million** American adults annually[1]

**Women** more likely to develop than men[1]

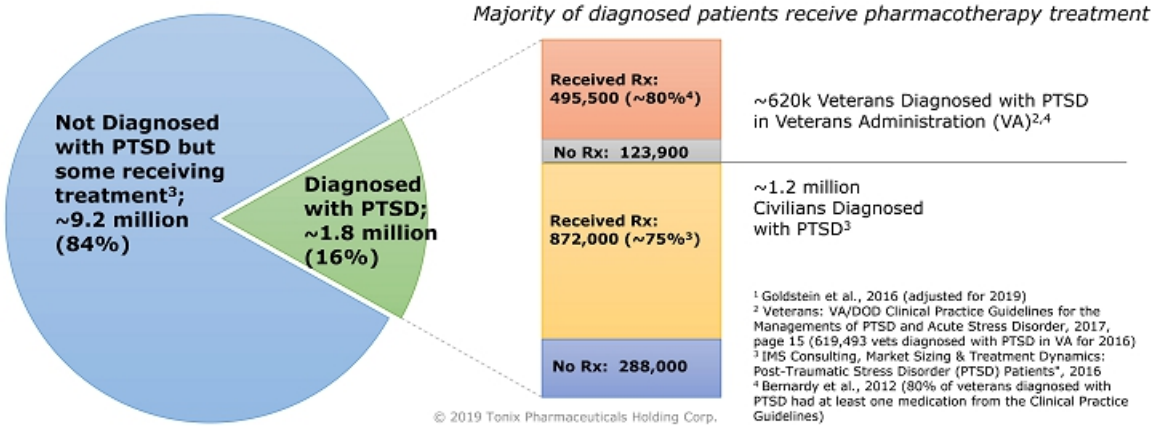
[1] Goldstein et al., 2016 (adjusted for 2019); [2]Norris, PTSD Res Quar. 2013;
[3]Analysis of VA Health Care Utilization among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans, from 1st Qtr FY 2002 through 2nd Qtr FY 2015, Washington, DC; Among 1.9M separated OEF/OIF/OND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

# PTSD Prevalence and Market Characteristics



**Prevalent Population with PTSD (U.S.)**
**~12 million[1]** (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 PTSD[3]

[1] Goldstein et al., 2016 (adjusted for 2019)
[2] Veterans: VA/DOD Clinical Practice Guidelines for the Managements 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)

# Unmet Need for Effective and Safe Therapies for Treatment of Military PTSD



**PTSD is signature wound of last 25 years of war**

- Affects servicemember health and performance, force readiness, retention
- Believed to be the underlying cause of suicide in many cases

**No FDA-approved products for PTSD since Pfizer's Zoloft® (sertraline) and GSK's Paxil® (paroxetine) circa 2000**

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

**U.S. Department of Defense (DoD) is working to understand and treat PTSD**

- Increased scrutiny of PTSD-related discharges for behavioral problems
- Wider recognition that PTSD is a service-related disability

# Tonmya: a Potential Bedtime Treatment for PTSD



**First investigational new drug to show treatment effect in military-related PTSD in two potential pivotal efficacy studies**

- Phase 2 study (P201/AtEase) showed Tonmya 5.6 mg had a strong signal of treatment effect at Week 12 as measured by CAPS-5[1]
- 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 Tonmya NDA submission
- No serious or unexpected adverse events related to Tonmya were reported

**FDA feedback and acceptance on new Phase 3 study (P302/RECOVERY) received in November 2018[2]**

[1] CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
[2] FDA Meeting Minutes, November 26, 2018

# Potential Therapeutic Advantages of Tonmya



**Tonmya 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
- Tonmya is believed to normalize memory processing and facilitate extinction consolidation (breaking the link between "triggers" and PTSD symptoms)

**Tonmya is *NEITHER* a benzodiazepine nor a narcotic**

- The active ingredient of Tonmya, cyclobenzaprine, does **NOT** interact with the same receptors as traditional hypnotic sleep drugs associated with retrograde amnesia; is **NOT** an opiate

