The AtEase Study: Efficacy and Safety of a Low Dose, Bedtime, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL) for the Treatment of Military-Related PTSD

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is among the most prevalent and disabling psychiatric conditions of Warfighters deployed to OEF/OIF/OND combat theaters. Only two pharmacotherapies, both selective serotonin reuptake inhibitors (SSRIs), are FDA-approved for PTSD. One failed to show efficacy in Veterans and males with PTSD, and the other was never studied in a predominantly military-related PTSD population. The serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine ER, also had no effect on PTSD or disability in the combat subsample (N=77) of a pooled analysis. These findings highlight the urgent unmet need for a pharmacotherapy with a distinct mechanism of action for military-related PTSD.

TNX-102 SL[#] is a proprietary formulation of cyclobenzaprine, unique among tricyclics for potent binding and antagonist activity at 5-HT_{2A}, α_1-adrenergic, and H_1-histaminergic receptors, presumed to result in improvement in sleep architecture and sympatholytic effects. TNX-102 SL was designed for bedtime sublingual administration and rapid transmucosal absorption, detectable in plasma in minutes. This bypasses first-pass hepatic metabolism, resulting in lower exposure to a long-lived active metabolite, norcyclobenzaprine, compared to the orally ingested products. This Phase 2 study was a double-blind, placebo-controlled randomized trial to assess the safety and efficacy of TNX-102 SL in military-related PTSD, with the hypothesis that symptoms of PTSD could be improved via TNX-102 SL effects on sleep and hyperarousal.

METHODS

The 'AtEase Study' was a Phase 2 multicenter, 12-week, double-blind placebo-controlled, randomized trial in adults meeting a DSM-5 diagnosis of PTSD, assessed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Patients were randomized to TNX-102 SL 2.8 mg, 5.6 mg (2 x 2.8 mg tablets), or placebo in a 2:1:2 ratio at 24 US sites (double dummy design). Eligible participants must have experienced PTSD Criterion A-qualifying trauma(s) during military service since 2001. Inclusion criteria: CAPS-5 score at baseline ≥ 29; no antidepressant treatment within 2 months; off other psychotropics. Exclusions: severe suicide risk; unstable medical conditions; substance use disorders in prior 6 months; lifetime bipolar 1 or 2, psychotic disorders, obsessive compulsive disorder, or antisocial personality disorder. The primary efficacy endpoint was mean change from baseline (MCFB) in CAPS-5 severity score between TNX-102 SL 2.8 mg and placebo. Secondary endpoints included: CAPS-5 symptom cluster scores; Clinical Global Impression – Improvement scale (CGI-I); Sheehan Disability Scale (SDS); Montgomery-Asberg Depression Rating Scale (MADRS). CAPS-5 raters were Masters-level or above mental health clinicians who underwent a rigorous rater training and certification program. A Safety Planning Intervention was employed for C-SSRS suicidal ideation > Type 1 during participation.

RESULTS

- 245 patients were randomized; 237 of those made up the safety population; 231 made up the modified intent-to-treat (mITT) population
- Completers: Placebo 73%; TNX-102 SL 2.8 mg 79%; TNX-102 SL 5.6 mg 84%

[#]TNX-102 SL is an Investigational New Drug and has not been approved for any indication

