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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Continuing Medical Education Commercial Disclosure

I, Gregory M. Sullivan, have the following commercial relationship to disclose:
Tonix Pharmaceuticals, Inc., Employee (Chief Medical Officer), Stockholder

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

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 peak 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-HT_{2A}, α_1-adrenergic, and histamine-H_1 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-5); had a total CAPS-5 severity score ≥ 29 at Screening and Baseline; were free of antidepressants ≥ 2 months and free of or washed off other psychotropics; and were not participating in a trauma-focused psychotherapy (TFP) during the study. Prior TFP had to have concluded >1 month before Screening.
- Exclusions: serious suicide risk; unstable medical illness; substance use disorders within 6 months; lifetime bipolar 1 or 2, psychotic, obsessive-compulsive, or antisocial personality disorders.
- Conducted at 24 US sites; patients randomized in a 2:1:2 ratio 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-5 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 secondaries: CAPS-5 cluster scores and remission rates
- CAPS-5 raters were ≥ Master's degree-level in mental health fields; underwent rigorous training and certification process; and there was CAPS-5 reliability monitoring throughout trial.
- For CAPS-5, maximum possible score is 80; and PTSD severity is as follows: 0-10 is asymptomatic/remission, 11-22 is mild, 23-34 is moderate, 35-46 is severe, and 47+ is extreme PTSD.

RESULTS

Of 245 patients randomized, 231 were included in the modified intent-to-treat (mITT) efficacy population (14 of the randomized patients failed to return for post-baseline efficacy assessment). The mITT comprised 90 on TNX-102 SL 2.8 mg, 49 on TNX-102 SL 5.6 mg, and 92 on Placebo, with completion rates of 79%, 84%, and 73%, respectively. Demographic and clinical characteristics were similar across the three groups (**Table 1**).

Table 1. Patient Demographics and Characteristics

Variable	TNX-102 SL 2.8 mg N=90	TNX-102 SL 5.6 mg N=49	Placebo N=92	Overall N=231
Females, no. (%)	6 (6.7%)	4 (8.2%)	6 (6.5%)	16 (6.9%)
Mean age, yrs (SD)	34.5 (8.3)	34.8 (9.0)	32.0 (6.5)	33.6 (7.8)
Weight, kg (SD)	90.9 (18.2)	90.8 (17.4)	91.6 (16.9)	91.1 (17.5)
BMI, kg/m2 (SD)	29.0 (5.2)	29.0 (4.7)	28.9 (4.4)	28.9 (4.8)
Education, some college or beyond	80 (88.9%)	41 (83.7%)	72 (78.2%)	193 (83.6%)
% currently employed	56 (62.2%)	33 (67.3%)	54 (58.7%)	143 (61.9%)
% in military service at time of index trauma	85 (94.4%)	49 (100%)	91 (98.9%)	225 (97.4%)
Number of: Active Duty/Reservists/Veterans	9/5/71	5/7/37	8/4/79	22/16/187
Number of: Law Enforcement Officers	5	0	1	6
Ave time since index trauma, yrs (SD)	7.3 (3.3)	6.2 (3.3)	7.1 (3.6)	7.0 (3.4)
Ave deployments, military/veterans (SD)	2.3 (2.15)	2.6 (2.1)	2.2 (1.84)	2.3 (2.00)
Baseline CAPS-5 Scores (SD)	39.5 (8.0)	39.3 (8.1)	39.5 (7.7)	39.5 (7.85)

- Primary analysis: The primary analysis did not demonstrate that TNX-102 SL 2.8 mg was different from Placebo at Week 12 (p=0.259, NS). Yet TNX-102 SL 5.6 mg showed a strong trend for difference from placebo in MCFB in CAPS-5 (p=0.053), with an effect size of 0.36 (Cohen's *d*); and several sensitivity analyses of TNX-102 SL 5.6 mg dose v. placebo on CAPS-5 MCFB were significant (See **Table 2**).
- The CAPS-5 Arousal & Reactivity cluster, sleep and startle items were significantly improved for the 5.6 mg dose, as were clinician- and patient-rated global measures, and work and social domains on the SDS.