**Tonmya is non-addictive**

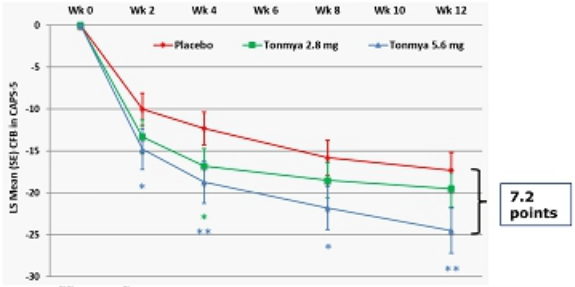
- Cyclobenzaprine is the active ingredient of an orally ingested immediate release tablet (Flexeril®), approved 40 years ago
- Flexeril's current labeling indicates no abuse and dependence concern at higher doses than Tonmya (15-30 mg/day v. 5.6 mg/day); NDA can be filed without drug abuse and dependency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

**Once-daily sublingual dose taken at bedtime enhances patient adherence**

# Tonmya Phase 2 Dose-Effect in Military-Related PTSD[1]

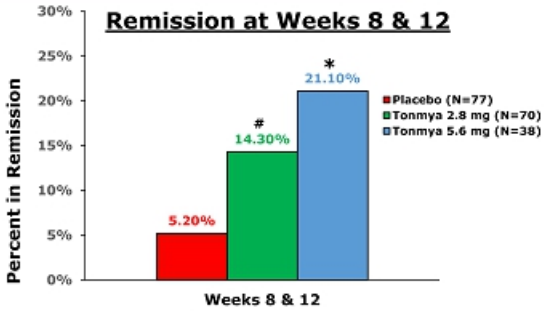


## PTSD Symptoms (CAPS-5[2] Score)




** p<0.01, * p<0.025, Tonmya 5.6 mg group with placebo, MMRM with multiple imputation (MI); #p=0.018, Tonmya 2.8 mg group with placebo, MMRM with MI

## Remission at Weeks 8 & 12




Remission = Loss of Diagnosis and CAPS-5 < 11
Asterisk and hashmark represent pairwise comparisons between Tonmya and Placebo; #p=0.08, Odds Ratio 3.01 (0.89, 10.18)
*p=0.02, Odds Ratio 4.60 (1.27, 16.66); logistic regression

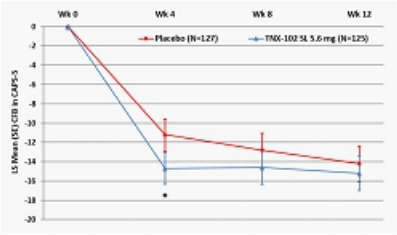
[1] Completed Phase 2 P201/AtEase study: Retrospective analysis of Tonmya 5.6 mg on CAPS-5 ≥33 (high-moderate) subgroup. Primary analysis of P201/AtEase, based on Tonmya 2.8 mg in participants with entry CAPS-5 ≥29 (moderate PTSD severity), was not statistically significant.
[2] CAPS-5 = Clinician administered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

# Primary Outcome (CAPS-5) in Phase 3 (mITT) and ≤9 Years Time Since Trauma Subgroups



## Phase 3 P301/HONOR Study[1]

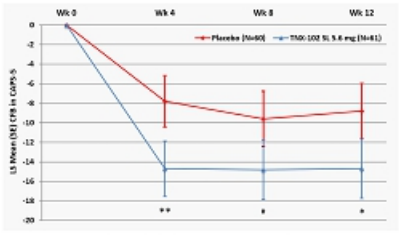
### Modified intent to treat (mITT) population