- **Table 1** shows selected demographics and **Table 2** lists index traumas

Table 1. Patient Demographics and Characteristics

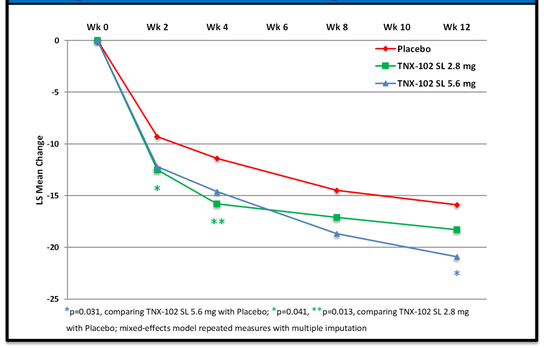
Variable	Placebo N=92	TNX-102 SL 2.8 mg N=90	TNX-102 SL 5.6 mg N=49
Females, no. (%)	6 (6.5%)	6 (6.7%)	4 (8.2%)
Mean age, yrs (SD)	32.0 (6.5)	34.5 (8.3)	34.8 (9.0)
Weight, kg (SD)	91.6 (16.9)	90.9 (18.2)	90.8 (17.4)
Body Mass Index (BMI), kg/m2 (SD)	28.9 (4.4)	29.0 (5.2)	29.0 (4.7)
Education, some college or beyond	72 (78.2%)	80 (88.9%)	41 (83.7%)
% currently employed	54 (58.7%)	56 (62.2%)	33 (67.3%)
% in military service at index trauma	91 (98.9%)	85 (94.4%)	49 (100%)
Active Duty/Reservists/Veterans	8/4/79	9/5/71	5/7/37
Law Enforcement Officers	1	5	0
Ave time since index trauma, yrs (SD)	7.1 (3.6)	7.3 (3.3)	6.2 (3.3)
Ave deployments, military/veterans (SD)	2.2 (1.84)	2.3 (2.15)	2.6 (2.1)
Baseline CAPS-5 Scores (SD)	39.5 (7.7)	39.5 (8.0)	39.3 (8.1)
Baseline MADRS Scores (SD)	17.3 (6.53)	17.6 (5.18)	16.1 (5.54)

Table 2. Index Trauma Categories

Index Traumas During Military Service Related to PTSD Dx	Patient Count
Being involved in an IED explosion or suicide bombing	35
Being attacked or ambushed	33
Witnessing death or injury of fellow soldiers	30
Witnessing IED explosion	29
Receiving incoming artillery, rocket, or mortar fire	10
Being wounded or injured	9
Being responsible for the death of a noncombatant	9
Witness suicide-related deaths or injury	9
Seeing ill or injured women or children you were unable to help	8
Witnessing death or injury of civilians	7
Handling or uncovering human remains	6
Sexual assault	6
Involved in serious vehicular accident (Humvee, helicopter, plane)	6
Shooting or directing fire at the enemy	5
All other categories	23

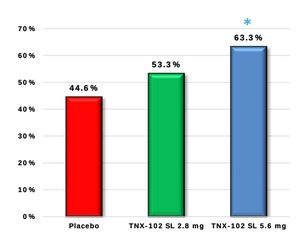
- **Figure 1** shows the visit by visit mean change from Baseline in total CAPS-5 score utilizing the MMRM with multiple imputation method

Figure 1. CAPS-5 Mean Change from Baseline



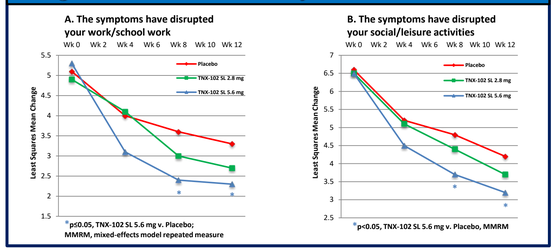
- The CAPS-5 sleep disturbance item was significantly improved at all assessments for the TNX-102 SL 5.6 mg group and Week 4 for 2.8 mg.
- **Figure 2** On a global scale, the CGI-I, 63.3% of TNX-102 SL 5.6 mg group responded at Week 12

Figure 2. CGI-I Responder Status



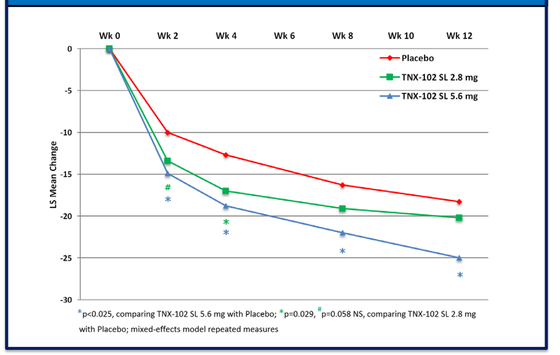
- From a functional perspective, the TNX-102 SL 5.6 mg group showed significant improvement over placebo in the work/school and the social/leisure domains of the Sheehan Disability Scale (**Figure 3A&B**)

