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Randomized clinical trial of bedtime sublingual cyclobenzaprine (TNX-102 SL) in military-related PTSD and the role of sleep quality in treatment response

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ABSTRACT

Effective posttraumatic stress disorder (PTSD) pharmacotherapy is needed. This 12-week randomized multicenter trial evaluated efficacy and safety of TNX-102 SL, a bedtime sublingual formulation of cyclobenzaprine, in patients with military-related PTSD randomized to TNX-102 SL 2.8 mg or 5.6 mg, or placebo. Primary analysis comparing change from baseline in Clinician-Administered PTSD Scale-5 score between 2.8 mg (n=90) and placebo (n=92) was not significant. Secondary analysis of 5.6 mg (n=49) vs placebo demonstrated a mean difference of -4.5 units, p=.05, or, accounting for missing data by multiple imputation, -5.0 units, p=.03. Clinician Global Impression – Improvement responder rate was greater in 5.6 mg than placebo (p=0.04), as was mean functional improvement in Sheehan Disability Scale social domain (p=.03) and trended in work domain (p=.05). Post-hoc analyses showed early sleep improvement predicted improvement in PTSD after 12 weeks for TNX-102 SL (p<.01), not for placebo. Most common administration site reaction in TNX-102 SL groups was oral hypoaesthesia (5.6 mg, 36%; 2.8 mg, 39%; placebo, 2%), while most common systemic adverse event was somnolence (5.6 mg, 16%; 2.8 mg, 12%; placebo, 6%). This provides preliminary evidence that TNX-102 SL 5.6 mg reduces PTSD symptoms, improves sleep and psychosocial function, and is well tolerated.

Clinicaltrials.gov Identifier: NCT02277704

1. Introduction

Posttraumatic stress disorder (PTSD) is a common, serious, and often chronic psychiatric condition affecting approximately 4.7% of adults in the United States each year. (Goldstein et al., 2016) Prevalence rates in U.S. military personnel who served in the war theaters in Iraq and Afghanistan have been estimated at 21-31%. (Thomas et al., 2010) The state of pharmacological treatment options for PTSD has recently been described by experts in the field as a "crisis" (Krystal et al., 2017) due to the critical lack of advancement.

Sleep disturbance in PTSD is considered a core feature and is characterized by non-restorative sleep, frequent arousals and trauma-related distressing dreams. (Germain, 2013; Krakow et al., 2001; Spoormaker and Montgomery, 2008) Sleep disturbance also is suggested to play a causal role in PTSD pathogenesis and maintenance. (Babson et al., 2011; Germain et al., 2004; Koren et al., 2002; McLay et al., 2010; Mellman et al., 2002; Wright et al., 2011) The frequency of brief arousals has been shown to be higher in PTSD, including arousals from rapid eye movement (REM) sleep, one indicator of reduced sleep quality in the disorder. (Breslau et al., 2004; Capaldi et al., 2011)

Many now consider PTSD a "disorder of recovery" from trauma, and, more specifically, a disorder of emotional memory processing that includes deficits in extinction of conditioned fear. (Maren et al., 2013; Rothbaum and Davis, 2003; Yehuda and LeDoux, 2007) Human studies of fear memory and stress responsiveness have highlighted the role of sleep quality, particularly the quality of REM and slow wave (SWS)

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sleep, in affective and memory processes relevant to recovery from severely traumatic experiences. (Datta and O'Malley, 2013; Pace-Schott et al., 2015; Straus et al., 2017)

Cyclobenzaprine is a tricyclic molecule that was FDA-approved in 1977 for short term use (up to two or three weeks) as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Originally developed before the identification and characterization of most central nervous system (CNS) synaptic receptors and transporters, cyclobenzaprine has subsequently been found to bind and functionally interact with several receptor systems. It has particularly potent binding activity and is a functional antagonist of serotonin$_{2A}$ (5-HT$_{2A}$), adrenergic−α_1 (α_1), and histaminergic$_1$ (H_1) receptors, and it also more weakly inhibits the serotonin (SERT) and norepinephrine (NET) reuptake transporters. (Daugherty et al., 2015)

TNX-102 SL[1] is a sublingual formulation of cyclobenzaprine intended to be used at bedtime so that cyclobenzaprine levels will rapidly rise during the onset of sleep and fall during awakening. The sublingual, transmucosal formulation of cyclobenzaprine also bypasses first-pass hepatic metabolism, increasing the ratio in plasma of the parent cyclobenzaprine to the long-lived active metabolite, norcyclobenzaprine, which has more minimal circadian variation. The parent cyclobenzaprine plasma levels dynamically change during onset of sleep and awakening, whereas the metabolite norcyclobenzaprine is persistent due to a long (3 day) half-life, with plasma levels at steady state that are relatively stable. Consequently, the rise and fall of cyclobenzaprine after TNX-102 SL administration aligns with the sleep phase of the circadian rhythm.

PTSD is a condition in which the nocturnal blockade of 5-HT$_{2A}$, α_1, and H_1 neuroreceptors would be predicted to improve several aspects of disturbed sleep and traumatic memory processing, which inspired the current clinical trial. By improving sleep quality, cyclobenzaprine SL is hypothesized to be permissive to sleep-dependent emotional processing, and may enhance extinction consolidation and reconsolidation, and attenuate generalization, allowing the types of processing of traumatic memories that are essential for typical recovery from trauma to progress. (Datta and O'Malley, 2013; Diering et al., 2017; Pace-Schott et al., 2015; Smith et al., 2017; Spoormaker et al., 2012; Spoormaker et al., 2010; Zuj et al., 2016)

The diagnostic criteria for PTSD were substantially updated in May, 2013 with the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force., 2013), and a new corresponding version of the Clinician Administered PTSD scale (CAPS-5) was subsequently published and was used in this study. Due to substantial differences in certain items and globally in how intensities and frequencies of items are combined into final severity scores, the minimum baseline CAPS-5 severity entry criterion for this study could not be directly translated from the literature. Instead, prior CAPS versions used in earlier studies served as a general guide in selecting the baseline CAPS-5 severity threshold for inclusion. Therefore, a *post hoc* assessment of the present treatment outcome data was carried out to determine the baseline CAPS-5 severity threshold for study inclusion in future treatment trials.

