Efficacy and Safety of a Low Dose, Bedtime, Proprietary, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL#) for the Treatment of Military-Related PTSD: Study Protocol of a Phase 3 Randomized Placebo-Controlled Trial (P301)

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#TNX-102 SL is an investigational new drug and has not been approved for any indication

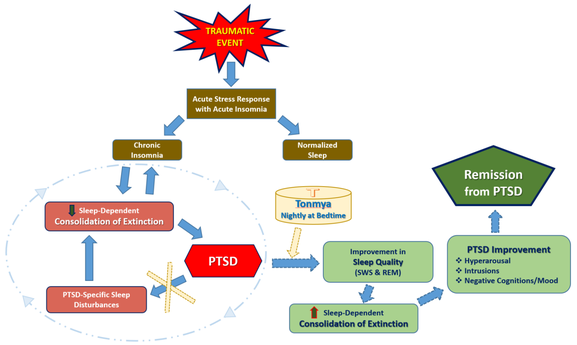
INTRODUCTION

Posttraumatic stress disorder (PTSD) is one of the most prevalent and disabling psychiatric conditions afflicting US Warfighters and is associated with symptom clusters of hyperarousal, re-experiencing (intrusion) phenomena, blunted mood and negative cognitions, and behavioral avoidance. Only two medications, both selective serotonin reuptake inhibitor (SSRI) antidepressants, have received Food and Drug Administration (FDA) approval for treatment of PTSD, in 1999 and 2001, respectively. A crisis has been declared by experts in the field in the development of evidence-based pharmacotherapy treatments for PTSD,[1] because since 2001 there has been no new pharmacological treatment approved by the FDA for PTSD. In the same period between 2001 and present, over 2.7 million military personnel served tours of duty in Iraq and Afghanistan.

In recent years, Tonix Pharmaceuticals has made substantial progress towards developing TNX-102 SL or Tonmya®#, a proprietary sublingual formulation of the tricyclic molecule cyclobenzaprine or TNX-102, as a bedtime medicine for the treatment of PTSD. TNX-102 potently binds to and antagonizes 5-HT_{2A}, α_1-adrenergic, and histamine-1 (H_1) receptors, each of which play roles in sleep regulation and nocturnal memory processing. The sublingual route results in rapid transmucosal absorption to blood and avoids first pass hepatic metabolism, reducing exposure to its active long-lived major metabolite, norcyclobenzaprine.

PTSD has come to be understood as a "disorder of recovery" in which new learning is impeded due to insufficient sleep-dependent memory processing, e.g. consolidation of extinction memory.[2] Vulnerability to memory intrusions and trauma-associated triggers continues if new extinction memory *consolidation* does not occur in sleep. Via sleep-period blockade of 5-HT_{2A}, α_1-adrenergic, and H_1 receptors, TNX-102 is hypothesized to enhance the sleep quality necessary for sleep-dependent recovery processes to occur (**Figure 1**).

Figure 1: Mechanistic Hypothesis for TNX-102 Action in PTSD



REM, rapid eye movement sleep; SWS, slow wave sleep

Proof of concept for TNX-102 SL in the treatment of PTSD was supported by results of a multicenter Phase 2 trial in military PTSD, P201/the "AtEase" Study, the results of which were announced in 2016 (**See Figure 2**: Highlights of the AtEase Study). Based on the Phase 2 results, TNX-102 SL was granted Breakthrough Therapy designation by the FDA for the treatment of PTSD. The Phase 3 study (P301/the "HONOR" Study), which is of similar design to AtEase, initiated enrollment in March 2017 to confirm the efficacy and safety of TNX-102 SL 5.6 mg in participants with military-related PTSD (**See Figure 3**).

Tonmya has been conditionally accepted by the FDA as the proposed trade name for TNX-102 SL (cyclobenzaprine HCl sublingual tablets) for PTSD

METHODS

- HONOR is a 12-week, multicenter, randomized, double-blind, placebo-controlled trial, investigating a fixed-dose of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken at bedtime for the treatment of military-related PTSD at 35 U.S. sites.
- Eligible participants (males/females) ages 18-75 years, experienced DSM-5 PTSD Criterion A-qualifying trauma(s) during military service since 2001; meet PTSD criteria as diagnosed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5); have an entry CAPS-5 severity score ≥ 33, not on antidepressants, and free or washed off other psychotropic medications.

