Bedtime Sublingual Transmucosal Cyclobenzaprine (TNX-102 SL) for the Treatment of Military-Related PTSD: Retrospective Analyses of the Mediators and Moderators of Treatment Response

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INTRODUCTION

Post traumatic stress disorder (PTSD) is one of the most prevalent and disabling psychiatric disorders in United State military personnel, and no treatment response has been observed in this population with the two FDA-approved medications for PTSD. The "AtEase Study" was a Phase 2 efficacy and safety trial of TNX-102 SL for military-related PTSD. TNX-102 SL is a patented sublingual tablet formulation of cyclobenzaprine designed for bedtime administration and rapid transmucosal absorption, which bypasses first-pass metabolism and has desirable parent and major metabolite pharmacokinetic profiles. The active ingredient in TNX-102 SL, cyclobenzaprine HCl, has potent 5-HT_{2A}-serotoninergic, α_1-adrenergic, and H_1-histaminergic receptor blocking properties and is hypothesized to improve global symptoms of PTSD through therapeutic effects on sleep disturbance and hyperarousal. TNX-102 SL is an investigational new drug and has not been approved for any indication. The FDA has recently granted Breakthrough Therapy designation for TNX-102 SL for the treatment of PTSD. The retrospective analyses presented here examine treatment response and remission to TNX-102 SL in military-related PTSD.

METHODS

AtEase was a multicenter, 12-week, double-blind placebo-controlled Phase 2 study. Inclusions: both sexes; ages 18-65; PTSD DSM-5 Criterion A trauma(s) during military service since 9/11/2001; current PTSD by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Baseline total CAPS-5 score ≥ 29; free of antidepressants ≥ 2 months; free of or washed off of other psychotropics; not participating in trauma-focused psychotherapy. Exclusions: serious suicide risk; substance use disorders within 6 months; lifetime bipolar psychotic, obsessive-compulsive, or antisocial personality disorders. Subjects were randomized in 2:1:2 ratio to TNX-102 SL 2.8 mg, TNX-102 SL 5.6 mg, Placebo at 24 U.S. sites; dynamic randomization (site, sex, current MDD). Primary efficacy analyses was comparison of mean change from baseline (MCFB) at Week 12 in CAPS-5 score between TNX-102 SL 2.8 mg and Placebo, mixed model repeated measures analysis (MMRM). Key 2◦ endpoints included: Clinical Global Impression–Improvement (CGI-I), Sheehan Disability Scale (SDS), PROMIS Sleep Disturbance (SD). Also: CAPS-5 clusters, Patient Global Impression of Change (PGIC). CAPS-5 raters ≥ Master's degree-level in mental health; rigorously trained/certified; and reliability monitoring over course of study.

RESULTS

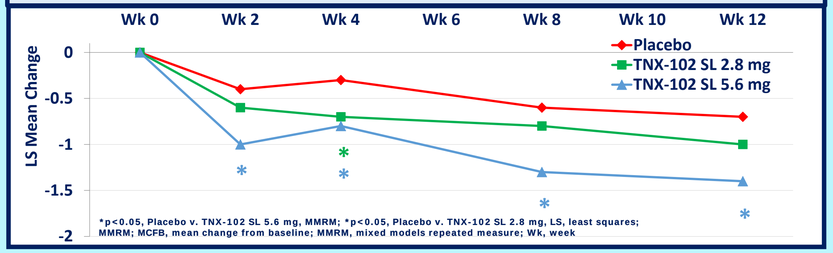
Topline Results: Of 245 participants randomized, 231 were included in the modified intent-to-treat (mITT) efficacy population. TNX-102 SL 2.8 mg dose (N=90) had a greater CAPS-5 change from baseline at Week 2 (mixed effects repeated measures, MMRM, p=0.040) and Week 4 (MMRM, p=0.030) but did not achieve a significantly greater CAPS-5 change from baseline at Week 12 (MMRM, p=0.259, NS) compared with placebo (N=92). TNX-102 SL 5.6 mg dose (N=49) had a strong trend (MMRM, p=0.053) for greater CAPS-5 change from baseline at Week 12 compared with placebo (N=92); effect size of 0.36 (Cohen's *d*). Pre-planned sensitivity analyses that accounted for missing data, as well as analysis of covariance (ANCOVA), showed statistically significant results for TNX-102 SL 5.6 mg v. placebo: MMRM with multiple imputation, p=0.031; MMRM with hybrid last observation carried forward (LOCF)/baseline observation carried forward (BOCF) imputation, p=0.037; and ANCOVA, p=0.038.

The CAPS-5 Arousal & Reactivity cluster was significantly improved for the 5.6 mg dose, as were global measures (CGI-I, PGIC), and work and social domains on the SDS. The CAPS-5 sleep disturbance item (E6) was significantly more improved in the 5.6 mg arm over placebo early by Week 2 and maintained at all other assessments (**Figure 1**); the 2.8 mg arm at Week 4 only. In contrast, the CAPS-5 exaggerated startle item (E4) in the 5.6 mg arm improved late, significantly so by Week 12. The most commonly reported adverse event was the administration site reactions of oral hypoaesthesia (tongue numbness). Systemic adverse events, consistent with marketed cyclobenzaprine orally ingested products, higher than placebo included somnolence, dry mouth, headache, and sedation (**Table 3**). Despite marginally increased rates of these systemic AEs in the 5.6 mg arm, 84% completed the study, and no TNX-102 SL 5.6 mg treated participants discontinued due to AE.