This Phase 2 multicenter study (NCT02277704) evaluated whether monotherapy with TNX-102 SL would be more effective than placebo for recovery from PTSD in a population who experienced index traumas during military service, i.e. a population with military-related PTSD. Improvement in PTSD severity was assessed using the CAPS-5 total score. It was also hypothesized that improvement in PTSD from TNX-102 SL therapy may be mechanistically related to upstream improvement in sleep quality, which was explored by *post hoc* analyses.

[1] TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication

2. Methods

2.1. Patient sample

Patient eligibility was based on: age 18-65 years old; service in United States (US) military; meeting PTSD diagnostic criteria by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5); screening and baseline CAPS-5 total $\geq$ 29; and the incurred trauma(s) that resulted in PTSD during military service were in 2001 or later. In addition, Homeland Security and law enforcement officers without military service could qualify if index trauma(s) were incurred during work in 2001 or later. Patients were in generally good physical health on basis of medical history, physical examination, screening laboratory results and electrocardiogram. Other eligibility criteria included willingness to refrain from antidepressants and other excluded psychotropic medications.

Exclusion criteria included: meeting lifetime diagnostic criteria for bipolar I or II, schizophrenia, other psychotic disorder, obsessive-compulsive disorder, major depressive disorder (MDD) with psychotic features, or antisocial personality disorder; meeting for alcohol or substance (other than tobacco) use disorders within six months of screening; antidepressant treatment within two months of baseline; trauma-focused psychotherapy within one month of screening; clinical or laboratory evidence of hepatic impairment or clinical hypothyroidism; body mass index $>$ 40; unstable medical condition; history of moderate or severe traumatic brain injury (TBI); moderate or severe sleep apnea not well-controlled by Continuous Positive Airway Pressure (CPAP) or oral device (mild or well-controlled sleep apnea was allowed at the discretion of the investigator); severe depression indicated by Montgomery-Åsberg Depression Rating Scale (MADRS) $\geq$ 30 at screening or baseline; or high risk of suicidal behavior as indicated by suicide attempt in prior year or suicidal ideation with active plan and/or intent in prior six months.

The research was conducted at 24 outpatient psychiatric research clinics in US, including two Veterans Administration (VA) centers and two academic medical centers. All activities were conducted in accordance with the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. The informed consent form and protocol received independent institutional review board (IRB) approval before study initiation. All patients provided written informed consent.

2.2. Study design

Patients were recruited by local advertising, outreach, and social media campaigns. The Mini International Neuropsychiatric Interview, version 7.0 for DSM-5 (MINI 7.0), was used at screening to rule out excluded psychiatric conditions and document comorbidities. Patients were randomly assigned in a 2:1:2 ratio to 12 weeks of double-blind, parallel, fixed-dose treatment using a "double-dummy" design with: TNX-102 SL 2.8 mg (1 x TNX-102 SL 2.8 mg tablet, 1 x placebo SL tablet); TNX-102 SL 5.6 mg (2 x TNX-102 SL 2.8 mg tablets); or placebo SL (2 x placebo SL tablets). A computer-generated, dynamic randomization algorithm accounting for sex, current MDD, and trial site was employed to minimize treatment imbalances. Patients were randomized after a comprehensive pre-randomization review of screening assessments, conducted by the sponsor medical monitors. Study visits took place at screening, baseline and at 1, 2, 4, 6, 8, 10, and 12 weeks, or at time of discontinuation if before Week 12; and, for those not entering a 12-week open-label extension study (NCT02421679), at follow-up one week later. Treatment was initiated at bedtime on day of randomization.

2.3. Efficacy assessments

While the screening CAPS-5 administration employed the CAPS-5

Past Month Version to confirm PTSD diagnosis, the CAPS-5 Past Week Version was used for the primary efficacy outcome measure. The primary endpoint was change from baseline to Week 12 in CAPS-5 Past Week Version total score, assessed at baseline and Weeks 2, 4, 8, and 12. This scale was administered by raters blind to randomization status. Key secondary outcome measures were the Patient-Reported Outcome Measurement Information System (PROMIS) Sleep Disturbance (Form 8a) scale, the Clinical Global Impressions-Improvement scale (CGI-I), and the Sheehan Disability Scale (SDS). The MADRS measured severity of depressive symptoms. All raters underwent initial training and credentialing for the clinician-administered measures. Dr. Weathers oversaw training and credentialing on the CAPS-5.

2.4. Safety assessments

Adverse events and any concomitant treatments were recorded at all visits. Safety measurements included changes from baseline in vital signs and weight, clinical laboratory results, electrocardiogram intervals, and suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).

2.5. Statistical methods

Analyses of efficacy outcomes were performed on the modified Intention-To-Treat (mITT) population, defined as all randomized patients who had at least one post-baseline CAPS-5 assessment.

The primary statistical model for hypothesis testing was a mixed-model repeated-measures analysis (MMRM) including all mITT patients and all three treatment groups. Covariates included the fixed categorical effects of treatment, site, sex, presence of current MDD, visit and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. The primary comparison was the contrast between TNX-102 SL 2.8 mg and placebo at Week 12. Data from the TNX-102 SL 5.6 mg arm was included when fitting the model, although the 5.6 mg to placebo contrast was a secondary comparison. 95% confidence intervals (CI) and least squares means with standard errors were determined for the difference from baseline in each study arm and for the treatment contrast. The MMRM model was used with various strategies for handling missing data including no imputation (the prespecified primary analysis), multiple imputation (MI), and a baseline observation/last observation carried forward (BOCF/LOCF) imputation method. For the two imputation approaches, discontinuations as a result of lack of efficacy or adverse event were considered missing-not-at-random and imputed based on baseline values of the treatment arm; whereas all other discontinuations were treated as missing-at-random and imputed based on the respective visit values of the treatment arm.

Continuous secondary measures were analyzed similarly to the primary endpoint. Baseline values of the secondary endpoints were used instead of baseline CAPS-5, employing the other covariates and interactions described for the primary analysis. Binary data over time was analyzed using repeated measures marginal logistic regression fit by restricted pseudo-likelihood. CGI-I, which has no baseline assessment, was analyzed by responder analysis with responder defined as those scored at endpoint as 1 (“very much improved”) or 2 (“much improved”). For responder analyses, patients with missing data were analyzed as non-responders.

Post-hoc analyses of the relationship between early improvement in sleep quality and improvement in PTSD severity at endpoint were analyzed using simple regression models with effects of treatment, sleep, and treatment by sleep interaction on PTSD improvement. The models allowed each treatment arm to have an independent slope and intercept; additionally, a pooled estimate for the TNX-102 SL 2.8 mg and 5.6 mg groups combined was calculated.