Figure 2: Highlights of Phase 2 AtEase Results Supporting the Phase 3 HONOR Study

- **TNX-102 SL 5.6 mg significantly reduced CAPS-5 score greater than placebo over 12-weeks by mixed-effects models repeated measures analysis (MMRM) with multiple imputation (p=0.031)**
- **Effect of TNX-102 SL 5.6 mg was preserved in the 85% of the sample with PTSD due to combat traumas (p=0.037, MMRM)**
- **CAPS-5 entry threshold of ≥33, rather than ≥29, was more similar to the entry threshold used in prior registration studies for PTSD using earlier versions of CAPS**
  - **Entry CAPS-5 ≥33 subsample in AtEase had effect size 0.53 supporting entry CAPS-5 ≥33 for the Phase 3 HONOR Study**
- **Correlation between improvement in sleep by week 4 of trial with week 12 improvement in PTSD by CAPS-5 supported hypothesis that treatment effects of TNX-102 SL in PTSD are medicated by changes in sleep**
- **TNX-102 SL 5.6 mg was well-tolerated with a high completion rate and no AE-related discontinuations; non-dose-related tongue numbness was common, generally transient, and never rated as severe. Systemic adverse events profile is consistent with marketed cyclobenzaprine orally-ingested products.**

- Approximately 550 participants will be randomized in a 1:1 ratio to placebo or TNX-102 SL 5.6 mg.
- The primary efficacy endpoint is mean change from baseline (MCFB) in CAPS-5 score at Week 12. Secondary endpoints include CGI-I score, the Sheehan Disability Scale (SDS), and PROMIS Sleep Disturbance scale.
- Safety monitoring includes following adverse events, changes from baseline in clinical labs, vital signs, and weight, changes on the Beck Depression Inventory-II and Columbia Suicide Severity Rating Scale, as well as monitoring patient-rated morning sedation and changes in sexual function.
- Participants' identities are protected under a Certificate of Confidentiality (CoC) provided by the FDA under the authority of Health and Human Services (HHS) for research conducted as part of IND 115936 by Tonix Pharmaceuticals and its contractors.

Sample Size and Interim Analysis: Sample size was determined using P201/"AtEase" efficacy data assuming an ~25% dropout rate. Using a two-sided test with an alpha of 0.05, a sample size of 275 per group provides a power of ~90% if the true effect size is 0.32. Yet, the effect size in AtEase for the subsample with entry CAPS ≥ 33 was 0.53, and this is the severity threshold for entry being used in the HONOR Study. If the true effect size is 0.53, again with a dropout rate of ~25%, a sample size of 105 per group provides a power of ~90%. Therefore an adaptive design was chosen for HONOR in which an interim analysis to reassess sample size and for stopping early for success will be performed 12 weeks after 50% of the subjects have been randomized. An independent unblinded analysis group will perform this analysis, and an independent data monitoring committee will make a recommendation based on the unblinded interim analysis results.

CAPS-5 Rater Training, Certification, Inter-Rater Reliability: For training and certification, the following is completed under supervision of Frank Weathers PhD (CAPS-5 author and expert):
Attend Didactic Talks: potential raters attend didactic sessions, provided at the IM, along with small group breakout training using CAPS-5 interview role playing with scripted patient symptoms.
Calibration Training: potential raters complete online calibration exercises that involve achieving a passing rating of a CAPS-5 interview. (Passing requires <6 1-pt difference and no > 1-pt differences from expert. Up to three calibration attempts on different interviews are allowed to pass.
Mock Interview: potential raters administer the CAPS-5 on a mock PTSD patient (scripted symptoms), complete the scoring procedures, and submit audio file/score sheet for expert review. By successfully completing all tasks, rater receives CAPS-5 rater certification from Dr. Weathers.
Inter-Rater Reliability (IRR): ≥10% of all CAPS-5 audiotaped interviews are sampled for IRR throughout study.

