The Efficacy and Safety of TNX-102 SL,* a Sublingual Formulation of Cyclobenzaprine, for 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.

Background

- Posttraumatic stress disorder (PTSD) is a serious, often chronic, and debilitating disorder impacting individuals, their families and society
- Current unmet need for pharmacotherapies for PTSD
  - Only two FDA-approved medications: one failed to show a benefit in military-related PTSD in large multicenter study; other was not tested in this population
  - Trials inconsistent in civilian males, one of the two drugs shown to be ineffective
  - Both with tolerability issues: sexual dysfunction, insomnia and withdrawal
- TNX-102 SL, a low dose sublingual formulation of cyclobenzaprine (CBP), a tricyclic molecule
  - 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 symptoms of PTSD
  - Potentially critical role of improving sleep in providing global benefit in PTSD by allowing sleep-dependent emotional memory (extinction) consolidation
- TNX-102 SL differs from orally administered CBP as it was designed to enhance sublingual transmucosal absorption at bedtime
  - Resulting in peak CBP plasma levels during sleep hours
  - Avoids first-pass metabolism, reducing formation of long-lived active metabolite, norcyclobenzaprine, with off-target functional activities
- The "AtEase Study" was conducted in order to assess the efficacy, safety, and tolerability of TNX-102 SL in the treatment of military-related PTSD

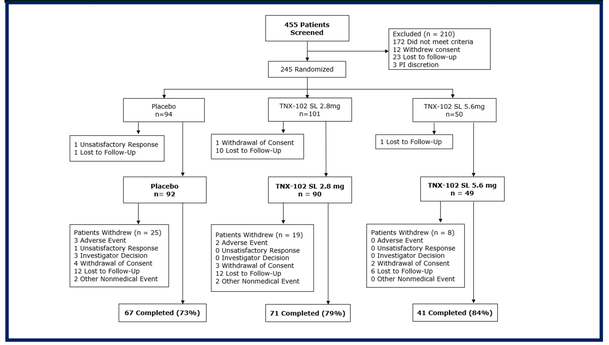
Methods

- Multicenter, 12-week, double-blind placebo-controlled (DB-PC) 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)
  - Total CAPS-5 severity score ≥ 29 at Screening and Baseline
  - Free of antidepressants ≥ 2 months and free of or washed off other psychotropics
- Exclusions included:
  - Serious suicide risk; unstable medical illness; substance use disorders within 6 months; and lifetime bipolar 1 or 2, psychotic disorders, obsessive compulsive disorder, or antisocial personality disorder
- Randomized in 2:1:2 ratio to receive TNX-102 SL 2.8 mg, TNX-102 SL 5.6 mg, or Placebo with dynamic randomization procedure to minimize trial-wide imbalances (by site, sex, and presence [yes/no] of current major depressive disorder.
- Conducted at 24 US sites (2 VA, 2 academic, 20 private)
- Primary efficacy analysis:
  - Comparison of mean change from baseline (MCFB) in CAPS-5 severity score between TNX-102 SL 2.8 mg and Placebo, analyzed via mixed-effects model repeated measures (MMRM)
- Key secondary endpoints were:
  - Clinical Global Impression – Improvement (CGI-I) scale,
  - Sheehan Disability Scale (SDS)
  - PROMIS Sleep Disturbance instrument
- Other secondary measures included CAPS-5 cluster scores and remission rates
- CAPS-5 raters were ≥ MA-level in mental health fields; underwent rigorous training and certification process; reliability monitoring throughout trial
- For CAPS-5, maximum possible score is 80; and PTSD severity is as follows: 0-10 is asymptomatic, 11-22 is mild, 23-34 is moderate, 35-46 is severe, and 47+ is extreme PTSD

Results

- 245 patients were randomized; 237 of those randomized made up the safety population; and 231 were included in the modified intent-to-treat (mITT) population (14 failed to return for post-baseline efficacy assessment); **Figure 1** shows the study consort diagram displaying total screens, randomizations, reasons for discontinuation and completers

Figure 1. TNX-CY-P201 Study Consort Diagram



- As seen in **Table 1**, demographic and clinical characteristics were similar across the three groups. Overall, 97.4% of the sample had military-related PTSD. Mean CAPS-5 scores for all groups were in the severe range at baseline.