Post-hoc analyses to determine the impact of baseline PTSD severity on response to treatment were conducted by exploring the subpopulations with higher CAPS-5 baseline entry threshold scores, above the protocol specified threshold of $\geq$29.

Effect sizes were computed using Cohen’s *d* to measure the magnitude of the treatment effect of TNX-102 SL over that of placebo.

All analyses were two-sided, performed at the α=0.05 level of significance, and without adjustment for multiple analyses.

3. Results

3.1. Demographic and clinical characteristics

The 24 sites enrolled patients from 1/2015 to 12/2015. As shown in Fig. 1, a total of 455 patients screened yielded 245 patients enrolled, and the 231 patients with at least one post-baseline primary outcome assessment made up the mITT population. A total of 179 (77.5% of mITT) patients completed the 12-week treatment period. There were no unexpected differences between the TNX-102 SL and placebo groups in the reasons provided for discontinuations (Fig. 1).

The mITT population included 225 (97.4%) patients in military service at time of the index trauma. Twenty-two patients were active-duty military and 16 were current reservists during the study period. Six patients (2.6%) in the mITT population were law enforcement officers. Table 1 provides baseline and demographic characteristics of the mITT population. The sample was predominantly male (n=215, 93.1%), mean (standard deviation; SD) age of 33.6 (7.8) years, 46.3% married or living with a partner, 29.4% single, and 23.4% separated/divorced. Race was 66.1% Caucasian, 24.5% African American, 2% Asian, 1.6% American Indian or Alaska Native, 2% multiple races, and 3.7% other; ethnicity was 18.8% Hispanic or Latino. Nearly all (95.6%) patients in military service at time of index trauma had served in the recent Iraq and/or Afghanistan conflicts. The mean (SD) number of deployments for the 225 in military service was 2.3 (2.0). For the total mITT sample, PTSD symptoms were attributed principally to traumas occurring during direct participation in combat in 197 patients (85.3%). The mean (SD) time since the index trauma was 7.0 (3.4) years. No clinically important differences in baseline demographic or clinical characteristics were identified between the three treatment groups.

3.2. Efficacy analysis

Table 2 lists the results of the analyses of the primary outcome measures, including two imputation approaches. While TNX-102 SL 2.8 mg had a greater change from baseline in CAPS-5 at Week 12 as compared to placebo, the primary analysis did not reach significance (least squares mean difference [LSMD], -2.2 units; p=0.26). In contrast, response to TNX-102 SL 5.6 mg was on the threshold of nominal significance (LSMD, -4.5 units; p=0.05) for greater improvement by the primary analysis method, and also was nominally significant when analyzed by either MMRM-LOCF/BOCF or MMRM-MI (p=0.04 and 0.03, respectively). The 5.6 mg group also showed greater continuing improvement from baseline throughout the 12 weeks compared with placebo (Fig. 2).

In an MMRM analysis of the clusters that comprise the CAPS-5, TNX-102 SL 5.6 mg reached significance on the arousal and reactivity cluster (p<0.05), but not the intrusion (p=0.16), avoidance (p=0.96) or mood/negative cognitions clusters (p=0.06). In fact, the avoidance cluster appeared unaffected by treatment.

Importantly, the TNX-102 SL 5.6 mg group had greater global improvement on the CGI-I scale (p=0.04; odds ratio=2.11) with a 63.3% response rate on 5.6 mg compared to 44.6% in the placebo group. The 2.8 mg group response on CGI-I was intermediate at a 53.3% response rate, but was numerically greater than placebo (p=0.24).

In terms of disability, the 5.6 mg group demonstrated numerically greater improvement in total SDS score but was not nominally significant (LSMD of -2.3; p=0.08). The 5.6 mg group did show nominally significantly greater improvement than placebo on the SDS social life

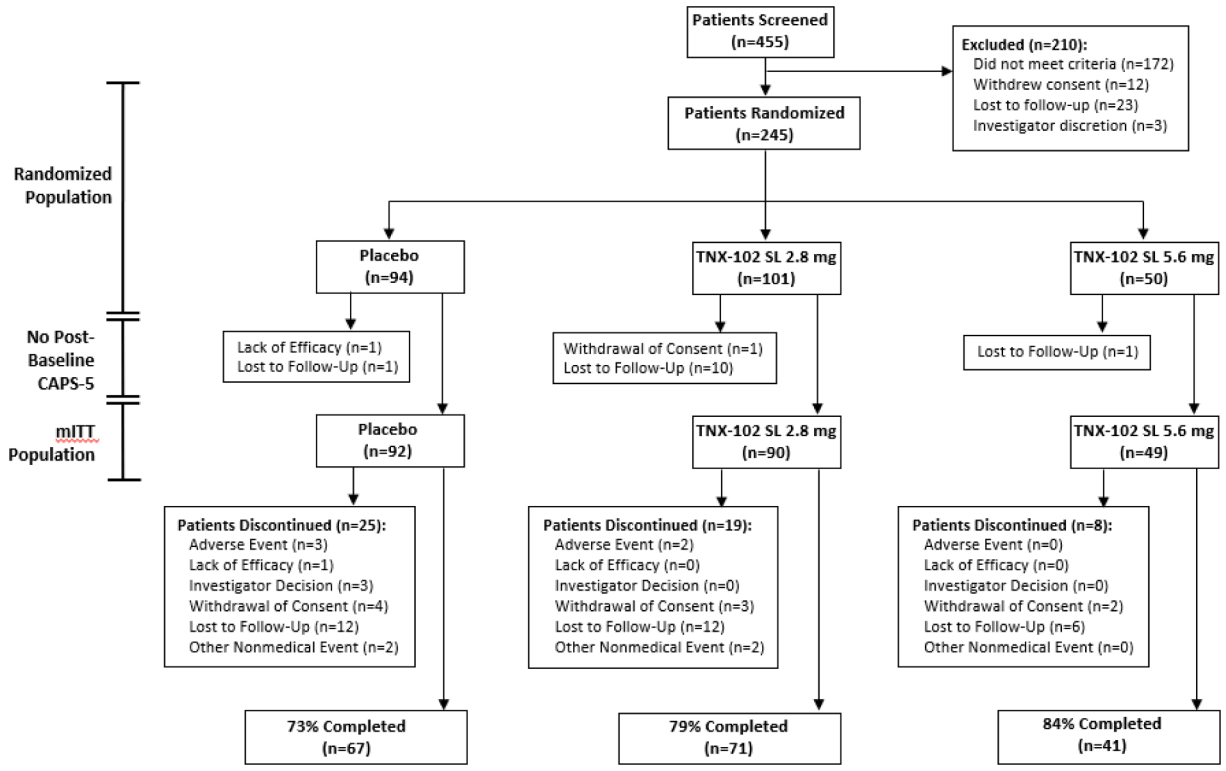

Fig. 1. Recruitment Flowchart
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; mITT = modified intention-to-treat; SL = sublingual

domain (LSMD of -1.0; p=0.03) and was on the threshold (LSMD of -1.0; p=0.05) for nominally significant improvement on the work domain.

