The AtEase Study:

A Phase 2 Multicenter Randomized Clinical Trial of the Safety and Efficacy of TNX-102 SL* in the Treatment of Military-Related PTSD

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*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 that is widely prevalent in United States military personnel
- There is an urgent unmet need for pharmacotherapies for this population
- TNX-102 SL is a low dose sublingual formulation of cyclobenzaprine (CBP), a tricyclic molecule with high affinity and functional antagonism for 5-HT_{2A}, α_1-adrenergic, and histamine-H_1 receptors, all with roles in sleep regulation
  - Targets sleep disturbance and hyperarousal, core PTSD symptoms
  - Hypothesized to play a critical role in PTSD global recovery by allowing sleep-dependent memory processing (e.g. extinction consolidation)
- TNX-102 SL differs from orally administered CBP; it was designed to enhance sublingual transmucosal absorption at bedtime, resulting in peak CBP plasma levels during sleep hours and reduced daytime exposure
  - Avoids first-pass hepatic metabolism, reducing formation of long-lived active metabolite, norcyclobenzaprine
- The "AtEase Study" was our first evaluation of the efficacy and safety of TNX-102 SL in military-related PTSD including combat-only PTSD

METHODS

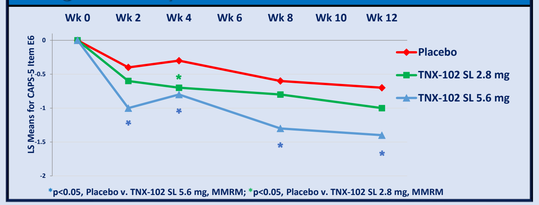
- Multicenter, 12-week, double-blind placebo-controlled Phase 2 study
- Inclusions: both sexes; ages 18-65; PTSD DSM-5 Criterion A trauma(s) during military service since 9/11/2001; current PTSD by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Baseline total CAPS-5 score ≥ 29; free of antidepressants ≥ 2 months; free of or washed off of other psychotropics; not participating in trauma-focused psychotherapy
- Exclusions: serious suicide risk; substance use disorders within 6 months; lifetime bipolar, psychotic, obsessive-compulsive, or antisocial personality disorders
- Randomized in 2:1:2 ratio to TNX-102 SL 2.8 mg, TNX-102 SL 5.6 mg, Placebo at 24 U.S. sites; 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 analysis (MMRM)
- Key 2◦ endpoints: Clinical Global Impression–Improvement (CGI-I), Sheehan Disability Scale (SDS), PROMIS Sleep Disturbance (SD). Also: CAPS-5 clusters, Patient Global Impression of Change (PGIC)
- CAPS-5 raters ≥ Master's degree-level in mental health; rigorously trained/certified; and reliability monitoring over course of study

RESULTS

Of 245 patients randomized, 231 were included in the modified intent-to-treat (mITT) efficacy population (14 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; completion rates of 79%, 84%, and 73%, respectively. **Table 1** shows demographic and clinical characteristics.

- Primary analysis: The primary analysis of 2.8 mg TNX-102 SL did not separate from Placebo at Week 12 (p=0.259, NS), however, the 5.6 mg arm showed a strong trend for improvement versus Placebo in MCFB in CAPS-5 (p=0.053, NS), with an effect size of 0.36 (Cohen's *d*); and sensitivity analyses of the 5.6 mg dose v. Placebo on CAPS-5 MCFB were statistically significant (see **Table 2**)
- The CAPS-5 Arousal & Reactivity cluster was significantly more improved for the 2.8 mg arm than Placebo at Weeks 2, 4 and 8 (p<0.05); the 5.6 mg arm was significantly more improved at Weeks 2, 8, and 12 (p<0.05)
- The sleep disturbance item (E6) of CAPS-5 was significantly more improved in the 5.6 mg arm over Placebo early by Week 2 and maintained at all other assessments (Weeks 4, 8, and 12); the 2.8 mg arm was significantly more improved at Week 4 only (See **Figure 1**)
- The exaggerated startle item (E4) of CAPS-5 was significantly more improved for the 5.6 mg arm over Placebo at Week 12
- The systemic adverse events reported were consistent with those reported with CBP; tongue numbness was common, generally transient, and never rated as severe; with overall good tolerability (see **Table 5**)

Figure 1. Sleep Disturbance MCFB Over 12 Weeks



*p<0.05, Placebo v. TNX-102 SL 5.6 mg, MMRM; *p<0.05, Placebo v. TNX-102 SL 2.8 mg, MMRM

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
Females, no. (%)	6 (6.7%)	4 (8.2%)	6 (6.5%)
Mean age, yrs (SD)	34.5 (8.3)	34.8 (9.0)	32.0 (6.5)
Weight, kg (SD)	90.9 (18.2)	90.8 (17.4)	91.6 (16.9)
BMI, kg/m^2 (SD)	29.0 (5.2)	29.0 (4.7)	28.9 (4.4)
Education, some college or beyond	80 (88.9%)	41 (83.7%)	72 (78.2%)
% currently employed	56 (62.2%)	33 (67.3%)	54 (58.7%)
% in military service at index trauma	85 (94.4%)	49 (100%)	91 (98.9%)
Active Duty/Reservists/Veterans	9/5/71	5/7/37	8/4/79
Law Enforcement Officers	5	0	1
Ave time since trauma, yrs (SD)	7.3 (3.3)	6.2 (3.3)	7.1 (3.6)
Ave deployments, military (SD)	2.3 (2.15)	2.6 (2.16)	2.2 (1.84)
Baseline CAPS-5 Scores (SD)	39.5 (8.0)	39.3 (8.1)	39.5 (7.7)
Baseline MADRS Scores (SD)	17.6 (5.18)	16.1 (5.54)	17.3 (6.53)