Table 1. Patient Demographics and Characteristics

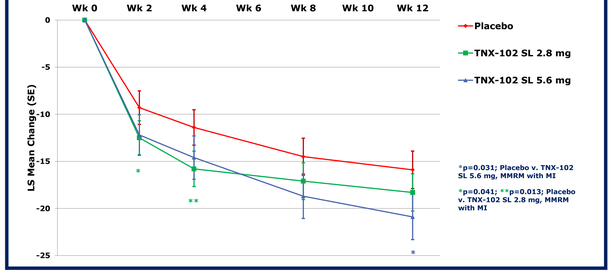
Variable	Placebo N=92	TNX-102 SL 2.8 mg N=90	TNX-102 SL 5.6 mg N=49	Overall N=231
Females, no. (%)	6 (6.5%)	6 (6.7%)	4 (8.2%)	16 (6.9%)
Mean age, yrs (SD)	32.0 (6.5)	34.5 (8.3)	34.8 (9.0)	33.6 (7.8)
Weight, kg (SD)	91.6 (16.9)	90.9 (18.2)	90.8 (17.4)	91.1 (17.5)
BMI, kg/m2 (SD)	28.9 (4.4)	29.0 (5.2)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

- The primary analysis, using mixed-effects model repeated measures (MMRM), did not demonstrate that TNX-102 SL 2.8 mg group was different from Placebo at Week 12 (p=0.259, NS).
- Yet the TNX-102 SL 5.6 mg group 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*)
- Several sensitivity analyses of TNX-102 SL 5.6 mg dose v. placebo were significant:

MMRM with multiple imputation (MI)	p=0.031
MMRM with hybrid LOCF/BOCF imputation	p=0.037
ANCOVA	p=0.038

Figure 2 represents the visit by visit mean change from Baseline in total CAPS-5 score utilizing the MMRM with MI method.

Figure 2. CAPS-5 Mean Change from Baseline (MCB)



- The CAPS-5 Arousal and Reactivity cluster was significantly more improved than placebo in the TNX-102 SL 2.8 mg arm for Weeks 2, 4 & 8, and the TNX-102 SL 5.6 mg arm for Weeks 2, 8 & 12.
- The TNX-102 SL 5.6 mg arm was also significantly more improved for the disturbed sleep item for all assessments and for exaggerated startle at Week 12

Figure 3 shows results of the Sheehan Disability Scale (SDS) domains for Work and Social functional improvement over the study, with both significantly more improved at Weeks 8 & 12 for the TNX-102 SL 5.6 mg group. At Week 12, SDS total for the 5.6 mg arm trended towards greater improvement (p=0.079)

Figure 3. Sheehan Disability Scale Domain Scores

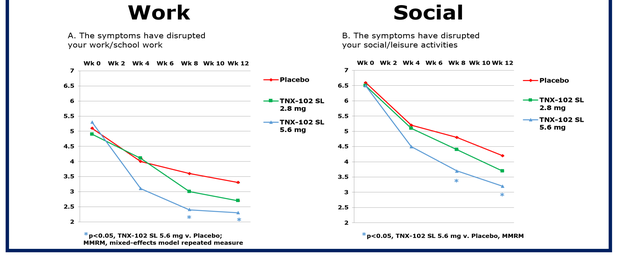
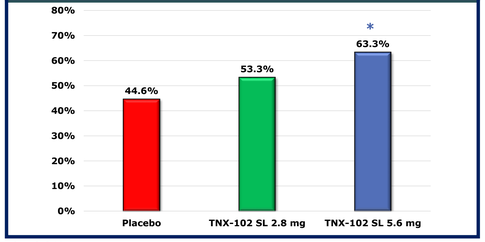


Figure 4 shows the responder analysis for the Clinical Global Impressions – Improvement (CGI-I) scale at Week 12, TNX-102 SL 5.6 mg had a significantly higher responder rate than placebo (p=0.041)

Figure 4. CGI-I Responder# Analysis



*p=0.041
#Responder defined as having a Week 12 CGI-I score of '2' (much improved) or '1' (very much improved)

Table 2 shows administration site and systemic AEs. The TNX-102 SL 5.6 mg group had minimally higher systemic AE rates for somnolence, dry mouth, headache, and sedation, yet there were no discontinuations in the group due to AE, suggesting they were tolerable

Table 2: Adverse Events* in Safety Population**

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%

*Adverse events occurring at a rate of >5% in either treatment arm; **N=237 for Safety Population
#Oral hypoaesthesia was the most common AE, was generally transient (<60 minutes), and rated as mild in 89% and moderate in 11% on TNX-102 SL.

Summary

- First large, multi-center, randomized, double-blind placebo-controlled Investigational New Drug trial demonstrating significant treatment effect in patients with military-related PTSD
- TNX-102 SL at 5.6 mg daily at bedtime for 12 weeks:
  - Reduced severity of PTSD (CAPS-5, Effect Size=0.36)
  - Reduced key symptoms (hyperarousal, insomnia, startle)
  - Improved global symptoms (CGI-I) and function (SDS work/school and social/leisure)
  - Tolerability evidenced by retention rate (84%) and low systemic side effects with no AE leading to discontinuations
- Results support advancing the clinical development of TNX-102 SL 5.6 mg for treatment of PTSD to Phase 3