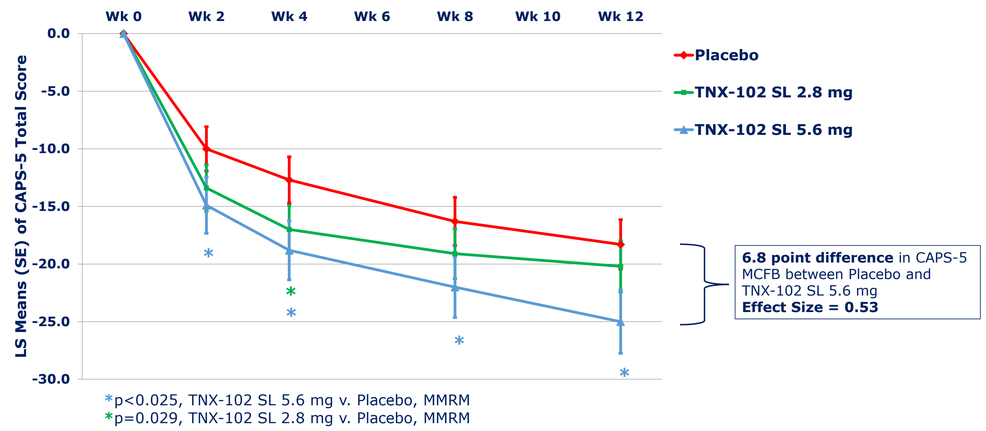
Table 2. Results of Primary and Secondary Analyses

Assessment	Domain	Analysis	p-Values	
			2.8 mg (N=90)	5.6 mg (N=49)
CAPS-5	Total	MMRM (Primary Analysis)	0.259^	0.053
	Total	MMRM with Multiple Imputation	0.211	0.031*
	Total	MMRM w/ Hybrid LOCF/BOCF	0.172	0.037*
	Total	ANCOVA	0.090	0.038*
CAPS-5 clusters/items	Arousal & Reactivity cluster (E)	MMRM	0.141	0.048*
	Sleep item (E6)	MMRM	0.185	0.010*
	Exaggerated Startle item (E4)	MMRM	0.336	0.015*
CGI-I	Responders	Logistic Regression	0.240	0.041*
PGIC	Mean score	MMRM	0.075	0.035*
Sheehan Disability Scale	Work/school item	MMRM	0.123	0.050*
	Social/leisure item	MMRM	0.198	0.031*

*p<0.05; ^Primary analysis p-value not significant comparing TNX-102 SL 2.8 mg v. placebo; BOCF, baseline observation carried forward; CGI-I, Clinical Global Impression - Improvement scale; LOCF, last observation carried forward; MMRM, mixed model repeated measures; PGIC, Patient Global Impression of Change

Retrospective Analysis Using CAPS-5 ≥ 33 as Threshold for Study Entry: For inclusion, previous registration studies of approved PTSD pharmacotherapies required a severity score of ≥50 at baseline on prior 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 and 0-4 for frequency (maximum possible score = 136). The protocol for AtEase included CAPS-5 severity of ≥29. Yet, retrospectively imputing a CAPS for DSM-IV (iCAPS-IV) in AtEase using the 17 common items and multiplying by 2, 10 subjects with iCAPS-IV ≤50 (range 44-50) were found. If instead an entry criterion of CAPS-5 ≥ 33 is used for AtEase patients, 20% of sample was excluded but all iCAPS-IVs are >50. A post-hoc analysis of efficacy was therefore conducted using baseline CAPS-5 ≥33. As seen in **Figure 4**, all assessment points are significant for TNX-102 SL 5.6 mg; Week 12 MCFB showed an effect size of 0.53.