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

~50% mITT Population

### *Time Since Trauma (TST) ≤9 yrs*

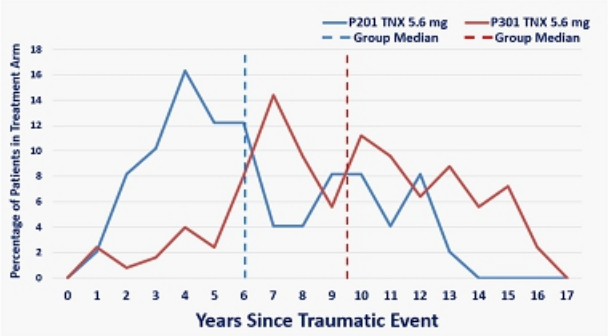



**p=0.004, *p=0.039, *p=0.069, TNX-102 SL 5.6 mg group v. placebo, using MMRM with MI

[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 (Tonmya 5.6 mg Groups)






**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

# Sustained Remission in Phase 2 and Phase 3 Studies:
## Retrospective Analyses of P201 Entry CAPS-5 ≥33 and P301 ≤9 Years Since Trauma Subgroups

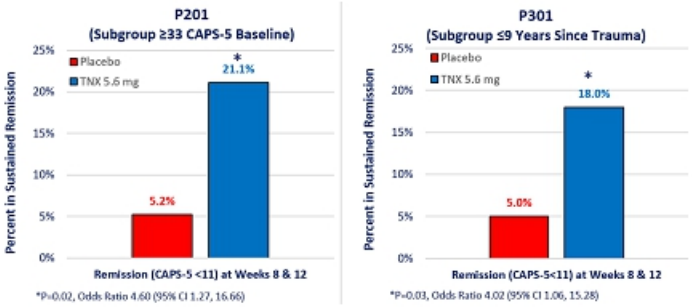


**Remission is a clinical state that is essentially asymptomatic**

**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 P201[1]**




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

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



| Category of Adverse Reaction<br>Preferred Term | P201<br>Placebo (N=94) | P201<br>TNX 2.8 mg (N=93) | P201<br>TNX 5.6 mg (N=50) | P301<br>Placebo (N=134) | P301<br>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*# | | | | | |
| Hypoaesthesia 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 Tonmya**

- 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

# Response to Tonmya for Female Participants in P301/HONOR Study[1]



**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 Tonmya 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 Tonmya 5.6 mg likely in mixed civilian and military PTSD population to be studied in upcoming 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 Tonmya for Non-Combat Traumas in P301/HONOR Study in ≤9 Years Time Since Trauma Subgroup[1]



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

**To determine the therapeutic effects of Tonmya 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, Tonmya 5.6 mg N=10):**

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

**Non-combat traumas treated with Tonmya 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 Tonmya**

[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

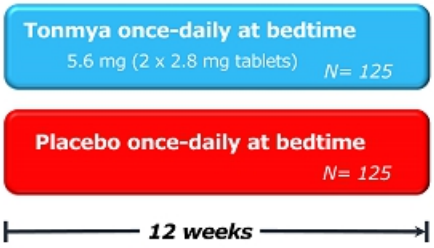
CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; MCFB = mean change from baseline; mITT = modified Intent-to-Treat sample; TST = time since trauma

# New Phase 3 P302/RECOVERY Study – Initiated 1Q 2019



## General study characteristics:

- Randomized, double-blind, placebo-controlled study with baseline CAPS-5[1] ≥ 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




## Primary endpoint:

- CAPS-5[1] mean change from baseline at Week 4 (Tonmya 5.6 mg vs. placebo)

## Key Secondary endpoints include:

- CAPS-5 mean change from baseline at Week 12 (Tonmya 5.6 mg vs. placebo)
- Change from baseline Clinical Global Impression – Severity scale
- Change from baseline Sheehan Disability Scale total score

**Potential pivotal efficacy study to support NDA approval**

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

# Late-Stage PTSD Drug Candidates



## Tonmya

- Phase 3 development focused on military-related and civilian PTSD; showed activity in treatment of military-related PTSD in large multi-center trials

## MDMA-assisted psychotherapy

- Indication – "drug assisted psychotherapy"
- Breakthrough therapy that is Phase 3-ready; showed activity in a Phase 2 study of PTSD; enrolling in Phase 3 study