Table 2. Results of Primary and Sensitivity Analyses

Assessment	Domain	Analysis	p-Values	
			2.8 mg	5.6 mg
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*

*p<0.05; ^Primary analysis not significant; BOCF, baseline observation carried forward; LOCF, last observation carried forward; MMRM, mixed model repeated measures

Retrospective Analysis Using CAPS-5 ≥ 33 as Threshold for Study Entry

For inclusion, prior registration studies of approved PTSD pharmacotherapies required a baseline severity score of ≥50 on previous versions of CAPS. Those versions scored PTSD 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). The AtEase protocol required CAPS-5 severity of ≥29 for enrollment. To compare the AtEase population with prior studies, we retrospectively imputed a CAPS-IV (iCAPS-IV) for DSM-IV in AtEase using the 17 common items and multiplying by 2. Using the iCAPS-IV, 10 subjects with iCAPS-IV ≤50 (range 44-50) were found. A retrospective analysis of the AtEase patients with CAPS-5 ≥33 at entry, excluded those 10 patients and 20% of the AtEase population. Analysis of efficacy in the population with baseline CAPS-5 ≥33 is shown in **Figure 2**. The CAPS-5 assessments MCFB are significant for TNX-102 SL 5.6 mg at all assessments at Weeks 2, 4, 8 and 12. Week 12 comparison of TNX-102 SL 5.6 mg with Placebo showed an effect size of 0.53 (see **Table 3**).

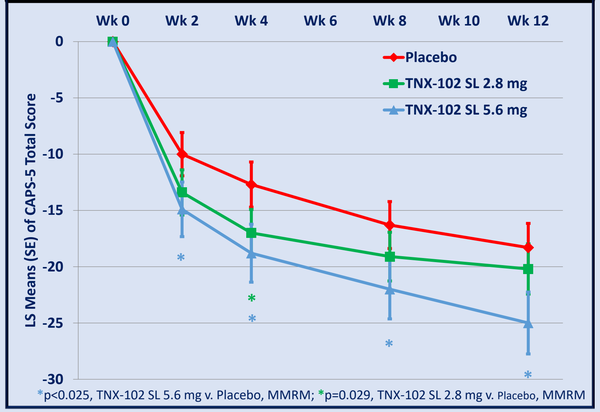
Table 3 shows p-values and effect sizes of CAPS-5 total and cluster scores, CAPS-5 items E6 & E2, CGI-I responders, and SDS total and item scores comparing TNX-102 SL 5.6 mg v. Placebo at Week 12 using the per protocol threshold of ≥29 and, separately, the subsample with CAPS-5 baseline score of ≥33. Effect sizes are substantial for CAP-5 total score and clusters B, D & E for the ≥33 subsample.

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

	PBO N=92, 5.6mg N=49; CAPS-5 ≥ 29		PBO N=77, 5.6mg N=38; CAPS-5 ≥ 33	
Outcome Measure	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/cognition)	0.35	0.062	0.39	0.065
Cluster E (arousal and reactivity)	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 (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 Responsibilities item	0.12	0.524	0.15	0.455

[1]Cohen's *d* for CAPS-5 and SDS outcome measures; odds ratio for CGI-I.
[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; Abbreviations: 5.6 mg=TNX-102 SL 5.6 mg; ES=Effect Size; N=number of patients; PBO=Placebo

Figure 2. 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

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 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 (**Table 4**). Moreover, the subset of combat-trauma patients with CAPS-5 ≥33 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) with the most substantial effect sizes observed with TNX-102 SL 5.6 mg (**Table 4**).

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

	PBO N=74, 5.6mg N=46; CAPS-5 ≥ 29		PBO N= 64, 5.6mg N=35; CAPS-5 ≥ 33	
Outcome Measure	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/cognition)	0.41	*0.035	0.42	0.061
Cluster E (arousal and reactivity)	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 (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 Responsibilities item	0.19	0.328	0.22	0.274

[1]Cohen's *d* for CAPS-5 and SDS outcome measures; odds ratio for CGI-I.
[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; Abbreviations: 5.6 mg=TNX-102 SL 5.6 mg; ES=Effect Size; N=number of patients; PBO=Placebo

Table 5 shows adverse events (AEs) for TNX-102 SL in PTSD. Despite marginally increased rates of a few systemic AEs in the 5.6 mg arm, 84% completed the study, and no one in the TNX-102 SL 5.6 mg arm discontinued due to AE. Tongue numbness was never rated as severe.

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

	Placebo (N=94)*	TNX-102 SL 2.8 mg (N=93)*	TNX-102 SL 5.6 mg (N=50)*
Systemic Adverse Events			
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 most common AE, generally transient (<60 minutes), 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 severity and provided global improvement, including on work & social function 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 TNX-102 SL 5.6 mg has substantial effect sizes on total and cluster scores on this subsample
- The subgroup of AtEase with combat PTSD had the most robust effects of TNX-102 SL 5.6 mg on CAPS-5 severity and cluster scores, and on overall functional improvement by SDS total score, work and social items
- The TNX-102 SL 5.6 mg group had a high completion rate and no AE discontinuations; tongue numbness was common, generally transient, and never rated as severe; with overall good tolerability