Figure 1. CAPS-5 Mean Change From Baseline Over 12 Weeks in ≥33 Entry Subsample



*p<0.025, TNX-102 SL 5.6 mg v. Placebo, MMRM
*p=0.029, TNX-102 SL 2.8 mg v. Placebo, MMRM

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

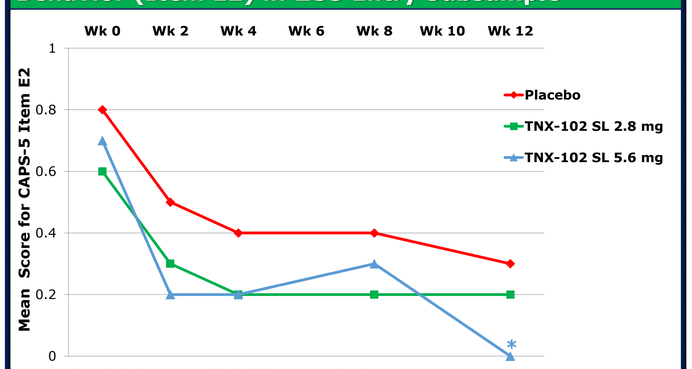
Outcome Measure	CAPS-5 ≥ 33[a]		CAPS-5 ≥ 29[b]	
	ES+	p-value	ES+	p-value
CAPS-5 Total Score	0.53	*0.013	0.36	0.053
CAPS-5 Cluster B (Intrusion)	0.46	*0.026	0.26	0.161
CAPS-5 Cluster C (Avoidance)	0.12	0.522	0.04	0.963
CAPS-5 Cluster D (Mood/Cognition)	0.39	0.065	0.35	0.062
CAPS-5 Cluster E (Arousal/Reactivity)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

*p<0.05, statistically significant; +ES = effect size; [a]Placebo n = 77, TNX-102 SL 5.6 mg n = 38; [b]Placebo n = 92, TNX-102 SL 5.6 mg n = 49;

Table 3 shows significance levels and effect sizes of CAPS-5 total and cluster scores comparing TNX-102 SL 5.6 mg v. Placebo at Week 12 using the subsample with CAPS-5 baseline entry criterion of ≥33 and, separately, the per protocol threshold of ≥29. Effect sizes are substantial for CAP-5 total score and Clusters B, D and E for the ≥33 subsample.

Effects of TNX-102 SL 5.6 mg on Reckless or Self-Destructive Behavior Item: New to the hyperarousal cluster in DSM-5 is an item for "***reckless or self-destructive behavior***," which can include dangerous driving, high-risk thrill-seeking, excessive alcohol or drug use, injurious behaviors to self or others, or suicidal behaviors. In the AtEase subsample (CAPS-5 ≥33 at entry), the effects of TNX-102 SL on this item are shown in **figure 2**. By Week 12, TNX-102 SL 5.6 mg significantly reduced this item (p=0.012) to a mean of zero. At baseline, mean item scores on this item for the three groups ranged from 0.6-0.8, seemingly low in severity. But only a small proportion of patients in each group scored >0 on this item at Baseline. The means (SD) at Baseline of only patients scoring >0 on this item are: Placebo (N=25 of 77) 2.5 (0.65); TNX-102 SL 2.8 mg (N=15 of 70) 2.7 (0.72); and TNX-102 SL 5.6 mg (N=9 of 38) 2.8 (0.67). By Week 12, these were reduced by: Placebo (N=19) -1.8 (1.34); TNX-102 SL 2.8 mg (N=11) -2.0 (1.18); and TNX-102 SL 5.6 mg (N=8) -2.9 (0.64).

Figure 2: CAPS-5 Reckless or Self-Destructive Behavior (Item E2) in ≥33 Entry Subsample



*p=0.012, TNX-102 SL 5.6 mg v. Placebo, MMRM

Safety: Overall TNX-102 SL was well tolerated. Adverse events occurring at > 5% rate in either TNX-102 SL group are summarized below in **Table 3.**

Table 3: Adverse Events*

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 (tongue numbness) was the most common AE, was generally transient (<60 minutes), and rated as mild in 89% and moderate in 11% on TNX-102 SL;
*Adverse events at a rate of >5% in either TNX-102 SL treated group in the safety population (N=237)

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 sample 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 per protocol of ≥29 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.
- 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-5 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.