3.3. Safety and tolerability

Similar proportions of patients from the three groups completed the 12 weeks of treatment (72.8% of placebo patients; 78.9% of TNX-102 SL 2.8 mg patients; and 83.7% of TNX-102 SL 5.6 mg patients). The reasons for study discontinuation and numbers of subjects within each treatment arm are summarized in Fig. 1.

No clinically relevant changes from baseline to endpoint were observed in laboratory parameters or vital signs for both treatment groups. Nor was there any clinically significant pattern of weight change in any of the treatment arms. Over the 12 weeks of the study, completers in the safety population showed a mean (SD) weight gain of 0.08 (3.01) kg for placebo (n=67), 0.09 (3.22) kg for 2.8 mg (n=71), and 0.64 (2.48) kg for 5.6 mg (n=41).

As shown in Table 3, the percentage of patients with at least 1 adverse event were 57.4%, 76.3% and 80.0% for placebo, TNX-102 SL 2.8 mg and TNX-102 SL 5.6 mg, respectively. Withdrawals due to adverse events numbered 3 on placebo, 2 on 2.8 mg, and 0 on 5.6 mg.

The most common treatment-emergent adverse events reported by at least 5% of patients in either TNX-102 SL-treated group are also listed in Table 3. Oral hypoaesthesia was the most common AE in the TNX-102 SL groups, with rates for TNX-102 SL 2.8 mg of 38.7%, TNX-102 SL 5.6 mg of 36.0% and placebo of 2.1%.

3.4. Post-hoc analysis of the relationship between early improvement in sleep quality and recovery from PTSD at endpoint

Recovery in PTSD is generally understood to be a process of new learning that involves extinction memory. Consolidation of extinction, in which short-term labile memory is processed to become stable long-term memory, occurs during sleep, with processing roles for both slow wave sleep (SWS) and rapid eye movement (REM) sleep. It is hypothesized that restoration of the *quality* of critical sleep stages may be in turn permissive to consolidation of extinction memory, thereby allowing re-establishment of normal recovery processes that manifest in clinical improvement over a course of several weeks.

The CAPS-5 sleep disturbance item (E6) improved over the 12 weeks of treatment, with sleep responding early to the TNX-102 SL 5.6 mg treatment (Week 2 LS mean difference [SE] from placebo of -0.7 [0.23], p<0.01; Week 4 of -0.5 [0.24], p=0.03; Week 8 of -0.7 [0.26], p<0.01; and Week 12 of -0.7 [0.26], p=0.01).

A more comprehensive measure of sleep quality, the PROMIS Sleep Disturbance (SD) 8a instrument, an 8-item self-report measure of both sleep quality and disturbance, was administered on Weeks 4, 8 and 12 of the trial. PROMIS SD T-scores showed similar early improvement for the 5.6 mg group at Week 4, although separation from placebo narrowed by Week 8 and was at trend level by Week 12 (Week 4 LS mean difference [SE] from placebo of -6.4 [1.69], p<0.001; Week 8 of -3.8 [1.89], p<0.05; and Week 12 of -3.1 [2.09], p=0.14).

To better understand the relationship between early response in sleep to treatment with TNX-102 SL and improvement in PTSD at Week 12, a post-hoc analysis examined the relationship between change from baseline at Week 4 for PROMIS SD T-scores and improvement in PTSD severity by Week 12 CAPS-5 total (minus sleep disturbance item E6) in completers in the three treatment arms.

Week 4 sleep did not correlate with treatment response among placebo patients (p=0.97) whereas for 2.8 mg there was a trend for a positive relationship (p=0.07). Consistent with the hypothesis that the PTSD response from TNX-102 SL is mediated by its direct effects on sleep quality, the 5.6 mg group presented the stronger positive relationship (p=0.015). Combining the two TNX-102 SL groups afforded the most power, showing the most significant effect (p=0.003) with a slope intermediate between the two groups individually (Fig. 3). Thus, early response in sleep quality at Week 4 was associated with Week 12 improvement in PTSD severity for TNX-102 SL but not for placebo.

Table 1
Baseline demographic data and mental health measures in modified intention-to-treat population.

Variable	Placebo *N*=92	TNX-102 SL 2.8 mg *N*=90	TNX-102 SL 5.6 mg *N*=49	Total *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/m^2 (SD)	28.9 (4.4)	29.0 (5.2)	29.0 (4.7)	28.9 (4.8)
Sleep apnea (mild and/or well-controlled), no. (%)	9 (9.6)	7 (7.5)	2 (4.0)	18 (7.6)
Education, No. (%) with some college or beyond	72 (78.2%)	80 (88.9%)	41 (83.7%)	193 (83.6%)
No. (%) currently employed	54 (58.7%)	56 (62.2%)	33 (67.3%)	143 (61.9%)
Unable to work due to PTSD, no. (%)	9 (9.8%)	10 (11.1%)	7 (14.3%)	26 (11.3%)
Military service at trauma, no. (%)	91 (98.9%)	85 (94.4%)	49 (100%)	225 (97.4%)
Combat trauma type for index trauma, no. (%)	74 (80.4%)	77 (85.6%)	46 (93.9%)	197 (85.2%)
Mean time since trauma, yrs (SD)	7.1 (3.6)	7.3 (3.3)	6.2 (3.3)	7.0 (3.4)
Mean deployments, military-only (SD)*	2.2 (1.8)	2.3 (2.2)	2.6 (2.2)	2.3 (2.0)
Baseline CAPS-5 Scores (SD)	39.5 (7.7)	39.5 (8.0)	39.3 (8.1)	39.5 (7.9)
Baseline SDS Total Score (SD)#	17.7 (6.5)	17.2 (7.1)	17.2 (6.0)	17.4 (6.6)
Baseline PROMIS Sleep Disturbance T-Score (SD)#	63.1 (7.4)	63.5 (8.0)	62.2 (8.0)	63.1 (7.7)
Baseline MADRS Scores (SD)	17.3 (6.5)	17.6 (5.2)	16.1 (5.5)	17.1 (5.8)
Lifetime suicidal Ideation with plan, no. (%)**	7 (7.4%)	9 (9.7%)	3 (6.0%)	19 (8.2%)
Lifetime actual suicide attempt, no. (%)**	6 (6.4%)	4 (4.3%)	3 (6.0%)	13 (5.6%)