## Other drugs currently (or recently) in Phase 2 development

- Rexulti® (brexpiprazole) - Otsuka/Lundbeck; atypical antipsychotic; positive clinical results from Phase 2 study reported in November 2018 for brexpiprazole, when used in combination with an approved PTSD medication, sertraline, but not as monotherapy
- NYX-783 - Aptinyx; NMDA receptor modulator (enrolling for 8-week Phase 2 study of 144 patients using 50 mg either once daily or once weekly)
- BNC-201 – Bionomics; nicotinic receptor modulator (program planned to resume after reformulation)

# Opportunities to Expand to Other Indications



**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
- Anxiety Disorders

**Psychiatric Symptoms of Neurological Disorders**
- Agitation in Alzheimer's
- Psychosis in Parkinson's, Alzheimer's and other dementias

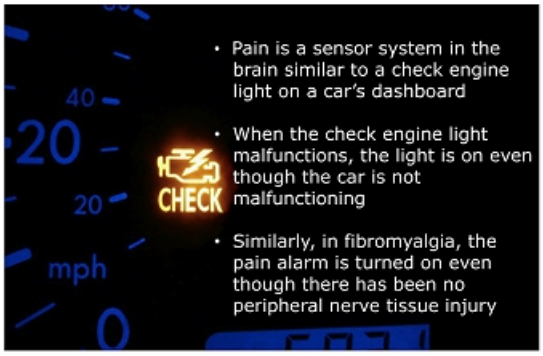
**Chronic Pain States**
- Chronic wide-spread pain (fibromyalgia)
- Osteoarthritis

**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*

# Fibromyalgia is a Chronic, Debilitating Disorder that Imposes a Significant Societal and Economic Burden






*Volkswagen Check Engine (Photograph). (2011, October 14). Wikipedia*

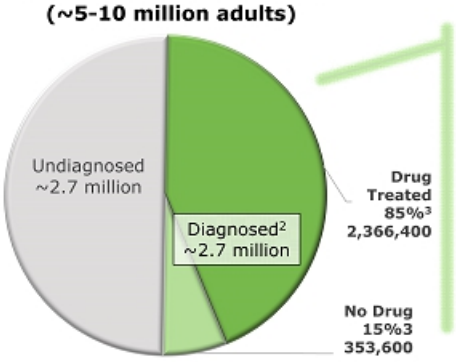
- Fibromyalgia is considered a neurobiological disorder characterized by[1]: chronic widespread pain, non restorative sleep, fatigue, diminished cognition
- Believed to result from inappropriate pain signaling in central nervous system in the absence of peripheral injury[1]
- Causes significant impairment in all areas of life[2]
  - 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 year[3]
  - Annual direct medical costs are twice those for non-fibromyalgia individuals[4]

[1] Phillips 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.

# Fibromyalgia: Market Characteristics



**U.S. Prevalence Rate 2-4%[1]**
**(~5-10 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/patient[3]
- Rotation through therapy common: average ~5 drugs/year[3]
- Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[4,5]

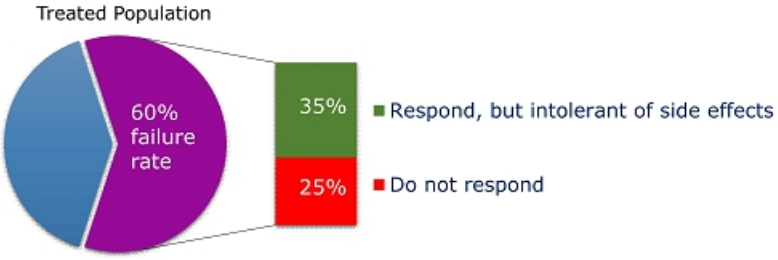
**Unmet Need**
- Majority of patients do not respond or cannot tolerate therapy[6]