Figure 3. Sheehan Disability Scale Domain Scores



- CAPS-5 has not previously been employed in a pharmacotherapy trial; entry severity threshold not clear - ≥ 29 used in AtEase
- Imputing CAPS for DSM-IV (iCAPS-IV), by using 17 common items and multiplying by 2, showed 4 subjects with iCAPS-IV < 50 (range 44-48)
- Using entry criterion of CAPS-5 ≥ 33, 20% of sample excluded but all iCAPS-IVs are > 50
- Analysis of patients with CAPS-5 ≥ 33 showed an effect size of 0.53 on mean change from baseline at Week 12 in TNX-102 SL 5.6 mg group **(Figure 4)**

Figure 4. CAPS-5 Mean Change from Baseline for CAPS ≥ 33



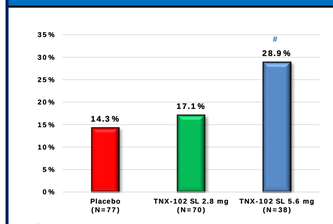
- **Table 3** shows the significance levels and effect sizes of the CAPS-5 cluster scores (MMRM analyses) using a CAPS-5 baseline entry criterion of ≥ 33 and the per protocol threshold of ≥ 29

Table 3. CAPS-5 Cluster Scores

	Entry criteria of CAPS-5 ≥ 33 5.6 mg vs Placebo		Entry criteria of CAPS-5 ≥ 29 5.6 mg vs Placebo	
CAPS-5 Cluster	Effect Size	P-value*	Effect Size	P-value*
Cluster B (Intrusion)	0.46	**0.026**	0.26	0.161
Cluster C (Avoidance)	0.12	0.522	0.04	0.963
Cluster D (Mood/Cognitions)	0.39	*0.065*	0.35	*0.062*
Cluster E (Arousal & Reactivity)	0.53	**0.012**	0.35	**0.048**

* MMRM, mixed-effects model repeated measures

Figure 5. CAPS-5 Remitters* in ≥ 33 Baseline CAPS-5



- **Figure 5** shows the rate of remission from PTSD in each arm in the ≥ 33 sample, with a trend for a greater rate in the TNX-102 SL 5.6 mg group compared with Placebo

- **Table 4** shows administration site and systemic AEs. The TNX-102 SL 5.6 mg group had minimally higher systemic AE rates for somnolence, dry mouth, headache, and sedation, yet there were no discontinuations in the group due to AE, suggesting they were tolerable

Table 4. Adverse Events*

Preferred Term	Placebo N=94	TNX-102 SL 2.8 mg N=93	TNX-102 SL 5.6 mg N=50
Local Administration Site Reactions			
Hypoaesthesia oral	2 (2.1%)	36 (38.7%)	18 (36.0%)
Paraesthesia oral	3 (3.2%)	15 (16.1%)	2 (4.0%)
Glossodynia	1 (1.1%)	3 (3.2%)	3 (6.0%)
Systemic Adverse Events			
Somnolence	6 (6.4%)	11 (11.8%)	8 (16.0%)
Dry mouth	10 (10.6%)	4 (4.3%)	8 (16.0%)
Headache	4 (4.3%)	5 (5.4%)	6 (12.0%)
Insomnia	8 (8.5%)	7 (7.5%)	3 (6.0%)
Sedation	1 (1.1%)	2 (2.2%)	6 (12.0%)

*Adverse events listed only for those occurring at >5% in either TNX-102 SL treatment arm in the safety population

CONCLUSIONS

The AtEase Study demonstrated that TNX-102 SL 5.6 mg is effective for the treatment of military-related PTSD. Evidence of efficacy on sleep and hyperarousal symptoms were consistent with the hypothesized mechanism of action of TNX-102 SL in PTSD. High completer rate and no discontinuations due to AE in 5.6 mg group suggested good tolerability. Threshold for trial entry of CAPS-5 ≥ 33 is appropriate for Phase 3.

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