Abbreviations: BMI = body mass index; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; kg = kilograms; m = meter; no. = number; SDS = Sheehan Disability Scale; PROMIS Sleep Disturbance = Patient-Reported Outcomes Measurement Information System - Sleep Disturbance instrument short form (8a); MADRS = Montgomery-Åsberg Depression Rating Scale

* Among *military-only* mITT population: placebo *N*=91, TNX-102 SL 2.8 mg *N*=85, TNX-102 SL 5.6 mg *N*=49;

SDS and PROMIS SD were missing 2 subjects in TNX-102 SL 5.6 mg group (TNX-102 SL 5.6 mg *N*=47);

** Safety population: placebo *N*=94, TNX-102 SL 2.8 mg *N*=93, TNX-102 SL 5.6 mg *N*=50

3.5. Post-hoc analysis of treatment response in subsample with higher CAPS-5 entry threshold

At the time of the design of the present study, there was no precedent using the new CAPS-5 in PTSD pharmacotherapy trials. A baseline CAPS-5 score of $\geq$ 29 was chosen as an inclusion criterion for this trial based on a simple mathematical extrapolation of the baseline inclusion criterion of CAPS for DSM-IV (CAPS-IV) total score $>$ 50. An observed inverse relationship between baseline CAPS-5 severity and improvement on CAPS-5 (β=-0.5, $p<0.001$) prompted the question of what would be a more appropriate level of baseline PTSD severity for CAPS-5 for assessment of a pharmacological treatment intervention in PTSD. To address this, we calculated an imputed CAPS-IV score for every patient in the mITT in order to estimate what would be the equivalent baseline minimum severity CAPS-5 score for entry to study compared to that typically used for studies that used CAPS-IV or earlier versions. A score of $\geq$ 33 on CAPS-5 was found to be the lowest threshold for which no subjects had an estimated CAPS-IV score of $\leq$ 50, suggesting the $\geq$ 33 was more similar to the $>$ 50 established for prior CAPS versions as the baseline severity for inclusion in precedent PTSD pharmacotherapy trials.

Therefore, for the *post-hoc* primary efficacy analysis of this subgroup with minimum baseline CAPS-5 score of $\geq$ 33, all patients with CAPS-5 baseline score between 29 and 32 were excluded, leaving for analysis the subgroup of patients with a severity threshold similar to precedent studies using prior CAPS versions. (Brady et al., 2000; Davidson et al., 2006; Davidson et al., 2001; Marshall et al., 2001; Tucker et al., 2001)

Table 4 shows the effect sizes and p-values for the primary analysis and multiple secondary analyses comparing TNX-102 SL 5.6 mg to placebo in the mITT population and in the subsample with baseline entry CAPS-5 score of $\geq$ 33. For the primary analytic method and endpoint analysis, change in total CAPS-5 score from baseline at 12-weeks by MMRM, the Cohen's *d* effect size for this TNX-102 SL 5.6 mg treatment effect in the subsample was 0.53, substantially larger than that found in the mITT population of 0.36 (with CAPS-5 $\geq$ 29). For the secondary analyses, Table 4 lists the effects in the CAPS-5 cluster subscores and selected CAPS-5 items scores, CGI-I response, and SDS total and domain subscores. The effect sizes in the subsample with baseline CAPS-5 entry total of $\geq$ 33 are either similar or greater than in the mITT population, suggesting CAPS-5 entry total of $\geq$ 33 for future pharmacotherapy trials with CAPS-5.

4. Discussion

In this proof of concept study, TNX-102 SL at 5.6 mg demonstrated an encouraging efficacy signal in those suffering from military-related PTSD, the PTSD subpopulation with the most critical unmet pharmacotherapy need.(Krystal et al., 2017) On CAPS-5, the 2.8 mg dosed group demonstrated only a weak trend for symptoms improvement, while the underpowered 5.6 mg dosed group demonstrated a substantial effect. It was shown that TNX-102 SL 5.6 mg (N=49) provided improvement at Week 12 in total CAPS-5 severity score. Compared to placebo, TNX-102 SL 5.6 mg produced a 5.0-point greater reduction from baseline in CAPS-5 total score by MMRM-MI analysis, a currently preferred approach for accounting for missing data. Despite the relatively smaller sample size of the 5.6 mg treatment arm, several preplanned analyses showed consistent effects on outcome measures of interest. Moreover, the 5.6 mg group reduced the CAPS-5 arousal and reactivity symptom cluster, and there was a trend for a greater treatment effect on the CAPS-5 mood and negative cognitions symptom cluster. Our findings are therefore comparable with the magnitudes of treatment effects of the only two FDA-approved medications for PTSD, the SSRIs paroxetine and sertraline. The effect size (ES) for the effect of TNX-102 SL 5.6 mg on total CAPS-5 improvement compared with placebo was 0.36 (by MMRM analysis). This is comparable to the effect of paroxetine on CAPS-2 improvement in its registration studies in predominantly civilian PTSD (ES of 0.42), and to the effect of sertraline in predominantly civilian PTSD (ES of 0.26) in its registration trials.(Excellence, 2005) It is important to emphasize the effect on total CAPS-5 in the present study was in a predominantly male (93%) sample with almost exclusively military-related PTSD. This contrasts with sertraline in a similar military PTSD sample which was no different than placebo in efficacy in a predominantly male (75%) sample of veterans in a multicenter Veterans Affairs trial.(Friedman et al., 2007) The effect size of TNX-102 SL 5.6 mg is also comparable to that of the SNRI venlafaxine extended release (ER) in a mostly civilian PTSD sample over 24 weeks of treatment.(Davidson et al., 2006)

TNX-102 SL 5.6 mg reduced the arousal and reactivity symptom cluster, which is in contrast to several (Brady et al., 2000; Davidson et al., 2006; Davidson et al., 2001; Martenyi et al., 2002) but not all (Marshall et al., 2001; Tucker et al., 2001) published PTSD studies with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

The efficacy of TNX-102 SL for PTSD was further supported by a

Table 2
Results of the primary outcome measure: change from baseline in week 12 CAPS-5.