Trial Information: https://theHONORstudy.com/

Figure 3: Phase 3 HONOR Study is Enrolling

- **To confirm Phase 2 AtEase findings in military-related PTSD:**
  - Larger adaptive design study
  - Enrollment started in 1Q 2017

Tonmya once-daily at bedtime
5.6 mg N ~ 275 (140*)

Placebo once-daily at bedtime
N ~ 275 (140*)

12 weeks ····· *open-label extension*

* Interim analysis

1H 2018 - IA outcome anticipated
2H 2018 – topline data anticipated, if 550 participants are studied

- **General study characteristics:**
- Randomized, double-blind, placebo-controlled, entrance CAPS-5 ≥ 33
- One unblinded interim analysis (IA) by an independent data monitoring committee at 50% randomized
- IA (N ~275) for efficacy stop, continuation as planned or sample size adjustment
- Potential to enroll 550 participants
- Approximately 35 U.S. clinical sites
- **Primary efficacy endpoint:**
- Mean change from baseline in total CAPS-5 at Week 12 compared between Tonmya 5.6 mg and placebo

MEDIATING RECRUITMENT CHALLENGES

Overcoming concerns about confidentiality: The CoC provides significant protection, but it is important to disseminate this information to prospective participants early in recruitment process, at prescreening.
Conveying the "mission" of this research: The military population is unique in the high level of altruism common to most, genuinely choosing to enroll in research for the purpose of helping determine if a drug may be efficacious and safe for the future treatment of PTSD in their military "brothers and sisters" and Country. Understanding this mission tends to be motivating and is conducive to *accurate reporting* of symptoms and change, as this offers the best chance to learn if a drug in a double-blind study is effective.
Providing access to the experimental treatment for all: The HONOR Study is followed by a 12-week open-label extension trial of TNX-102 SL 5.6 mg (P303). Prospective double-blind study participants almost invariably want to know how the experimental treatment may or may not work for them. Awareness there is 100% chance of receiving TNX-102 SL after completing 12 weeks of double-blind treatment (50% chance of getting TNX-102 SL) is encouraging for taking on the mission.
Adapting to the demographics of a military/Veteran population: The AtEase Study provided important demographics specific to this population. For example, 84% had some college or beyond, with many in school during the study; and 62% were employed, making daytime site visits difficult for many. This taught the importance for sites to provide flexible visit hours, offering evenings and/or weekend visits when needed. Minimizing visits, assessment time, and burden was also a priority in the design of HONOR.
Respecting the sensitivity of traumatic memories and the difficulties in being forthcoming: Participating in CAPS-5 interviews can be painful, is potentially destabilizing, and recalling traumas and associated morbidity is often among what is most ardently avoided in PTSD. Providing privacy, uninterrupted attention, and respect for the great efforts being made by participants during the CAPS-5 interviews was identified as essential for establishing a collaborative relationship and likely a significant factor in retention.
Appreciating the major differences in military culture: At a minimum, site staff need to be aware of the marked difference in military culture, and, for those without military experience or significant military cultural competence training, that most assumptions are likely to be incorrect and potentially alienating. Emphasis on these differences and how to avoid pitfalls in interactions with military/Veterans is provided to sites at the IM, with encouragement for training (suggested: www.deploymentpsych.org/military-culture).

CONCLUSIONS

- The 'HONOR' study is an ongoing, FDA-registration quality, randomized placebo-controlled Phase 3 trial to confirm the efficacy and safety of TNX-102 SL 5.6 mg taken daily at bedtime as a potential pharmacotherapy for the treatment of PTSD.
- In addition to centralized rater training to ensure proper administration of CAPS-5 interview, ensuring confidentiality, understanding the barriers to seeking treatment and unique demographics, and appreciating the differences in military from civilian culture are essential features for recruiting and retaining a population with military-related PTSD.
- Results of the interim analysis are expected in the first half of 2018, and results from complete enrollment, if necessary, are expected in the second half of 2018.

CITATIONS

[1] Krystal JH, et al. *Biol Psychiatry*. 2017 Mar 14. [Epub ahead of print]: [2] Pace-Schott, et al. Biology of Mood & Anxiety Disorders. 2015;5:3.

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