Phase 2 Multisite Double-Blind Placebo-Controlled Trial of TNX-102 SL* in Military-Related Posttraumatic Stress Disorder (PTSD): Mediators and Moderators of Treatment Response

Gregory Sullivan[1], Judy Gendreau[1], R Michael Gendreau[2], Jean Engels[3], Perry Peters[1], Ashild Peters[1], Seth Lederman[1]

[1]Tonix Pharmaceuticals Inc, [2]Gendreau Consulting, [3]Engels Consulting

*TNX-102 SL is an investigational new drug and has not been approved for any indication.

INTRODUCTION

- Posttraumatic stress disorder (PTSD) is a seriously impairing psychiatric condition with particularly high prevalence in United States (US) military personnel deployed to zones of conflict
- There is an urgent need for evidence-based pharmacotherapies for military-related PTSD
- TNX-102 SL is a patented low dose sublingual formulation of cyclobenzaprine (CBP), a tricyclic molecule with high affinity & functional antagonism for 5-HT_{2A}, α_1-adrenergic, and histamine-H_1 receptors, all involved in sleep regulation
  - Targets sleep disturbance & hyperarousal, core PTSD symptoms
  - Potentially plays a critical role in overall recovery from PTSD by allowing sleep-dependent memory processing (e.g. extinction consolidation)
- TNX-102 SL differs from orally ingested CBP; the sublingual tablet was designed to enable transmucosal absorption at bedtime, resulting in peak CBP plasma levels during sleep hours and reduced daytime exposure
  - Produces circadian pattern of rapid rise and fall of plasma CBP during normal sleep phase
  - Avoids first-pass hepatic metabolism, substantially reducing formation and plasma levels of long-lived undesirable active metabolite, norcyclobenzaprine
- The "AtEase Study" was our first clinical study demonstrating the therapeutic benefits of TNX-102 SL in military-related PTSD.
- Based on the results of the AtEase study, the FDA has designated TNX-102 SL for PTSD a Breakthrough Therapy.

METHODS

- Phase 2 multicenter, 12-week, double-blind placebo-controlled study conducted at 24 trial sites in the US
- Inclusions: men and women; ages 18-65; PTSD DSM-5 Criterion A trauma(s) incurred during military service since 9/11/2001; current PTSD by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Baseline CAPS-5 score ≥29; free of antidepressants ≥2 months from baseline; free of or washed off of other psychotropics; not participating in trauma-focused psychotherapy ≥1 month from baseline
- Exclusions: serious suicide risk; substance/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; dynamic randomization (site, sex, current MDD)
- Primary efficacy analysis: comparison of mean change from baseline (MCFB) at Week 12 in CAPS-5 score between TNX-102 SL 2.8 mg and Placebo, mixed model repeated measures (MMRM) analysis without imputation
- Key secondary endpoints: Clinical Global Impression–Improvement (CGI-I) scale, Sheehan Disability Scale (SDS), PROMIS Sleep Disturbance instrument. Also: CAPS-5 clusters, Patient Global Impression of Change (PGIC), Montgomery-Åsberg Depression Rating Scale (MADRS)
- CAPS-5 raters with ≥ Master's degree-level in mental health; rigorously trained/certified; reliability monitoring over study