Change from Baseline at Week 12	Primary Analysis:MMRM[#] without MI			Sensitivity Analysis:MMRM[#] with MI			Sensitivity Analysis:MMRM[#] with LOCF/BOCF		
		TNX-102 SL			TNX-102 SL			TNX-102 SL	
	PBO (N=92)	2.8 mg (N=90)	5.6 mg (N=49)	PBO (N=92)	2.8 mg (N=90)	5.6 mg (N=49)	PBO (N=92)	2.8 mg (N=90)	5.6 mg (N=49)
***N* at Week 12**	67	71	40	NA	NA	NA	92	90	49
Mean (*SD*)	-18.0 (11.91)	-20.6 (12.64)	-22.6 (13.65)	NA	NA	NA	-14.6 (12.49)	-17.2 (13.54)	-19.1 (14.65)
LS Mean (*SE*)	-17.0 (1.98)	-19.2 (1.99)	-21.5 (2.41)	-15.9 (1.99)	-18.3 (1.98)	-20.9 (2.41)	-13.8 (1.94)	-16.4 (1.95)	-18.6 (2.41)
95% CI	(-20.9, -13.1)	(-23.1, -15.3)	(-26.3, -16.8)	(-19.8, -12.0)	(-22.2, -14.4)	(-25.6, -16.2)	(-17.6, -9.9)	(-20.2, -12.5)	(-23.3, -13.9)
LS Mean Difference (SE) from PBO	NA	-2.2 (1.94)	-4.5 (2.31)	NA	-2.4 (1.95)	-5.0 (2.33)	NA	-2.6 (1.92)	-4.9 (2.31)
95% CI	NA	(-6.0, 1.6)	(-9.1, 0.1)	NA	(-6.2, 1.4)	(-9.6, -0.5)	NA	(-6.4, 1.2)	(-9.4, -0.3)
p-value	NA	0.259	0.053	NA	0.211	0.031*	NA	0.172	0.037*

Abbreviations: BOCF = baseline observation carried forward; LOCF = last observation carried forward; LS = least squares; MI = multiple imputation; MMRM = mixed models repeated measures; NA = not applicable; PBO = placebo

[#] LS mean, LS mean differences, 95% confidence intervals and p-values were obtained from the MMRM model with the fixed categorical effects of treatment, site, sex, presence of current major depressive disorder, visit and treatment by visit interaction as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. An unstructured covariance matrix was used. *P*-values compared the change from baseline for each of the active treatment groups to placebo.

[*] *p*-value < 0.050

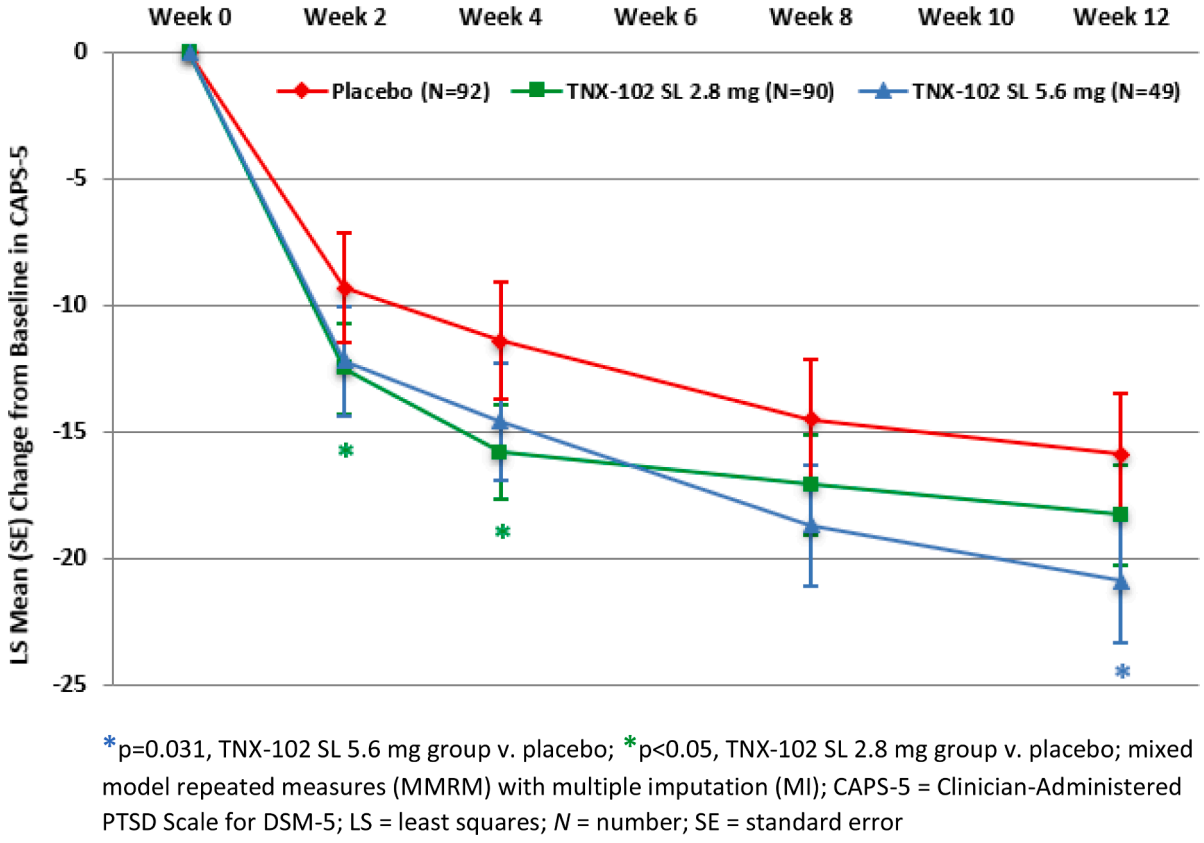

Fig. 2. Mean Change from Baseline in CAPS-5 at All Assessments Analyzed by MMRM with MI
*p=0.031, TNX-102 SL 5.6 mg group v. placebo; *p<0.05, TNX-102 SL 2.8 mg group v. placebo; mixed model repeated measures (MMRM) with multiple imputation (MI); CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; LS = least squares; *N* = number; SE = standard error

responder analysis of the CGI-I scale for the 5.6 mg arm, which demonstrated greater treatment responders than placebo at Week 12 (p=0.04; logistic regression). And TNX-102 SL 5.6 mg reduced disability on social function assessed by the SDS and was on the border (p=0.05) on reduction of disability on work function, both the domains of which were a full unit more improved compared to placebo. The effect sizes of TNX-102 SL 5.6 mg over 12 weeks in military-related PTSD on total SDS and the social and work domains were 0.33, 0.34, and 0.38, respectively.

