Bedtime Sublingual Transmucosal Cyclobenzaprine (TNX-102 SL) for the Treatment of Military-Related PTSD:

Retrospective Analyses of the Mediators and Moderators of Treatment Response

Presented by
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What is Military-Related PTSD and Why Study It?

- Proposed indication for TNX-102 SL* is for the treatment of posttraumatic stress disorder (PTSD):
  - Affects 8.6 million U.S. adults[1]
- Definition of military-related PTSD:
  - Any PTSD that has developed in response to any DSM-5 PTSD Criterion A-qualifying trauma(s) that occurred during military service – includes combat and non-combat traumas
- Why target military-related PTSD?
  - No treatment response observed in U.S. military population with the two FDA-approved selective serotonin reuptake inhibitors (SSRIs) for PTSD[2,3,4]
  - No other type of pharmacological treatment had been shown to be effective in any large multicenter clinical trial in a U.S. military population

TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and is not approved for any indication.

[1]Kessler et al., *Arch Gen Psych* 2005; Prevalence rate of 3.5% applied to U.S. Census estimate of 247M U.S. adult (≥18) population in 2015; [2] Friedman MJ et al. J Clin Psychiatry 2007;68:711-20. [3] Zoloft® Package Insert, Pfizer, NY, NY; August 2014. [4] Paxil® Package Insert, Glaxo, June 2014; (www.census.gov/quickfacts/table/PST045215/00);

What is TNX-102 SL?

- TNX-102 SL is a patented[1] sublingual eutectic formulation of cyclobenzaprine (CBP) for transmucosal absorption
  - Tricyclic molecule with high affinity for target receptors considered to play key roles in sleep physiology and nocturnal emotional memory processing
  - Functional studies show antagonism at each of[2]
    - 5-HT_{2A}
    - α_1-adrenergic
    - Histamine-H_1
  - No recognized risk of addiction

- TNX-102 SL is designed for bedtime administration with desirable nighttime pharmacokinetic profile and pharmacodynamics effects
  - Rapid systemic exposure and increased bioavailability during sleep period
  - Avoids first-pass metabolism reducing exposure to long-lived active metabolite, norcyclobenzaprine (nCBP)
    - $t_{1/2}$~72 hours
    - Less selective for target receptors -> undesirable off-target functional activities
    - Exposure (AUC_{0-48}) for CBP/nCBP of 1.9 for TNX-102 SL vs. 1.2 for oral IR tablet[2]

- TNX-102 SL has been designated a Breakthrough Therapy for PTSD by the U.S. Food and Drug Administration (FDA)

[1] Notice of Allowance for Eutectic Proprietary Protectic™ Formulation Patent issued by the U.S. Patent and Trademark Office; [2] Daugherty et al. Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015 Toronto, Ontario, Canada. [3] Lederman et al. European Congress of Rheumatology, Rome, June 2015; IR, immediate-release

Rationale for Targeting of Sleep for Treatment of PTSD

- PTSD is a disorder of recovery
  - Most people exposed to an extreme trauma recover in a few weeks
  - New learning, e.g. extinction, and memory processing are essential to recovery
  - In PTSD, memory processing, e.g. extinction consolidation,[1,2] may be impeded due to insufficient sleep quality

- TNX-102 SL targets sleep quality
  - Potent binding and antagonism at receptors that regulate sleep quality[3], e.g. 5-HT_{2A}, α_1-adrenergic, and histamine H_1 receptors, during the sleep period is hypothesized to be permissive to sleep quality-dependent recovery processes from trauma and PTSD

[1] Pace-Schott et al. Biol Mood Anxiety Disord 2015;5:3. [2] Menz et al. J Neurosci 2016;36(7):2148. [3] Daugherty et al., Abstract 728, Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015,Toronto Ontario, Canada

Phase 2 AtEase Study in Military-Related PTSD

Placebo at bedtime once-daily

N= 92

TNX-102 SL at bedtime once-daily

2.8 mg

N= 90

TNX-102 SL at bedtime once-daily

5.6 mg (2 x 2.8 mg)