1. American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
2. Vincent et al., 2013; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population
3. Robinson, et al., 2012; 85% received drug treatment
4. Vincent et al, Arthritis Care Res 2013;65:786
5. Product sales derived from IMS MIDAS; IMS NDTI 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 Sustained Benefit from the Three FDA-Approved Drugs[1]



- 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



- Currently-approved medications may have side effects that limit long-term use[1]
  - 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 simultaneously[2]
  - The typical patient has tried six different medications[3]
- Substantial off-label use of narcotic painkillers and prescription sleep aids[3]
  - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment[4]
- 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 for Fibromyalgia: Summary of a completed Phase 3 F301 study



**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
- 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-F Function Domain, Daily Sleep Quality Diary, PROMIS Sleep Disturbance

**Efficacy results:**

- mITT population: 425 (81.9%) of 519 patients
- The primary analysis was not statistically significant. However, retrospective analysis showed average pain improvement (secondary endpoint) after 12 weeks of treatment showed statistical significance ($P<0.05$, MMRM)
- Significant improvements observed in sleep quality, patient global impression of change and fibromyalgia-specific measures (secondary analyses).

# TNX-102 SL for Fibromyalgia: F301 Study Results and Program Updates



**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:
  - hypoaesthesia (tongue or oral numbness)
  - glossodynia (burning sensation or other tongue discomfort)
  - oral paraesthesias (tingling sensations)
  - abnormal product taste (bitter or noticeable taste)
- The severity and incidence of oral AE are similar to those reported in our PTSD studies using TNX-102 SL 5.6 mg.

**Conclusion:**

- The promising results and highly relevant efficacy findings support further investigation of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) as a chronic treatment for FM.

**Program updates:**

- Clear guidance and support received from FDA* to advance the FM program. The long-term safety exposure data from the PTSD program may support the fibromyalgia NDA*.
- 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

# TNX-102 SL: Potential Treatment for Agitation in Alzheimer's Disease (AAD)



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

- Includes emotional lability, restlessness, irritability and aggression[1]

**Link between disturbed sleep and agitation in Alzheimer's[1-3]**

- 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 2050[4]

**FDA-designated Fast Track development program**

**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 approval[5]**

[1]Rose, K.et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias, 30*:78
[2]Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association, 18*, 396.
[3]Canevelli, M., et al. (2016). *Frontiers in medicine, 3*.
[4]The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: https://www.alz.org/facts/
[5]FDA comments on final protocol received October 2018

# New Addition to Tonix's Pipeline: TNX-1300* for the Treatment of Cocaine Intoxication



**Recombinant protein that degrades cocaine in the bloodstream[1]**

- Double-mutant cocaine esterase

**In-licensed from Columbia University (Univ. of Kentucky and Univ. of Michigan)**

**Phase 2 study completed by Rickett Benckiser (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 (incl dry mouth, nausea); nervous systems disorders (incl headache, dizziness) and skin and subcutaneous tissue disorders (incl hyperhidrosis, dermatitis)

**TNX-1300 for the treatment of cocaine intoxication has U.S. FDA Breakthrough Therapy designation (BTD)**

**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.

# About TNX-1300



**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 plants[1]
- The gene encoding CocE was identified and the protein was extensively characterized[1-3]
- 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 temperature[4]

[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



**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.*

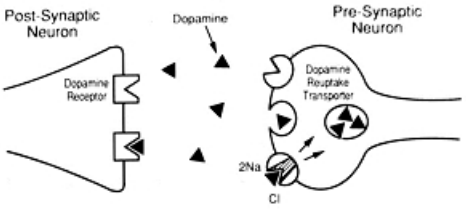
**Cocaine intoxication:** deleterious effects on the body, especially cardiovascular system.

- 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.