RESULTS

- Of 245 participants randomized, 231 were included in the modified intent-to-treat (mITT) efficacy population (**Figure 4**)
- The mITT comprised 92 participants on Placebo, 90 on TNX-102 SL 2.8 mg, and 49 on TNX-102 SL 5.6 mg (**Figure 4**)
- The completion rates for the mITT were 73% for Placebo, 79% for TNX-102 SL 2.8 mg, and 84% for TNX-102 SL 5.6 mg (**Figure 4**)
- **Table 1** shows demographic and clinical characteristics
- The TNX-102 SL 2.8 mg treatment group's change from baseline in CAPS-5 total score was not significantly different from Placebo at Week 12 (p=0.259, not significant)
- 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 0.36
- Sensitivity analyses that correct for missing data were statistically significant for the comparison of TNX-102 SL 5.6 mg dose and Placebo on CAPS-5 MCFB, as was 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 8, and the 5.6 mg arm at Weeks 2, 8, and 12 (**Figure 1**)
- The sleep disturbance item (E6) of CAPS-5 improved early in treatment for the 5.6 mg group, significantly more improved than Placebo by Week 2 and all other assessments; sleep in 2.8 mg group was significantly more improved at Week 4 (**Figure 2**)
- The exaggerated startle item (E4) of CAPS-5 was significantly more improved for the 5.6 mg arm over Placebo at Week 12
- CGI-I responder analysis showed a significantly greater response rate in the 5.6 mg group over Placebo at Week 12 (**Table 3**)
- The 5.6 mg arm showed trend for greater reduction in SDS total score and work/school disability domain, and significantly greater improvement in social life domain (**Table 3**) at Week 12
- Subgroup analysis of combat-only type traumas (N=197) showed significant effects of TNX-102 SL 5.6 on CAPS-5 total severity, clusters B and E, and functional improvement by SDS (**Table 4**)
- Reported systemic adverse events (AE) were consistent with those reported with orally ingested CBP-containing products; AE of tongue numbness, related to the oral site of administration, was most common in TNX-102 SL groups, generally transient, and never rated as severe; overall good tolerability with high completion rate (84%) and no withdrawals due to AE in 5.6 mg group (**Table 6**)

Table 1. Participant Demographics and Clinical Characteristics

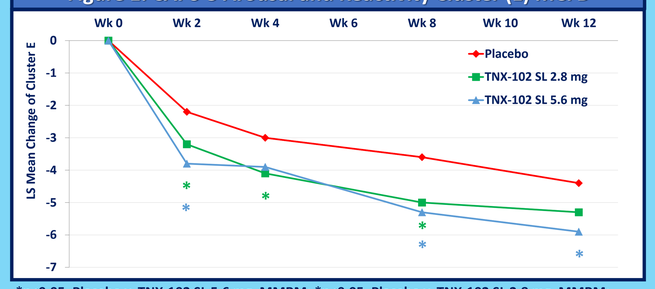
Variable	Placebo N=92	TNX-102 SL 2.8 mg N=90	TNX-102 SL 5.6 mg N=49
Females, no. (%)	6 (6.5%)	6 (6.7%)	4 (8.2%)
Age, yrs (SD)	32.0 (6.5)	34.5 (8.3)	34.8 (9.0)
Weight, kg (SD)	91.6 (16.9)	90.9 (18.2)	90.8 (17.4)
BMI, kg/m^2 (SD)	28.9 (4.4)	29.0 (5.2)	29.0 (4.7)
Education, some college or more	72 (78.2%)	80 (88.9%)	41 (83.7%)
Currently employed, no. (%)	54 (58.7%)	56 (62.2%)	33 (67.3%)
In military at trauma, no. (%)	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
Time since trauma, yrs (SD)	7.1 (3.6)	7.3 (3.3)	6.2 (3.3)
Deployments, military (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. Results of Primary and Sensitivity Analyses

	CAPS-5 LS MCFB at Week 12			CAPS-5 LS Mean Difference from PBO		p-Values	
		TNX-102 SL		TNX-102 SL		TNX-102 SL	
	PBO	2.8 mg	5.6 mg	2.8 mg	5.6 mg	2.8 mg	5.6 mg
MMRM (Primary Analysis)	-17.0	-19.2	-21.5	-2.2	-4.5	0.259^	0.053
MMRM with MI	-15.9	-18.3	-20.9	-2.4	-5.0	0.211	0.031*
MMRM w/Hybrid LOCF/BOCF	-13.8	-16.4	-18.6	-2.6	-4.9	0.172	0.037*
ANCOVA	-16.2	-19.7	-21.3	-3.5	-5.1	0.090	0.038*