N= 49

12 weeks

CAPS-5, Clinician-Administered PTSD Scale for DSM-5

- Randomized, double-blind, placebo-controlled trial in military-related PTSD
- Efficacy analysis from 231 patients; 24 U.S. clinical sites
- Enrolled patients with baseline CAPS-5 score ≥ 29
- **Primary Efficacy Analysis:**
  - Difference in CAPS-5 score change from baseline between TNX-102 SL 2.8 mg and placebo at week 12
- Key Secondary Measures:
  - PROMIS Sleep Disturbance, CGI-I, SDS

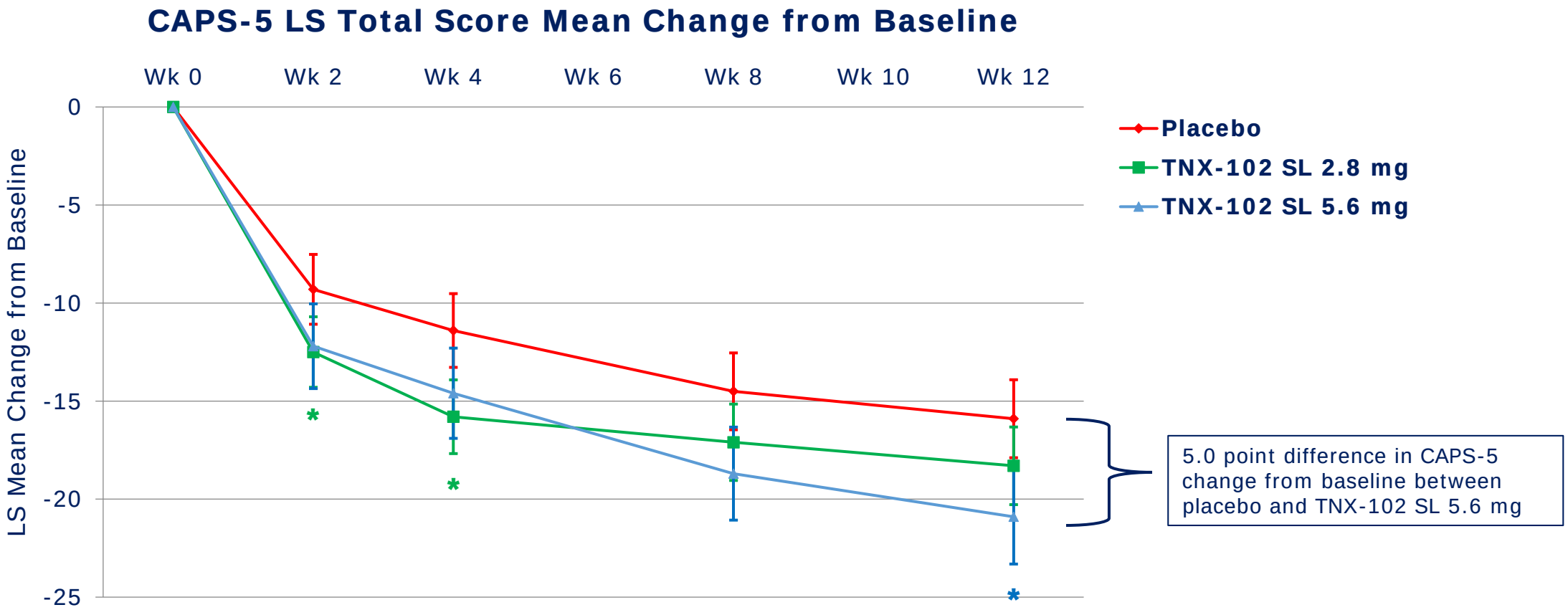
AtEase Study Results:
Primary and Sensitivity Analyses of CAPS-5 Change from Baseline

- TNX-102 SL 2.8 mg dose (N=90) had a greater CAPS-5 change from baseline at Week 2 (MMRM, p=0.040) and Week 4 (MMRM, p=0.030) but did not achieve a significantly greater CAPS-5 change from baseline at Week 12 (MMRM, p=0.259, NS) compared with placebo (N=92)