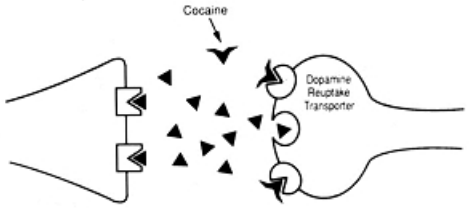
# Cocaine Action



- **Cocaine acts to inhibit the Dopamine Reuptake Transporter**
  - Binds to transporter and blocks reuptake of dopamine from synapse



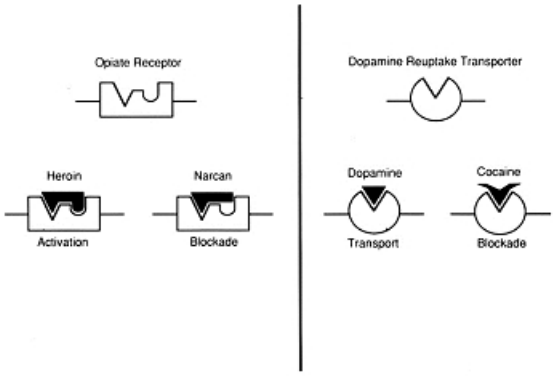

- **No antagonist has been developed for cocaine**
  - Unlike situation for opiates which can be blocked by naloxone ("Narcan") or naltrexone



# Cocaine Action – Lack of "Antidote"

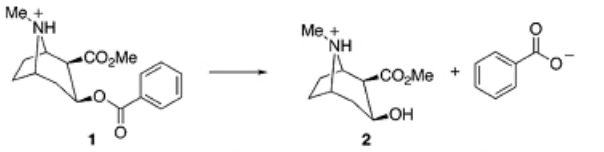


- **Cocaine binding site on Dopamine Reuptake Transporter is too small or simple for a blocker**
  - Antagonists of cocaine binding have the same function as cocaine
- **Naltrexone exploits the complexity of the opiate binding site**
  - Addictive opiates are "agonists", which means their binding and activity can be dissected by antagonists like naloxone



# CocE is a Catalyst that Breaks Cocaine Down into Less Toxic Metabolites[1-4]






Cocaine | Ecgonine Methyl Ester | Benzoic Acid

- Metabolites ecgonine methyl ester and benzoic acid are neither pleasurable nor addictive

[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.

# 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 year[1]

- 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.

# Mortality Due to Cocaine Overdose



**Cocaine is involved in 20% of overdose deaths in the U.S.**

- In 2016, 10,375 deaths due to cocaine overdose[1]
- In 2017, about 13,900 deaths occurred in the U.S. due to cocaine overdose.[2]

**Overdose deaths involving cocaine increased 34% from 2016 to 2017.** [3,4]

[1] Overdose Death Rates - National Institute on Drug Abuse - https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates; accessed May 11, 2019
[2] Kariisa M et al. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. *MMWR Weekly* / May 3, 2019 / 68(17);388–395 - https://www.cdc.gov/mmwr/volumes/68/wr/mm6817a3.htm?s_cid=mm6817a3_w;
[3] Cocaine deaths up in U.S. and opioids are a big part of it. Associated Press. https://www.msn.com/en-us/news/us/cocaine-deaths-up-in-us-and-opioids-are-a-big-part-of-it/ar-AAAOxs8?ocid=se; accessed May 11, 2019
[4] Fottrell, Q. MarketWatch, Fatal drug overdoses involving cocaine and other stimulants have surged by over 52%, May 3, 2019 - https://www.marketwatch.com/story/fatal-drug-overdoses-involving-cocaine-and-other-stimulants-have-surged-by-over-52-2019-05-03; accessed May 11, 2019

# Treatment for Cocaine Intoxication



## Current Standard of Care

- Patients present with acute agitation, hyperthermia, tachycardia, arrhythmias, and hypertension
- Potential life-threatening sequalae 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
- FDA Breakthrough Therapy Designated product
- 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

# TNX-601 (Tianeptine Oxalate): A Potential Clinical Candidate for PTSD



**Pre-IND Candidate**

**Targeting a Condition with Significant Unmet Need**

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

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

- Tianeptine sodium (amorphous), first marketed for depression in France in 1989, is approved as an antidepressant in the EU, Russia, Asia and Latin America; established post-marketing experience
- Identified new oxalate salt with improved pharmaceutical properties ideal for reformulation
- Preliminary human pharmacokinetic and safety data (non-IND study) from selected formulation expected in second half 2019