*p<0.05; ^Primary analysis not significant; ANCOVA, analysis of covariance; BOCF, baseline observation carried forward; LOCF, last observation carried forward; LS, least squares; MCFB, mean change for baseline; MI, multiple imputation; MMRM, mixed model repeated measures; PBO, placebo

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



*p<0.05, Placebo v. TNX-102 SL 5.6 mg, MMRM; *p<0.05, Placebo v. TNX-102 SL 2.8 mg, MMRM; MCFB, mean change from baseline; MMRM, mixed models repeated measure

Figure 2. CAPS-5 Sleep Disturbance Item (E6) MCFB

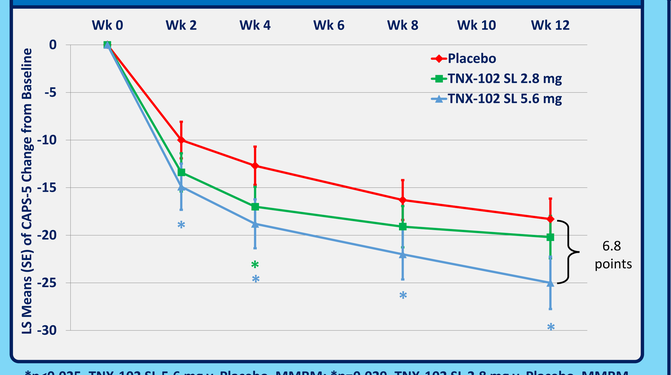
*p<0.05, Placebo v. TNX-102 SL 5.6 mg, MMRM; *p<0.05, Placebo v. TNX-102 SL 2.8 mg, MMRM; MCFB, mean change from baseline; MMRM, mixed models repeated measure

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

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 baseline score and final outcome. The original CAPS-5 entry criterion of ≥29 was based on picking an entry criterion similar to previous registration studies of approved PTSD pharmacotherapies that required a baseline severity score of ≥50 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 & 0-4 for frequency (maximum possible score = 136). To compare the AtEase population with prior studies, we imputed a CAPS-IV (iCAPS-IV) for DSM-IV in AtEase using the 17 common items and multiplying by 2. Using this imputed score, 10 participants with iCAPS-IV ≤50 (range 44-50) were identified. A retrospective analysis of the AtEase participants choosing a CAPS-5 score of ≥33 at entry excluded all 10 of those participants and, overall, 20% of the AtEase mITT population. Treatment efficacy in AtEase subsample with baseline CAPS-5 ≥33 is shown in **Figure 3**. CAPS-5 MCFB differences are significantly greater for TNX-102 SL 5.6 mg than Placebo at all visits; Week 12 comparison of TNX-102 SL 5.6mg with Placebo showed an effect size of 0.53 (**Table 3**).

Figure 3. CAPS-5 MCFB 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 Outcome Measures for TNX-102 SL 5.6 mg vs. Placebo in Military-Related PTSD for Both Entry Thresholds

Outcome Measures	PBO N=92, 5.6 mg N=49; CAPS-5 ≥ 29		PBO N=77, 5.6 mg N=38; CAPS-5 ≥ 33	
	ES[1]	p-value[2]	ES[1]	p-value[2]
CAPS-5				
Total Score	0.36	0.053	0.53	0.013*
Cluster B (Intrusion)	0.26	0.161	0.46	0.026*
Cluster C (Avoidance)	0.04	0.963	0.12	0.522
Cluster D (Mood/Neg Cog)	0.35	0.062	0.39	0.065
Cluster E (Arousal & React)	0.35	0.048*	0.52	0.012*
E6 (Sleep Item)	0.51	0.010*	0.51	0.013*
E2 (Reckless/Self Destruct)	0.15	0.140	0.30	0.012*
CGI-I				
CGI-I (Responders)	2.11#	0.041*	2.29	0.042*
SDS				
Total Score	0.33	0.079	0.35	0.093
Work/School Item	0.34	0.050	0.41	0.040*
Social/Leisure Item	0.38	0.031*	0.35	0.116
Family Life/Home Resp	0.12	0.524	0.15	0.455