- TNX-102 SL 5.6 mg dose (N=49) had a strong trend (MMRM, p=0.053) for greater CAPS-5 change from baseline at Week 12 compared with placebo (N=92); Effect size of 0.36 (Cohen's *d*)
  - Pre-planned sensitivity analyses that accounted for missing data, as well as ANCOVA, showed statistically significant results for TNX-102 SL 5.6 mg v. placebo:
    - MMRM with multiple imputation p=0.031
    - MMRM with hybrid LOCF/BOCF imputation p=0.037
    - ANCOVA p=0.038

ANCOVA, analysis of covariance; BOCF, baseline observation carried forward; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; LOCF, last observation carried forward; MMRM, mixed-effect model repeated measures; N, number; NS, not significant

AtEase Study Results: Primary Endpoint
CAPS-5 Total Score by MMRM with MI



*p=0.031, comparing placebo and TNX-102 SL 5.6 mg, *p<0.05, comparing placebo and TNX-102 SL 2.8 mg, by MMRM with MI, mixed-effect model repeated measures with multiple imputation; CAPS-5, Clinician Administered PTSD Scale for DSM-5; LS Mean, least squares mean

AtEase Study Results: Safety and Tolerability

- **Trial Completion Rates: 73% Placebo; 79% TNX-102 SL 2.8 mg; 84% TNX-102 SL 5.6 mg**

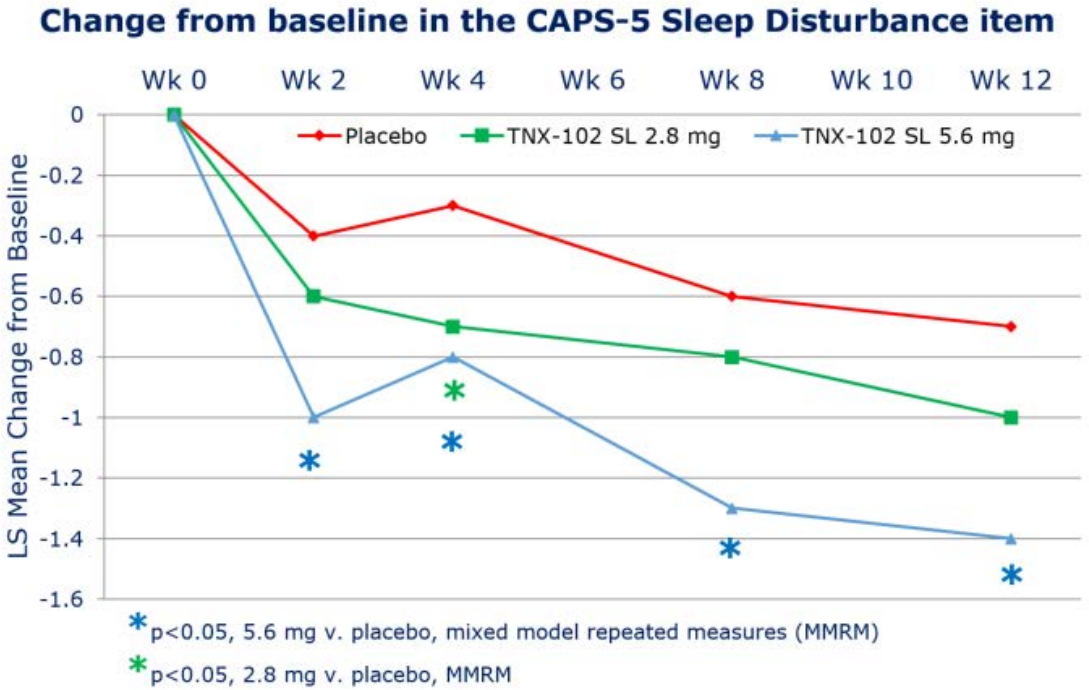
- **Systemic adverse events (AEs) and local administration site reactions occurring at ≥5% rate in either TNX-102 SL group:**

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)

