**INTRODUCTION**

- Posttraumatic stress disorder (PTSD) is a seriously impairing mental health disorder that occurs after experiencing, witnessing, or hearing about traumatic events.
- TNX-102 SL is a patented low dose sublingual formulation of the serotonin (5- and 6-) receptor agonist, TNX-102, designed to avoid first-pass hepatic metabolism, substantially increase systemic exposure, and improve clinical outcomes.
- TNX-102 SL is a breakthrough therapy for PTSD, approved by the FDA in 2021.

**METHODS**

- Phase 2 multicenter, 12-week, double-blind placebo-controlled study conducted at 24 sites in the U.S.
- Inclusions: men and women ages 18-65, PTSD DSM-5 Criterion C traumatic event (military or civilian) in the past year, and current PTSD by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (ES=0.7) and CAPS-5 intrusion cluster B (ES=0.5).
- Exclusions: serious suicide risk; alcohol use disorders within 6 months; lifetime bipolar I or II; psychotic, obsessive-compulsive, or antisocial personality disorders.
- Randomized in 2:2:1 ratio to Placebo, TNX-102 SL 2.8 mg, TNX-102 SL 5.6 mg.
- Primary efficacy analysis: comparison of mean change from baseline (at Week 12) in CAPS-5 total score between TNX-102 SL 2.8 mg and Placebo, mixed model repeated measures (MMRM) analysis without imputation.

**RESULTS**

- Of 245 participants randomized, 231 were included in the efficacy intent-to-treat (mITT) population (94.5% completion rate).
- The mITT comprised 92 participants on Placebo, 90 on TNX-102 SL 2.8 mg, and 50 on TNX-102 SL 5.6 mg (Figure 1).
- The completion rates were 98.9% for TNX-102 SL 2.8 mg and 100% for TNX-102 SL 5.6 mg (Figure 2).
- Table 1 shows demographic and clinical characteristics.
- Table 2 shows results of primary and secondary analyses.
- Table 3 shows week 12 outcome measures.

**CONCLUSIONS**

- TNX-102 SL 5.6 mg reduced total CAPS-5 symptoms and provided overall improvement in PTSD severity.
- A retrospective analysis indicated a significant trend in CAPS-5 severity score of 2.833 is more aligned with previous PTSD pharmacotherapy registration trials that used similar thresholds (ES=0.7). TNX-102 SL 5.6 mg was well-tolerated with no serious AEs, and no changes in vital signs or lab parameters were observed.
- The TNX-102 SL 5.6 mg group was well-tolerated with no serious AEs, and no changes in vital signs or lab parameters were observed.

**Supporting Information**

- Table 4. Week 12 Outcome Measures for TNX-102 SL 5.6 mg vs. Placebo in Military-Related PTSD for Both Entry Thresholds.
- Table 5. Changes in Heart Rate, Blood Pressure, and Body Weight Over 12 Weeks of Study in the mITT Population.
- Table 6. Adverse Events at a rate of 25% in all trials treated group.

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**Figure 1. CAPS-5 Arousal and Reactivity Cluster (E) MCFB**

**Figure 2. CAPS-5 Sleep Disturbance Item (E) MCFB**

**Figure 3. CAPS-5 MCFB Over 12 Weeks in 233 Entry Subsample**

**Figure 4. Disposition Diagram**

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**Table 1. Participant Demographics and Clinical Characteristics**

**Table 2. Results of Primary and Sensitivity Analyses**

**Table 3. Table 4. Week 12 Outcome Measures for TNX-102 SL 5.6 mg vs. Placebo in Military-Related PTSD for Both Entry Thresholds**

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**Table 5. Changes in Heart Rate, Blood Pressure, and Body Weight Over 12 Weeks of Study in the mITT Population**

**Table 6. Adverse Events at a rate of 25% in all trials treated group.**

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**Using Baseline CAPS-5 ≥ 33 as Threshold for Study Entry**

A retrospective analysis of baseline severity was conducted to assess the relationship between CAPS-5 total score and outcome. The original TNX-102 SL 5.6 mg arm was significantly more improved at Week 12 (Figure 4).

**Moderators of Treatment Response: Greater Baseline Severity [as Threshold for Entry] & Combat PTSD**

- A retrospective analysis of baseline severity was conducted to assess the relationship between TNX-102 SL 5.6 mg dose and Placebo on MCFB-MITT, as well as ANCOVA (Table 2).
- The TNX-102 SL 5.6 mg group showed a strong trend for improvement versus Placebo in MCFB in CAPS-5 (p=0.053), with a Cohen’s d effect size of 0.38.
- Sensitivity analysis that corrects for missing data was statistically significant for the comparison of TNX-102 SL 5.6 mg and Placebo on CAPS-5-MITT, as well as ANCOVA (Table 2).
- The CAPS-5 Arousal & Reactivity cluster (E) was significantly more improved for the 2.8 mg group than Placebo at Weeks 2, 4, and 6, and the 5.6 mg arm at Weeks 2, 8, and 12 (Figure 1).
- The sleep disturbance item (ES) of CAPS-5 improved early in treatment for the 5.6 mg group, significantly more improved than Placebo by Week 2 and all other comparisons; sleep was 2.8 mg group was significantly more improved at Week 4 (Figure 2).
- The exaggerated startle item (ES) of CAPS-5 was significantly more improved for the 5.6 mg arm over Placebo Week 12 (Table 2).
- Subgroup analysis of PTSD severity (mITT) showed significant effects of TNX-102 SL 5.6 mg on CAPS-5 total severity, clusters B and E, and functional improvement by MITT (Table 4).
- The TNX-102 SL 5.6 mg group showed a strong trend for improvement versus Placebo in MCFB in CAPS-5 (p=0.053), with a Cohen’s d effect size of 0.38.

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**Safety and Tolerability**

- TNX-102 SL 5.6 mg was well-tolerated with no serious AEs, and no changes in vital signs or lab parameters were observed.
- The TNX-102 SL 5.6 mg group was well-tolerated with no serious AEs, and no changes in vital signs or lab parameters were observed.