Adverse events associated with TNX-102 SL were not serious, with the most common being oral hypoaesthesia in 38% that occurred after dosing and was generally transient, mild, and never rated as severe. Early withdrawal rates were comparable between groups, but it is notable that the completion rate was highest for the 5.6 mg group, at 83.7%, compared with 78.9% for the 2.8 mg group and 72.8% for placebo.

Recovery from PTSD is generally understood to involve new learning

Table 3
Adverse Event Characteristics and Most Common AEs Reported[#]

	Placebo (*N*=94)[*]	TNX-102 SL 2.8 mg (*N*=93)[*]	TNX-102 SL 5.6 mg (*N*=50)[*]
Percentage with at least one adverse event	57.4%	76.3%	80.0%
Number of study discontinuations due to adverse event	3	2	0
Number of study discontinuations due to lack of efficacy	1	0	0
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%

[#] at rate of 5% or greater in either TNX-102 SL-treated group
[*] Safety Population

in the form of extinction of conditioned defensive responses that developed in reaction to the traumatic experience.(Maren et al., 2013; Rothbaum and Davis, 2003; Yehuda and LeDoux, 2007) Consolidation of extinction, the memory process in which labile short term extinction memory becomes long term stable extinction memory, is known to depend on quality of both SWS and REM sleep stages.(Datta and O'Malley, 2013; Pace-Schott et al., 2015; Straus et al., 2017) The molecular targets of TNX-102 SL, specifically nocturnal blockade of 5-HT_{2A}, α_1, and H_1 neuroreceptors, each have differential roles in the improvement of disturbed sleep. The relationship established between early sleep improvement and Week 12 PTSD recovery with TNX-102 SL treatment but not placebo is supportive evidence of the mechanistic hypothesis that improved sleep quality is a mediator of TNX-102 SL treatment response in PTSD. Yet, since correlation does not establish causation, to definitively establish whether sleep quality is a mediator of PTSD recovery with TNX-102 SL, studies with polysomnographic and autonomic biomarker monitoring during treatment are needed.

This trial was the first multicenter pharmacotherapy trial to employ the most recent version of the CAPS, known as the CAPS-5, which has substantial differences in item number and content and an alternate method for determining item severity score. To establish a more appropriate CAPS-5 PTSD baseline severity for participant inclusion in future pharmacotherapy trials, *post-hoc* analyses further explored the finding from the primary analysis that baseline severity was robustly related to degree of reduction of CAPS-5 with treatment (see Supplementary Table 1). It was established that a higher CAPS-5 baseline threshold for inclusion of $\geq$ 33 rather than $\geq$ 29 defined a population more similar to precedent pharmacotherapy studies that used older CAPS versions and who by *post-hoc* analysis responded more robustly to TNX-102 SL. The effect size of the treatment effect of TNX-102 SL on reduction in CAPS-5 score, comparing the 5.6 mg group and placebo, in this subsample with baseline CAPS-5 $\geq$ 33 was shown to be notably higher at 0.53 rather than the 0.36 found in the mITT sample. These analyses established the baseline CAPS-5 inclusion threshold of $\geq$ 33 for Phase 3 testing of TNX-102 SL 5.6 mg in PTSD.

It also became clear during the course of this program that the CAPS-5 may not be an ideal clinical trial outcomes instrument. The CAPS-5 was designed to serve as a diagnostic tool following the DSM-5 PTSD criteria. It was not necessarily designed to be used frequently and repeatedly during the course of a patient's therapy, or to be sensitive to change in clinical status related to a treatment. We believe many patients in this study struggled with the repetitive nature of the CAPS-5 being administered multiple times, and this may limit the ability of the instrument to accurately measure symptoms improvement. We also found that several items of the CAPS-5 were insensitive to change in this study population, and believe consideration should be given to the use of a specific array of CAPS-5 items as a discrete study endpoint.

Limitations of this study include the failure to identify a significant effect of drug in the prespecified primary analysis comparing TNX-102