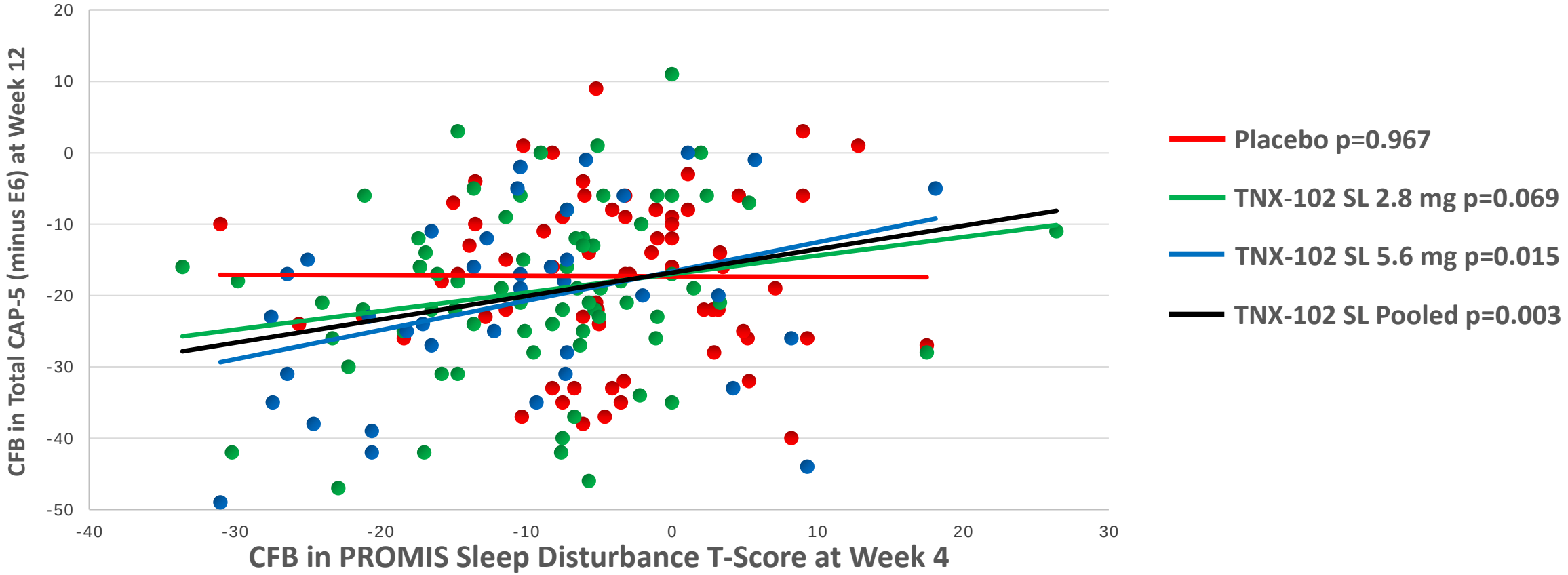
Sleep as a Mediator of PTSD Treatment Response

- Mechanism of action of TNX-102 SL is hypothesized to be through improvement in sleep quality
- Sleep responded early in treatment with TNX-102 SL, by Week 2 on CAPS-5 sleep disturbance (SD) item
- PROMIS SD instrument administered on Weeks 4, 8 and 12
- In a *post hoc* analysis, examined the relationship between early response on sleep by PROMIS SD at Week 4 and change in severity of PTSD by the Week 12 endpoint in the three treatment groups (next slide)
  - For change in severity, used CAPS-5 total change from baseline *without* the sleep item (E6) to avoid co-linearity effects between the two variables



