A Retrospective Analysis of the Efficacy of TNX-102 SL in Military-Related PTSD: Determining the Appropriate Severity Threshold for Trial Entry Using the Clinician-Administered PTSD Scale for DSM-5

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Objective

The "AtEase" study was conducted to evaluate the safety and efficacy of TNX-102 SL^, a sublingual formulation of cyclobenzaprine HCl, in the treatment of patients with military-related posttraumatic stress disorder (PTSD). Cyclobenzaprine is a tricyclic molecule with potent binding and antagonist activity at three neuroreceptors known to be involved in sleep regulation: 5-HT_{2A}, α_1-adrenergic, and H_1-histaminergic receptors. TNX-102 SL is hypothesized to treat PTSD by targeting sleep disturbance, which in turn is permissive to critical sleep-dependent processing of emotional memories necessary for recovery from trauma. Efficacy in AtEase was assessed using the current version of the Clinician-Administered PTSD Scale (CAPS), which is based on the PTSD criteria in the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5), known as the CAPS-5. Considering major changes to the scoring system compared to prior versions of CAPS, a retrospective analysis was conducted to determine if the selected CAPS-5 severity threshold of ≥29 at baseline for study entry in AtEase was of comparable severity to the threshold of ≥50 in prior CAPS versions, which was the threshold in the registration studies of previously approved PTSD pharmacotherapies. Finding a higher entry score was more comparable, an efficacy analysis was reassessed on the AtEase subsample with the higher CAPS-5 severity threshold for entry.

Study Design and Analysis

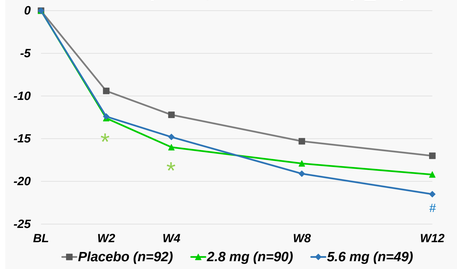
The AtEase study was a Phase 2, multicenter, 12-week, randomized double-blind, placebo-controlled trial in adults with military-related PTSD. Patients were randomized to TNX-102 SL 2.8 mg, 5.6 mg or placebo in a 2:1:2 ratio. The primary efficacy endpoint was the mean change from baseline (MCFB) in total CAPS-5 severity score at Week 12, analyzed using a mixed model repeated measures (MMRM) approach. To be eligible, participants must have experienced a PTSD DSM-5 Criterion "A"-qualifying trauma incurred during military service since 2001. The CAPS-5 severity score is calculated by summing scores of the first 20 items of the scale, which are each rated 0-4 based in both intensity and frequency of the symptom evaluated (maximum possible score of 80). A baseline CAPS-5 severity score ≥29 was also required for inclusion for the purpose of only enrolling patients with at least as severe PTSD symptoms as required in prior registration studies of approved PTSD pharmacotherapies. Those studies employed a prior version of the CAPS which had 17 items based on DSM-III-R or DSM-IV diagnostic criteria, and was scored by summing both the 0-4 intensity and 0-4 frequency scores for each item (maximum possible score = 136); the threshold for entry was ≥50. After completion of the present trial, an imputed CAPS for DSM-IV score (iCAPS-IV) was calculated for every patient using the 0-4 severity scores of the 17-items CAPS-5 has in common with CAPS-IV, and multiplying by 2 to account for the 0-8 intensity and frequency ratings for each CAPS-IV item (rather than the 0-4 score for intensity and frequency on CAPS-5). A retrospective reassessment of the efficacy analysis of AtEase was subsequently performed using the subsample with the determined higher comparable threshold.