[1]Cohen's *d* for CAPS-5 and SDS outcome measures; [2]CAPS-5 and SDS outcome: p-values from MMRM comparing TNX-102 SL 5.6 mg and Placebo; CGI-I: p-values from a repeated measure logistic regression (Responder: "1" very much improved or "2" much improved at week 12); *p<0.05, not adjusted; #odds ratio for CGI-I. Abbreviations: 5.6 mg= TNX-102 SL 5.6 mg; ES= Effect Size; N= number of patients; PBO= Placebo

Sub-Group Analysis of Combat PTSD

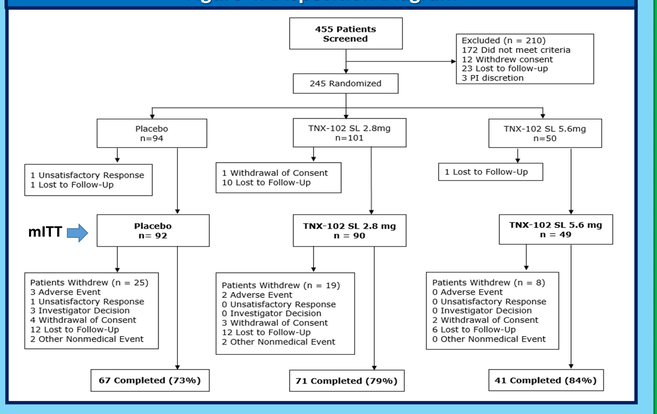
We defined military-related PTSD as resulting from any DSM-5 Criterion A-qualifying trauma that occurred during military service. Yet, the majority of index traumas (85.0%) in our AtEase study were directly related to combat activities and would be considered combat PTSD as strictly defined. A sub-group analysis of patients whose index traumas were combat-related (N=197) was performed; significantly greater improvement in the CAPS-5 total, CAPS-5 clusters (intrusion, mood and hyperarousal), certain items (e.g., sleep quality), and the global measures, and work and social function items on the SDS was observed in the 5.6 mg group relative to placebo (**Table 4**). Moreover, the subset of combat-trauma participants with CAPS-5 ≥33 treated with TNX-102 SL 5.6 mg had statistically significant improvement over Placebo in both hyperarousal (cluster E) and intrusion (cluster B) as well as certain key items (e.g., sleep, reckless and self-destructive behavior) (**Table 4**). In addition, the subset of combat-trauma participants with CAPS-5 ≥33 treated with TNX-102 SL 5.6 mg had statistically significant improvement over Placebo in the total Sheehan Disability Scale.

Table 4. Week 12 Outcome Measures for TNX-102 SL 5.6 mg vs. Placebo in Combat-Only PTSD for Both Entry Thresholds

Outcome Measures	PBO N=74, 5.6 mg N=46; CAPS-5 ≥ 29		PBO N=64, 5.6 mg N=35; CAPS-5 ≥ 33	
	ES[1]	p-value[2]	ES[1]	p-value[2]
CAPS-5				
Total Score	0.42	0.037*	0.57	0.013*
Cluster B (Intrusion)	0.26	0.183	0.50	0.031*
Cluster C (Avoidance)	0.04	0.824	0.11	0.570
Cluster D (Mood/Neg Cog)	0.41	0.035*	0.42	0.061
Cluster E (Arousal & React)	0.40	0.036*	0.57	0.012*
E6 (Sleep Item)	0.58	0.003*	0.58	0.010*
E2 (Reckless/Self Destruct)	0.15	0.178	0.30	0.019*
CGI-I				
CGI-I (Responders)	2.15	0.049*	2.12	0.082
SDS				
Total Score	0.41	0.039*	0.47	0.032*
Work/School Item	0.40	0.026*	0.40	0.015*
Social/Leisure Item	0.50	0.013*	0.51	0.028*
Family Life/Home Resp	0.19	0.328	0.22	0.274