Sleep as Mediator of PTSD Treatment Response

Week 4 Sleep Change by PROMIS SD v. Week 12 CAPS-5 Response*

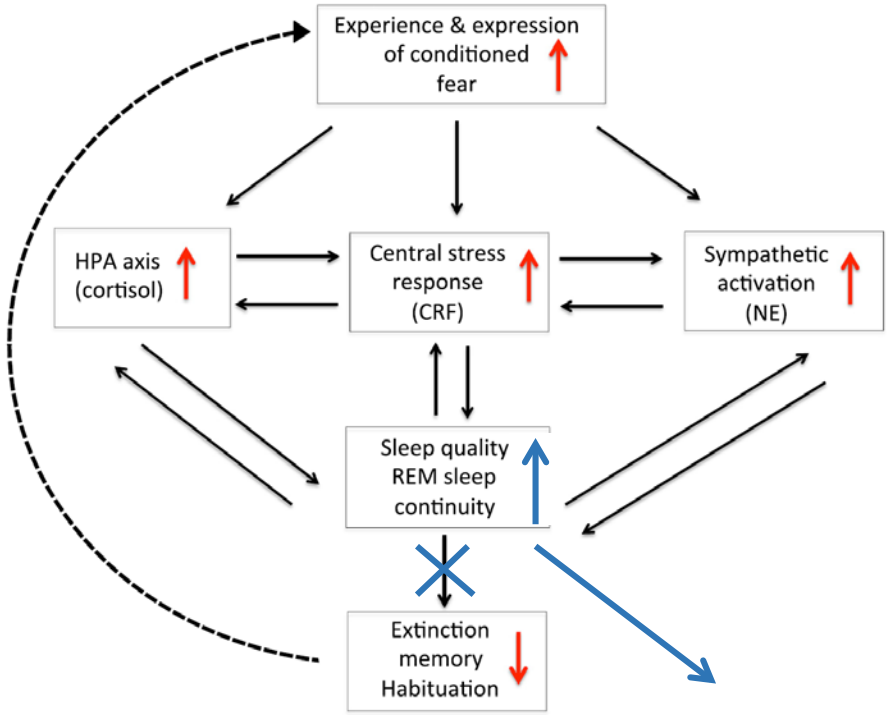


*CAPS-5 without sleep item (E6)
CFB, change from baseline

Summary of Hypothesized Mechanism of Action in PTSD

Recovery in PTSD Resulting from Treatment with TNX-102 SL is Mediated by Improvement in Sleep Quality

- Recovery is a learning process, e.g. depends on extinction learning
- Extinction learning occurs in the daytime
- Consolidation (STM->LTM) of extinction occurs during sleep; roles for both REM and SWS
- Restoring quality of critical sleep stages may be permissive to consolidation of extinction memory and thereby allow normal recovery



LTM, long term memory; STM, short term memory; REM, rapid eye movement; SWS, slow wave sleep

Diagram adapted from Pace-Schott et al. Biol Mood Anxiety Disord 2015;5:3

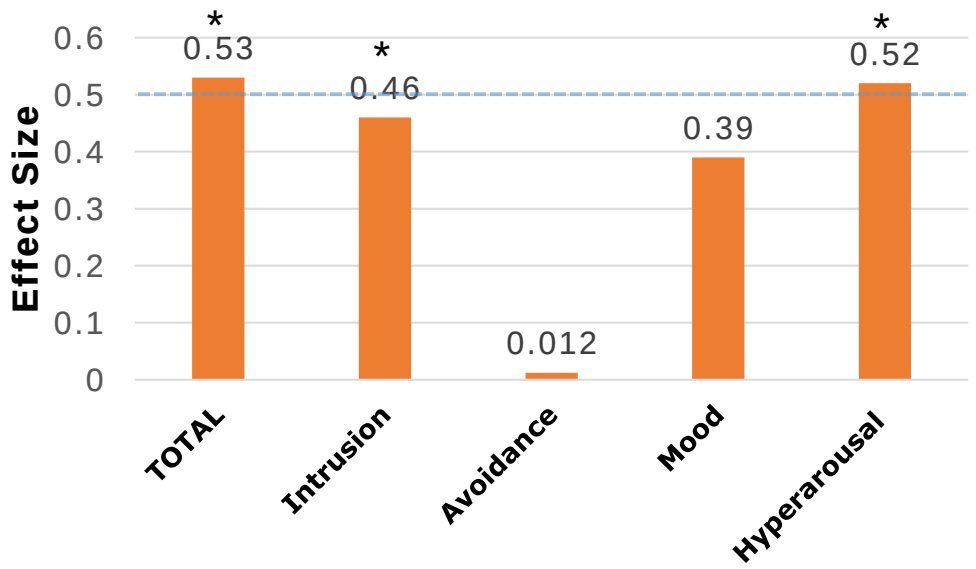
Assessing CAPS-5 Entry Threshold in AtEase