Retrospective Analysis of Sleep as a Potential Mediator of Treatment Response: Recovery in PTSD is generally understood to be a new learning process involving extinction learning. Consolidation of extinction, in which short term memory is processed to become long term memory, occurs during sleep, with processing roles for both slow wave sleep (SWS) and rapid eye movement sleep (REM). It is hypothesized that restoration of *quality* of critical sleep stages may be permissive to consolidation of extinction memory and thereby allow normal recovery over several weeks. As seen in **Figure 1**, sleep responded early in treatment with TNX-102 SL. A more comprehensive measure of sleep quality, the PROMIS SD instrument, an 8-item self-report of sleep quality and disturbance, was administered on Weeks 4, 8 and 12.

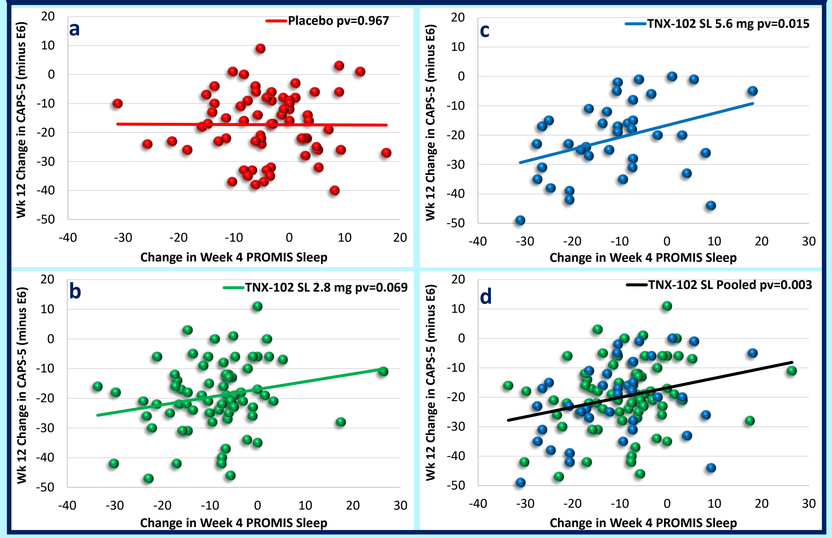
To better understand the relationship between early response in sleep and improvement in PTSD at Week 12, a retrospective analysis examined the relationship between PROMIS SD T-scores at Week 4 and change in PTSD severity by Week 12 in completers in the three treatment groups. To avoid co-linearity effects between these two variables, Week 12 CAPS-5 total change from baseline *without* the sleep item (E6) was used. The regression model included treatment, sleep, and treatment by sleep interaction.

Figure 1. CAPS-5 Sleep Disturbance Item (E6) MCFB



Week 4 sleep and treatment response were not related among placebo participants (Figure 2a) whereas for 2.8 mg there was a trend for a positive relationship (Figure 2b). Consistent with the hypothesis that the PTSD response from TNX-102 SL is mediated by its direct effects on sleep quality, it may be seen the strongest positive relationship for the two variables was found in the 5.6 mg group (Figure 2c). Combining the two TNX-102 SL groups afforded the most power, showing the most significant effect (Figure 2d) with a slope intermediate between the two groups individually. Thus, early sleep response at Week 4 predicted Week 12 improvement in PTSD severity in the TNX-102 SL groups but not in placebo.

Figures 2a-d: Sleep Mediator of PTSD Treatment Response Week 4 Sleep Change v. Week 12 CAPS-5 Response

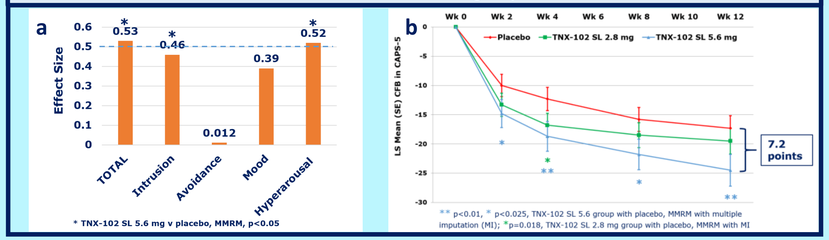


CAPS-5, Clinician-Administered PTSD Scale for DSM-5; E6, CAPS-5 sleep item; pv, p-value; Wk, week

Assessment of CAPS-5 Entry Threshold in AtEase: For inclusion, prior registration studies of approved PTSD pharmacotherapies required a baseline severity score of >50 on previous versions of CAPS. Those versions scored severity based on 17 items using DSM-III-R or DSM-IV criteria, each item rated on 0-4 for intensity & 0-4 for frequency (maximum possible score = 136). The AtEase protocol required CAPS-5 (20 items) severity of ≥29 for enrollment, derived by direct extrapolation from prior version threshold ((Score of 50/17 items)/2) x 20 items =29.4.