[1]Cohen's *d* for CAPS-5 and SDS outcome measures; [2]CAPS-5 and SDS outcome: p-values from MMRM comparing TNX-102 SL 5.6 mg and Placebo; CGI-I: p-values from a repeated measure logistic regression (Responder: "1" very much improved or "2" much improved at week 12); *p<0.05, not adjusted; #odds ratio for CGI-I. Abbreviations: 5.6 mg= TNX-102 SL 5.6 mg; ES= Effect Size; N= number of patients; PBO= Placebo

Figure 4. Disposition Diagram



Safety and Tolerability

TNX-102 SL up to 5.6 mg (2 x 2.8 mg tablets) was well-tolerated as evidenced by the high (84%) completion rate (**Figure 4**) and no AE-related discontinuations in the 5.6 mg group. No clinically significant changes in heart rate, systolic and diastolic blood pressure, or body weight were observed in participants treated with TNX-102 SL for the 12 weeks of study among completers of the safety population (**Table 5**).

Table 6 shows adverse events (AEs) for TNX-102 SL in the AtEase study. Despite marginally increased rates of a few systemic AEs in the TNX-102 SL 5.6 mg group (somnolence, headache, sedation) compared to Placebo, no participant dropped out due to AE. The most common AE, tongue numbness, a non-dose related local administration site reaction, occurred at similar rate in the two TNX-102 SL groups (39% & 36%).

Few AEs were related to sexual dysfunction in the study. In Placebo, one (1.1%) participant reported decreased libido and one (1.1%) reported erectile dysfunction. In TNX-102 SL groups, one (1.1%) 2.8 mg participant reported decreased libido, one (2.0%) 5.6 mg participant reported increased libido and one (2%) 5.6 mg participant reported disturbance in sexual arousal.

Table 5. Changes in Heart Rate, Blood Pressure, and Body Weight Over 12 Weeks of Study by Treatment Group

Measure	Placebo (N=67)*	TNX-102 SL 2.8 mg (N=71)*	TNX-102 SL 5.6 mg (N=41)*
ΔHR (bpm)	+1.0 (11.30)	+2.8 (11.09)	+1.4 (12.03)
ΔSBP (mmHg)	-0.1 (10.17)	-0.5 (10.59)	-4.4 (11.23)
ΔDBP (mmHg)	-1.4 (7.33)	+1.1 (9.05)	-1.5 (7.37)
ΔWeight (kg)	+0.08 (3.01)	+0.09 (3.22)	+0.64 (2.48)

bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; kg, kilogram; mmHg, millimeters of mercury; SBP, systolic blood pressure; * Completers of the safety population

Table 6: Adverse Events (at rate of ≥5% in either drug-treated group)

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%
Local 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 most common AE, generally transient (<60 minutes), non-dose related and rated mild in 89% and moderate in 11% on TNX-102 SL; *Safety Population (N=237)

CONCLUSIONS

- TNX-102 SL 5.6 mg reduced total CAPS-5 symptoms and provided overall improvement and reduction in disability in military-related PTSD
- A retrospective analysis indicated a study entry CAPS-5 severity score of ≥33 is more aligned with previous PTSD pharmacotherapy registration trials that used prior CAPS versions, and the effect sizes (ES) of TNX-102 SL 5.6 mg are substantial (ES=0.5) on total and cluster B and E scores in this subsample
- The subgroup of AtEase participants with PTSD from combat-type traumas had beneficial effects of TNX-102 SL 5.6 on CAPS-5 total severity (ES=0.6) and clusters B (ES=0.5) and E (ES=0.6), and on overall functional improvement by SDS total score, work and social items
- The TNX-102 SL 5.6 mg was well-tolerated with a high completion rate and no AE-related discontinuations; non-dose related tongue numbness was common, generally transient, and never rated as severe. No clinically significant changes in weight or vital signs over the 12 weeks of study were observed.
- Sexual dysfunction is a common complaint in treatments with selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor classes. Low rates of reported sexual dysfunction AEs with TNX-102 SL, similar in rates to Placebo, may potentially be an advantage for TNX-102 SL as a treatment for PTSD.