- Score of ≥29 on CAPS-5 (20 items) required at screening & baseline
  - >50 on prior versions of CAPS (17 items) typical in previous drug registration trials
  - Extrapolation from prior versions of CAPS: ((50/17 items)/2) x 20 items = 29.4
- *Post-hoc* analysis to impute CAPS for DSM-IV (iCAPS-IV) scores for each subject
  - Baseline iCAPS-IV score calculated by summing 17 items in common with CAPS-5 and multiplying by two (for 0-8 intensity + frequency rather than 0-4)
  - 4.3% of the sample had baseline iCAPS-IV of ≤ 50
  - Choosing CAPS-5 ≥33 results in all iCAPS-IV > 50
  - 80% of mITT had baseline CAPS-5 of ≥ 33
- Primary analysis of AtEase was run for subgroup with baseline CAPS-5 ≥ 33

AtEase Retrospective Analysis:
Effect Sizes for Total CAPS-5 and Cluster Scores

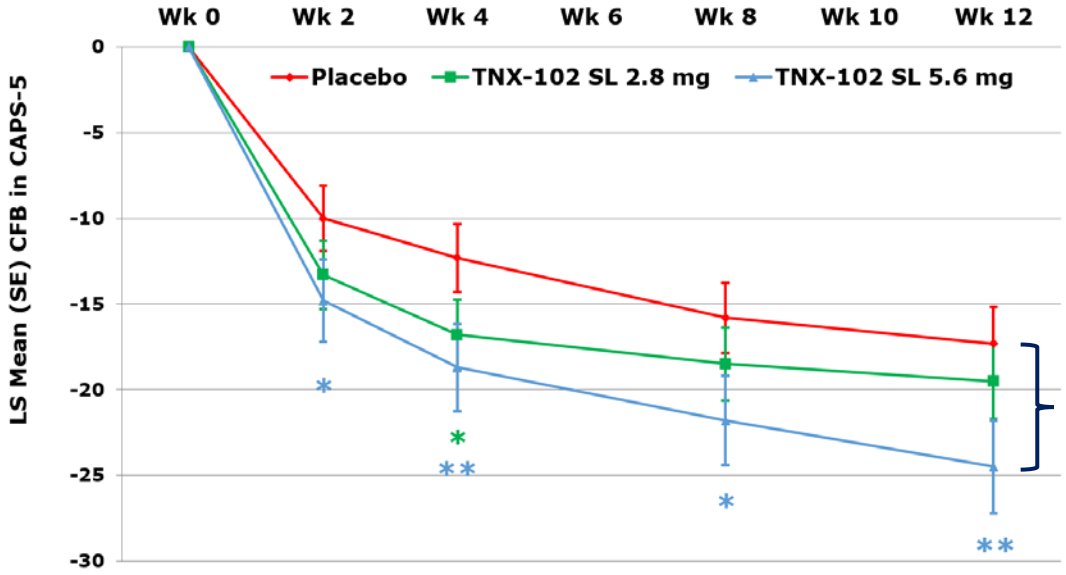
- **Effect sizes calculated for total CAPS-5 and clusters for patients with entry CAPS-5 ≥33**
  - Larger effect size, in moderate range of 0.5, for total CAPS-5 and intrusion and hyperarousal clusters