To compare the AtEase population with prior studies, we retrospectively imputed a CAPS for DSM-IV (iCAPS-IV) for each participant's baseline using the 17 common items and multiplying by 2. Using the iCAPS-IV, 4.3% of the sample were found to be ≤50 (range 44-50). Using instead a CAPS-5 ≥33 at entry, all of these participants were excluded as was about 20% of the AtEase population. The primary analysis of AtEase was next performed on the subgroup with CAPS-5 entry threshold ≥33. The CAPS-5 assessments MCFB are significant for TNX-102 SL 5.6 mg at all assessments at Weeks 2, 4, 8 and 12 (**Figures 3**). Week 12 comparison of TNX-102 SL 5.6 mg with placebo showed moderate effect sizes of about 0.5 for total CAPS-5 and the hyperarousal and intrusion clusters (**Figure 4**).

Figure 3: (a) Effect Sizes of Total CAPS-5 & Clusters and (b) Total CAPS-5 Mean Change from Baseline at All Assessments in CAPS-5 Baseline ≥ 33 Subgroup



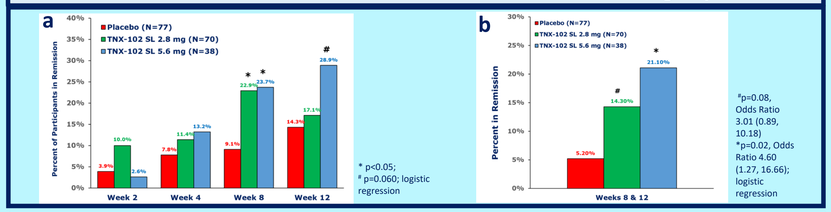
* TNX-102 SL 5.6 mg v placebo, MMRM, p<0.05

** p<0.01, * p<0.025, TNX-102 SL 5.6 group with placebo, MMRM with multiple imputation (MI); *p=0.018, TNX-102 SL 2.8 mg group with placebo, MMRM with MI

Remission from PTSD: Optimal outcome of treatment is achievement of remission, a virtually asymptomatic state. The definition of remission used in AtEase was "Loss of Diagnosis and Endpoint CAPS-5 Score <11". As seen in **Figure 4a**, by Week 8, there were significantly more remitters in both 2.8 mg and 5.6 mg groups. By week 12, the 5.6 mg group trended for higher rate than placebo (rates increased in both groups).

Sustained Remission from PTSD: Remission is more clinically meaningful if it is sustained. In order to look at sustained remission in AtEase, the rates of participants who met remission status at *both* Week 8 and Week 12 were determined (**Figure 4b**). 21% of the TNX-102 SL 5.6 mg participants met for sustained remission v. 5% of placebo (p=0.02).

Figure 4: (a) Remission Rates from PTSD at Each Assessment and (b) Sustained Remission at Both Weeks 8 & 12 in CAPS-5 Baseline ≥ 33 Subgroup



* p<0.05;
# p=0.060; logistic regression

#p=0.08, Odds Ratio 3.01 (0.89, 10.18)
*p=0.02, Odds Ratio 4.60 (1.27, 16.66); logistic regression

Table: Adverse Events (at rate of ≥5% in either drug-treated group)

	Placebo	TNX-102 SL 2.8 mg	TNX-102 SL 5.6 mg
Systemic Adverse Events	(N=94)*	(N=93)*	(N=50)*
Somnolence	6.4%	11.8%	16.0%
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%
Administration Site Reactions			
Hypoaesthesia oral[#]	2.1%	38.7%	36.0%
Paraesthesia	3.2%	16.1%	4.0%
Glossodynia	1.1%	3.2%	6.0%

[#]Oral hypoaesthesia (tongue numbness) was most common AE, generally transient (<60 minutes), and rated mild in 89% and moderate in 11% on TNX-102 SL; *Safety Population (N=237)

CONCLUSIONS

- Phase 2 clinical investigation established that TNX-102 SL 5.6 mg is the potential efficacious and safe dose to treat PTSD in a military-related PTSD population (TNX-102 SL 5.6 mg, N=49 v. placebo, N=92)
  - Established CAPS-5 ≥33 as entry threshold for Phase 3 studies to confirm AtEase findings
- Relationship between early sleep improvement and Week 12 PTSD recovery supports mechanistic hypothesis that improved sleep quality is a mediator of TNX-102 SL treatment response
- TNX-102 SL 5.6 mg treatment resulted in sustained remission between Weeks 8 and 12 in 21% of participants that was statistically significant relative to placebo and approximately 4X the rate in placebo in the CAPS-5 ≥33 subgroup (TNX-102 SL, N=38 v. placebo, N=77)
- Phase 3 clinical investigation of TNX-102 SL 5.6 mg in military-related PTSD is ongoing