Results

Efficacy

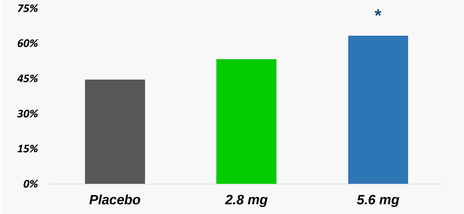
The efficacy population was comprised of 231 patients randomized to the three treatment arms. The pre-specified primary efficacy analysis of the TNX-102 SL 2.8 mg arm compared to placebo (n=92) did not achieve statistical significance (p=0.259). In contrast, the TNX-102 SL 5.6 mg treatment arm (n=49) demonstrated a strong trend towards greater improvement in CAPS-5 at Week 12 (p=0.053; see **Figure 1**). Three sensitivity analyses of this comparison were found to be significant and included: MMRM with multiple imputation (p=0.031); MMRM with hybrid last-observation-carried-forward/baseline-observation-carried forward imputation (p=0.037), and analysis of covariance (p=0.038). Additionally, the TNX-102 SL 5.6 mg treatment group was superior to placebo on the Clinical Global Impression - Improvement (CGI-I) scale responder analysis (p=0.041, logistic regression) as seen in **Figure 2** (responder defined as having a score of 'much improved' or 'very much improved' at Week 12).

Figure 1: CAPS-5 LS Mean Change From Baseline (n=231; baseline severity ≥ 29)



#p=0.053, comparing TNX-102 SL 5.6 mg and placebo
*p<0.05, comparing TNX-102 SL 2.8 mg and placebo

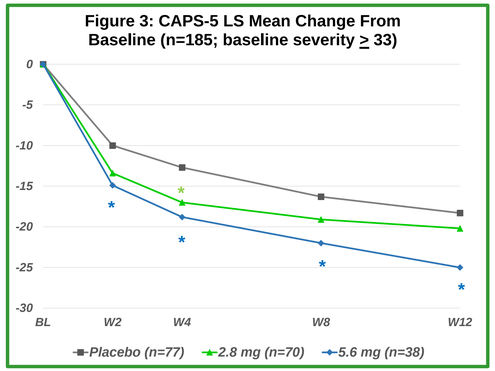
Figure 2: CGI-I Responders (n=231; baseline severity ≥ 29)



*p=0.041, comparing TNX-102 SL 5.6 mg and placebo

Upon calculating the iCAPS-IV score for each patient, it was found that four patients had an iCAPS-IV score < 50 (range 44 – 48). By using a minimum CAPS-5 entry score of 33, all imputed iCAPS-IV baseline scores were above 50, and only 20% of the sample not meeting this threshold was excluded. **Figure 3** shows the mean change from baseline in total CAPS-5 severity scores over the 12 weeks of the study among the subgroup with the baseline threshold ≥ 33. The TNX-102 SL 5.6 mg group significantly separated from placebo at all assessment points, and the effect size for the Week 12 comparison of CAPS-5 MCFB was 0.53. **Table 1** shows the p-values and effect sizes of the CAPS-5 total score and four clusters in the retrospective analysis subset with a minimum CAPS-5 entry score of 33.

Figure 3: CAPS-5 LS Mean Change From Baseline (n=185; baseline severity ≥ 33)



*p<0.05, comparing TNX-102 SL 5.6 mg and placebo
*p=0.029, comparing TNX-102 SL 2.8 mg and placebo

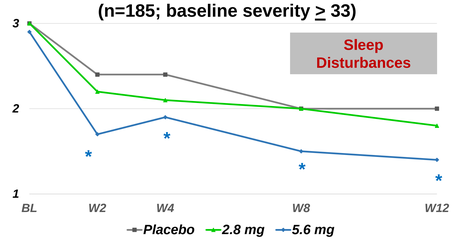
Table 1: Week 12 CAPS-5 Total Score and Symptom Cluster Comparisons for TNX-102 SL 5.6 mg v. Placebo

Outcome Measure	CAPS-5 ≥ 33[a]		CAPS-5 ≥ 29[b]	
	ES+	p-value	ES+	p-value
CAPS-5 Total Score	0.53	*0.013	0.36	0.053
CAPS-5 Cluster B (Intrusion)	0.46	*0.026	0.26	0.161
CAPS-5 Cluster C (Avoidance)	0.12	0.522	0.04	0.963
CAPS-5 Cluster D (Mood/Cognition)	0.39	0.065	0.35	0.062
CAPS-5 Cluster E (Arousal/Reactivity)	0.52	*0.012	0.35	*0.048