Effect Sizes in Subgroup with ≥ 33 CAPS-5 Entry Score



* MMRM, mixed-effects model repeated measures, p<0.05

CAPS-5 Change in Subgroup with ≥ 33 CAPS-5 Entry Score

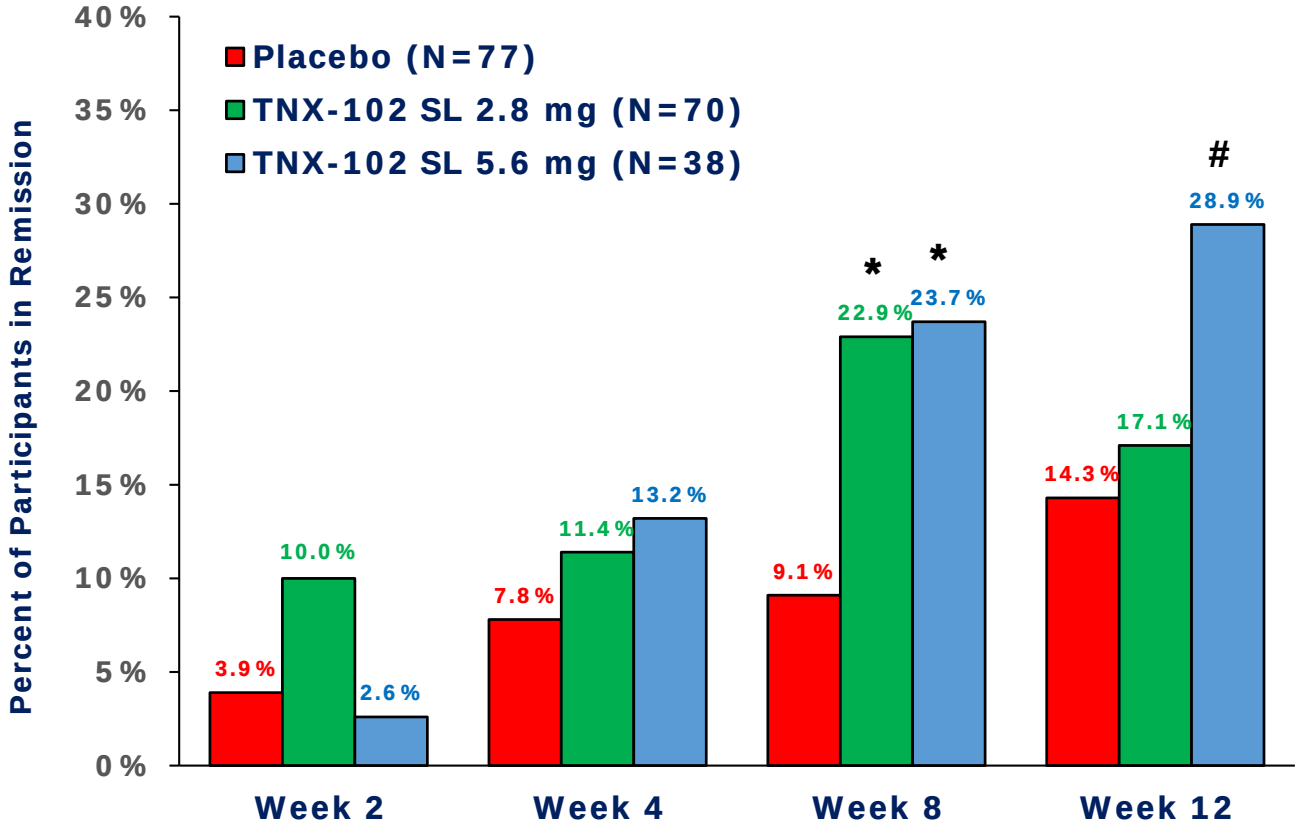


** p<0.01, * p<0.025, TNX-102 SL 5.6 group with placebo, MMRM with multiple imputation (MI); *p=0.018, TNX-102 SL 2.8 mg group with placebo, MMRM with MI

- **Based on findings of post-hoc imputed CAPS, a baseline CAPS-5 score ≥33 was set as PTSD severity inclusion criterion in Phase 3 trial**

AtEase Study Retrospective Analysis: Remission from PTSD (CAPS-5 Baseline ≥33 Subgroup)