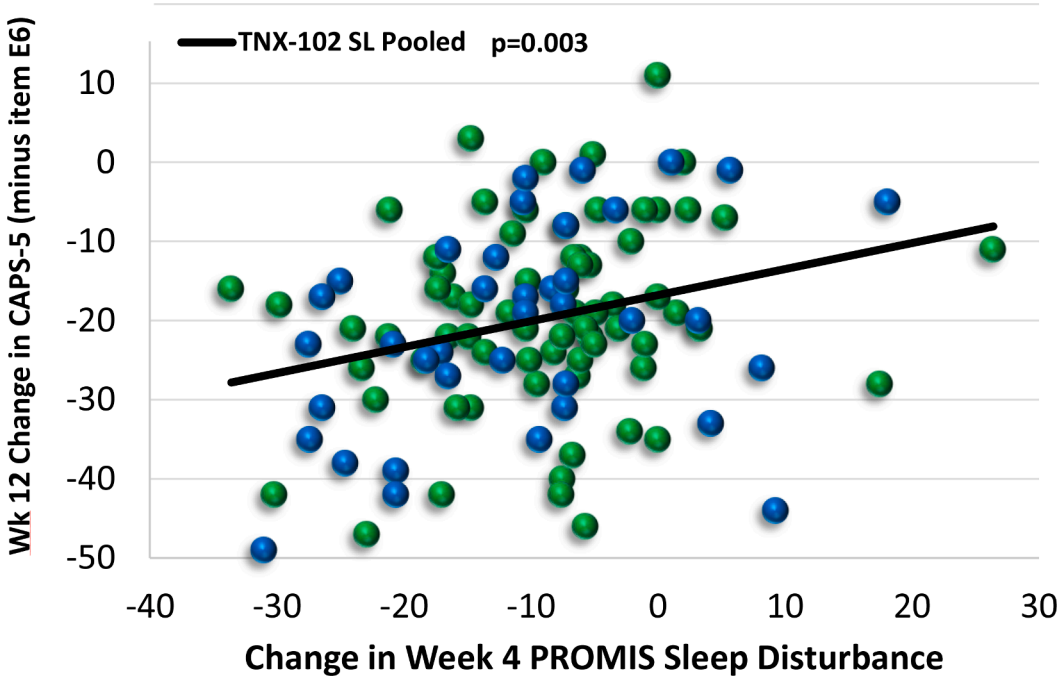

Fig. 3. Week 4 Sleep Improvement by PROMIS SD versus Week 12 Change in CAPS-5 total (minus item E6) in the Pooled TNX-102 SL 2.8 mg and 5.6 mg Groups
Blue spheres represent data from patients on TNX-102 SL 5.6 mg; green spheres on TNX-102 SL 2.8 mg
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for DSM-5; Item E6, sleep disturbance item on CAPS-5; PROMIS, Patient-Reported Outcomes Measurement Information System; Wk, week

Table 4
Effect sizes and P-values for overall study results in the mITT population and the subsample with baseline entry CAPS-5 total ≥ 33 comparing TNX-102 SL 5.6 mg and placebo.

	Entire Sample (mITT) CAPS-5 ≥ 29		Subsample with Baseline CAPS-5 ≥ 33	
	PBO *N*=92 TNX-102 SL 5.6mg *N*=49		PBO *N*=77 TNX-102 SL 5.6mg *N*=38	
Outcome Measure	**ES**	***p*-value**[1]	**ES**	***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**
Item B2 (Recurrent distressing dreams)	0.25	*0.071*	0.24	0.192
Item B3 (Flashbacks)	0.23	*0.056*	0.30	**0.050**
Item B5 (Physical reactions to triggers)	0.30	0.121	0.46	**0.025**
Item D5 (Less interest)	0.31	*0.063*	0.37	*0.083*
Item D6 (Feeling distant/cut off from others)	0.41	**0.033**	0.43	**0.045**
Item E2 (Reckless/Self Destructive item)	0.15	0.140	0.30	**0.012**
Item E4 (Exaggerated Startle item)	0.35	**0.015**	0.43	**0.016**
Item E5 (Problems with concentration)	0.22	0.274	0.38	*0.071*
Items E6 (Sleep disturbance item)	0.51	**0.010**	0.51	**0.013**
CGI–I (responders)	2.11[3]	**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

p<0.05 for bolded *p*-values; *p*<0.10 for italicized *p*-values
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale; CGI-I = Clinical Global Impression – Improvement scale; ES = effect size; mITT = modified Intention-To-Treat sample; PBO = placebo; SDS = Sheehan Disability Scale
[1] *p*-value of mITT for TNX-102 SL 5.6 mg (N=49) v. placebo (N=92)
[2] *p*-value of subsample of mITT with baseline CAPS-5 ≥ 33 for TNX-102 SL 5.6 mg (*N*=38) v. placebo (*N*=77)
[3] Odds ratio for CGI-I rather than ES;

SL 2.8 mg to placebo on CAPS-5 improvement after 12-weeks (p=0.26, NS), and the TNX-102 SL 5.6 mg group marginally failed for a p-value <0.05. The design of the study, with a 2:2:1 ratio for subject in placebo, 2.8 mg, and 5.6 mg, was inadequately powered for the higher dose; although dose effects were observed. Moreover, none of the *post-hoc* efficacy analyses would survive correction for multiple comparisons, making the results proof-of-concept at best. The study was also limited in the assessment of efficacy of TNX-102 SL in females with military-related PTSD who only made up 7% of the sample, which was too small a sample for meaningful statistical analyses. Finally, *post-hoc* analyses suggested the minimal CAPS-5 baseline score for eligibility of CAPS-5 ≥ 29 was lower than the minimal score for entry in precedent pharmacotherapy trials using CAPS-IV > 50, and CAPS-5 ≥ 33 is a more appropriate baseline threshold score for future pharmacotherapy trials using CAPS-5.

Yet despite being underpowered, TNX-102 SL 5.6 mg evidenced a clear signal for a treatment effect by the primary analytic method of MMRM (no imputation), which was slightly above the threshold of nominal significance (p=0.05) for comparison with placebo and demonstrated a reasonable effect size (Cohen's $d = 0.36$) relative to the two FDA-approved PTSD pharmacotherapies. And, notably, both pre-specified analytic methods that accounted for missing data, MMRM with MI (p=0.03) and MMRM with hybrid LOCF/BOCF imputation (p=0.04), were nominally significant. Other strengths include recruitment of a sample almost exclusively with military-related PTSD, predominantly of the combat trauma type (85% of sample), from the recent conflicts in Iraq and Afghanistan, and the relatively recent time since index traumas (mean of 7 years prior); each of these factors contributed to a greater homogeneity of the sample with the presumption of greater uniformity of response to specific molecular neuroreceptor treatment targeting. This is also a population with PTSD for which no prior well-controlled multicenter study had shown a treatment effect, highlighting the critical and ongoing unmet medical need in military-related PTSD (Krystal et al., 2017) that TNX-102 SL 5.6 mg is preliminarily suggested to address.

In summary, in this study population with military-related PTSD, TNX-102 SL at a 5.6 mg dose improved sleep quality and demonstrated a positive signal for efficacy in reducing PTSD severity and related disability. The treatment was well-tolerated over the 12-week treatment period with a favorable adverse event profile and high completion rate. This signal of efficacy was corroborated by a greater response rate on the CGI-I and greater improvement in SDS work and social function. Taken together, these encouraging results indicate that targeting sleep quality may lead to substantial recovery of the syndrome and psychosocial function in this historically treatment-refractory military population with PTSD.

Author statement

All activities were conducted in accordance with the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. The informed consent form and protocol received independent institutional review board (IRB) approval before study initiation. All patients provided written informed consent.

Conflict of interest disclosures

GMS, PP, AP, BLD and SL are employees of Tonix Pharmaceuticals, Inc. (Tonix) and own stock and/or have options in the company.

RMG- consulted with Tonix on the design and conduct of this study

JG- previously employed by Tonix and contributed to the design and conduct of this study

JE – consulted for Tonix on statistical analyses in the study

BV – primary statistician consulting for Tonix as an employee of Rho, Inc.

FWW - consulted for Tonix Pharmaceuticals on the CAPS-5 rater training and credentialing in the study

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113974.

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