**Filed patent application on novel salt**

- Issued patent on steroid-induced cognitive impairment and memory loss issues

**Clinical evidence for PTSD**

- Several studies have shown tianeptine to be active in the treatment of PTSD[1-4]

[1] Frančišković 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] Aleksandrovskiĭ IA, et al. Zh Nevrol Psikhiatr 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

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



**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.

# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT X · Fusilev (levoleucovorin) for injection · vela

**Gregory Sullivan, MD**
Chief Medical Officer

Columbia University Department of Psychiatry · New York State Psychiatric Institute

**Bradley Saenger, CPA**
Chief Financial Officer

Shire · VERTEX · Steward · pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank · svb Silicon Valley Bank · American Capital

# Board of Directors



| | |
|---|---|
| **Seth Lederman, MD**<br>Chairman | **Gen. David Grange (U.S. Army, ret.)**<br>Pharm-Olam, PPD, McCormick Foundation |
| **Margaret Smith Bell**<br>Standard Life Investments, Putnam Investments, State Street Research | **Adeoye "Oye" Olukotun, MD**<br>Squibb, BMS, Mallinckrodt, Esperion |
| **Daniel Goodman, MD**<br>Psychiatrist, co-founder Psychogenics | **John Rhodes**<br>Chair, NYS Public Service Commission, CEO, NYS Dept. of Public Service, Booz Allen |
| **Patrick Grace**<br>(qp) global family offices, Grace Institute Foundation, WR Grace, Chemed | **James Treco**<br>First Chicago, Salomon Brothers/Citigroup |

# Milestones – Recently Completed and Upcoming



| | |
|---|---|
| ☑ July 2018 | Completed P301/HONOR study interim analysis - result did not support study continuation but strengthened new Phase 3 study |
| ☑ August 2018 | Presentation of P301/HONOR study results at Military Health System Scientific Symposium |
| ☑ October 2018 | Met with FDA and received preliminary agreement on the design of new Phase 3 study of Tonmya for PTSD (P302/RECOVERY study) |
| ☑ November 2018 | Received FDA minutes confirming agreement on the design of P302/RECOVERY study |
| ☑ March 2019 | Met with FDA to discuss new FM Phase 3 study design using TNX-102 SL 5.6 mg |
| ☑ March 2019 | P302/RECOVERY study initiated |
| ☑ April 2019 | Received FDA formal minutes with clear guidance and support on new Phase 3 FM study |
| ☑ May 2019 | In-licensed TNX-1300, BTD product in Phase 2 development for cocaine intoxication |
| ☐ Second Half 2019 | Preliminary human pharmacokinetic and safety data (non-IND study) from selected TNX-601 (tianeptine oxalate) formulation expected |
| ☐ First Half 2020 | Topline data from P302/RECOVERY study expected |

# Summary



**Two Phase 3 Programs in indications affecting millions of Americans**

- Tonmya for PTSD: affects 12 million adults in U.S.; currently in Phase 3 with data expected next year; bedtime treatment
- TNX-102 SL for Fibromyalgia: affects between 5-10 million adults in U.S.; ready for Phase 3

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

- TNX-102 SL for Agitation in Alzheimer's Disease: Fast Track designation; ready for Phase 2/3
- TNX-1300 for Cocaine Intoxication: biologic and new molecular entity with Breakthrough Therapy designation; ready for Phase 2

**Pipeline products to improve biodefense and leverage PTSD expertise**

- TNX-801: smallpox-preventing vaccine in preclinical development; demonstrated protective vaccine activity in mice; GMP viral production process in development
- TNX-701: oral radioprotection drug in preclinical development; demonstrated radioprotective effect in mice
- TNX-601: tianeptine oxalate in formulation development for daytime treatment of PTSD

TONIX PHARMACEUTICALS

NASDAQ: TNXP

*Thank you*!