[a] *placebo n = 77; 5.6 mg n = 38*
[b] *placebo n = 92; 5.6 mg n = 49*
** p-value < 0.05, statistically significant*
+ ES = effect size

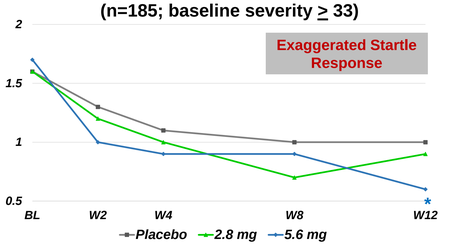
The treatment response pattern of two items within the Arousal and Reactivity cluster are illustrative of the hypothesized mechanism of action of TNX-102 SL in PTSD. Consistent with direct receptor effects, sleep disturbance is a *biological* symptom that responds to TNX-102 SL 5.6 mg early and robustly from Week 2 onward as seen in **Figure 4**. In contrast, recovery from exaggerated startle is considered to involve new learning (extinction), and thus is a more *behavioral* process for which sleep-dependent memory processing is critical. Supportive of this mechanistic hypothesis, it can be seen in **Figure 5** that exaggerated startle only responds after a substantial period of treatment with TNX-102 SL 5.6 mg at Week 12

Figure 4: Mean CAPS-5 Item E6, (n=185; baseline severity ≥ 33)



*p<0.05, comparing TNX-102 SL 5.6 mg and placebo

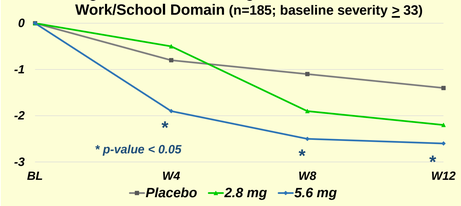
Figure 5: Mean CAPS-5 Item E4 (n=185; baseline severity ≥ 33)



*p=0.016, comparing TNX-102 SL 5.6 mg and placebo

Return of function is one of the most important goals of treatment, and returning to work or further education has been particularly problematic for veterans of the Iraq and Afghanistan conflicts suffering from PTSD. In this light, it is notable that for the TNX-102 SL 5.6 mg arm, work/school disability, as measured by the Sheehan Disability Scale, significantly improves over placebo by Week 4 and continues to improve through Week 12 of treatment (**Figure 6**).

Figure 6: LS Mean Change From Baseline of SDS Work/School Domain (n=185; baseline severity ≥ 33)



Safety

Overall TNX-102 SL was well tolerated. Adverse events occurring at > 5% rate in either TNX-102 SL group are summarized in **Table 2**.

Table 2: Adverse Events in Safety Population (n=237)*

Systemic Adverse Events	Placebo (N=94)	TNX-102 SL 2.8 mg (N=93)	TNX-102 SL 5.6 mg (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 was the most common AE, was generally transient (<60 minutes), and rated as mild in 89% and moderate in 11% on TNX-102 SL.

Summary

- The AtEase study is one of the first pharmacotherapy trials to employ the latest version of the CAPS, which is based on the definition of PTSD in the DSM-5. The analyses described herein demonstrated that a CAPS-5 severity score of ≥33 for study inclusion is more comparable to the severity threshold used in past registration trials of the approved PTSD pharmacotherapies.
- Retrospective analysis of the AtEase sample using this ≥33 threshold for entry demonstrated substantially larger effect sizes, compared with ≥29, of the TNX-102 SL 5.6 mg on total CAPS-5 (0.53 v. 0.36) and the Arousal & Reactivity (0.52 v. 0.35), Intrusion (0.46 v. 0.26), and Mood/Cognitions (0.39 v. 0.35) clusters
- The CAPS-5 severity score of ≥33 was determined to be appropriate for inclusion in planned Phase 3 testing of TNX-102 SL 5.6 mg in PTSD
- Overall TNX-102 SL was well tolerated. Oral hypoesthesia (or tongue numbness) was most common, generally transient, and never rated as severe.

^TNX-102 SL is an Investigational New Drug and has not been approved for any indication.