Low-Dose Sublingual Cyclobenzaprine (TNX-102 SL*) in Military-Related PTSD: Results of a Phase 2 Randomized, Placebo-Controlled Multicenter Trial

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INTRODUCTION

Evidence-based pharmacotherapies for military-related posttraumatic stress disorder (PTSD) are lacking. TNX-102 SL is a low-dose sublingual (SL) formulation of cyclobenzaprine (CBP), a tricyclic molecule previously FDA-approved for short-term use in muscle spasm at higher total daily oral doses (15-30 mg/day). Intended for bedtime administration, TNX-102 SL is rapidly absorbed via SL mucosa, resulting in CBP plasma levels ~4 hours into the sleep period and falling sharply thereafter. Because the SL route bypasses first-pass hepatic metabolism, there is reduced formation of a long-lived active metabolite, norcyclobenzaprine, with off-target functional activities. CBP is unique among tricyclics for high affinity and functional antagonism for 5-HT2A, adrenergic, and histaminergic H1 receptors, all with roles in sleep regulation. TNX-102 SL is hypothesized to target sleep disturbance and nocturnal hyperarousal, potentially providing global benefit in PTSD by allowing sleep-dependent emotional memory (e.g. extinction) consolidation necessary for recovery. The "AtEase Study" was conducted to assess the efficacy, safety and tolerability of TNX-102 SL in the treatment of military-related PTSD.

METHODS

- Multicenter, 12-week, double-blind placebo-controlled (DB-PC) Phase 2 study.
- Eligible participants were: male or female, ages 18-65; incurred PTSD DSM-5 Criterion A (trauma(s) during military service and since 9/11/2001; met current PTSD by Clinician-Administered PTSD Scale for DSM-5 (CAPS-S); had a total CAPS-S severity score ≥ 29 at Screening and Baseline; were free of antidepressants ≥ 2 mo prior to entry; and free of or withdrawn from other psychotropics; and were not pregnant or breast-feeding.
- Conducted at 24 US sites: patients randomized to TNX-102 SL 2.8 mg, TNX-102 SL 5.6 mg, or Placebo; dynamic randomization minimized imbalances by site, sex, and current major depression.
- Primary efficacy analysis: comparison of mean change from baseline (MCFB) at Week 12 in CAPS-S severity score between TNX-102 SL 2.8 mg and Placebo, via mixed-effects model repeated measures (MMRM).
- Key secondary endpoints were: Clinical Global Impression - Improvement (CGI-I) scale, Sheehan Disability Scale (SDS) and PROMIS Sleep Disturbance. Others secondary: CAPS-S cluster scores and remission rates.
- CAPS-S raters were ≥ Master’s degree level in mental health fields; underwent rigorous training and certification process; and were CAPS-S reliability monitoring throughout trial.
- For CAPS-S, maximum possible score is 70 and PTSD severity as follows: 0-10 is asymptomatic/emission, 11-22 is mild, 23-34 is moderate, 35-46 is severe, and >47 is extreme PTSD.

RESULTS

Table 1: Patient Demographics and Characteristics

Table 2: Results of Primary and Secondary Analyses

Table 3: Week 12 CAPS-5 Total Score and Cluster Score Comparisons for TNX-102 SL 5.6 mg v. Placebo

CONCLUSIONS

- The AtEase study identified 5.6 mg as an effective dose for TNX-102 SL as a potential treatment for military-related PTSD, with an effect size of 0.36.
- Retrospective analysis of the AtEase study using an entry severity threshold of 33, more comparable to prior registration studies, indicates substantially larger effect sizes for TNX-102 SL 5.6 mg compared with protocol ≥29 total on CAPS-S (0.53 v. 0.36) and the Arousal & Reactivity (0.52 v. 0.35), Intrusion (0.46 v. 0.26) and MoodClusters (0.39 v. 0.23) clusters.
- TNX-102 SL 5.6 mg in the ≤33 subsample significantly reduced reckless or self-destructive behaviors, potentially fulfilling a critical need in the military and veteran populations with PTSD who have elevated rates of suicidal behaviors, and vehicular and other accidents resulting from high risk behaviors.
- The CAPS-S severity score of ≤33 was determined to be appropriate for inclusion in planned Phase 3 clinical investigation of TNX-102 SL 5.6 mg in PTSD.
- TNX-102 SL was well tolerated. Oral hypoaesthesia was most common, generally transient, and never rated as severe.