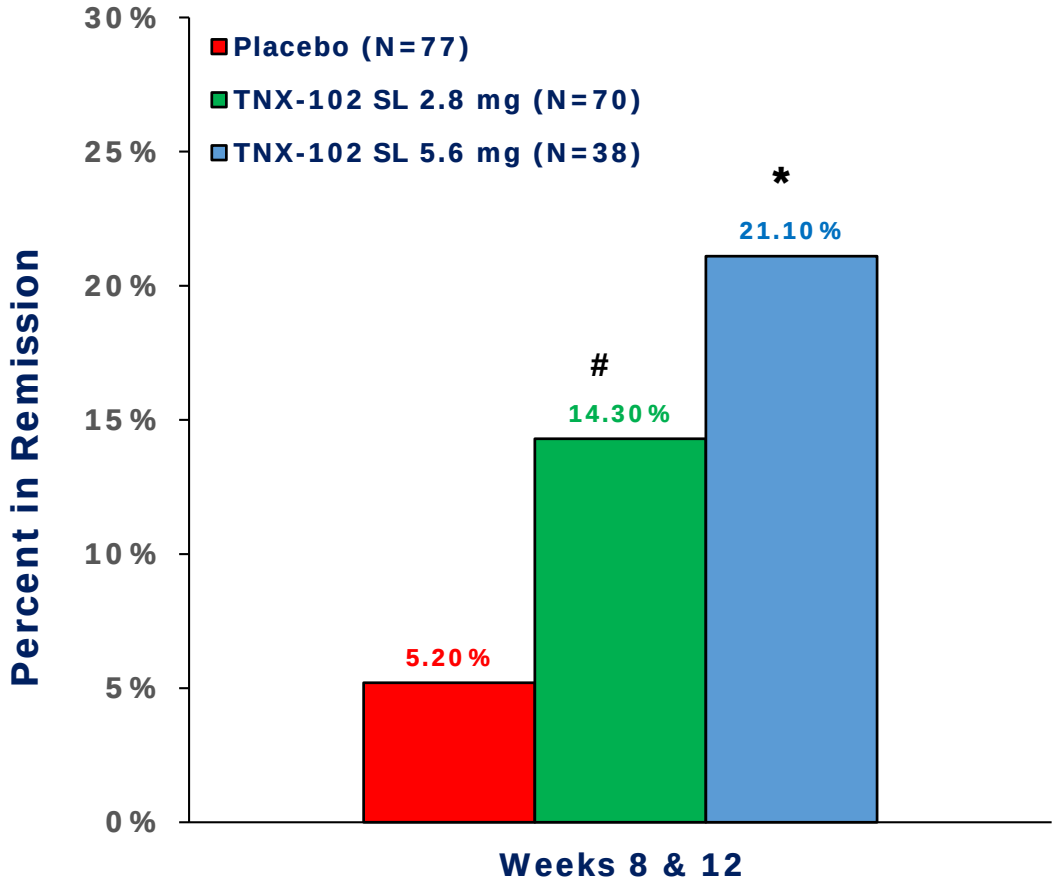
- Optimal outcome of treatment is achievement of remission, a virtually asymptomatic state
- Definition of remission used in AtEase was "*Loss of Diagnosis and Endpoint CAPS-5 Score <11*"
- By Week 8, significantly more remitters in both 2.8 mg and 5.6 mg groups
- By week 12:
  - 5.6 mg group trended for higher rate than placebo (rates increased in both groups)



Asterisks and hashmark represent pairwise comparisons, TNX-102 SL group v. placebo, logistic regression
* $p<0.05$; # $p=0.060$

AtEase Study Retrospective Analysis:
Sustained Remission in CAPS-5 Baseline ≥33 Subgroup

- Remission is more clinically meaningful if it is sustained
- In order to look at sustained remission in AtEase:
  - Determined rates of participants who met remission status at *both* Week 8 and Week 12
- 21% of the TNX-102 SL 5.6 mg participants met for sustained remission v. 5% of placebo (p=0.02)
- In Phase 3, open label extension study of TNX-102 SL 5.6 mg will allow a look at sustained remission beyond Week 12



Remission = Loss of Diagnosis and CAPS-5 < 11
Asterisk and hashmark represent pairwise comparisons between TNX-102 SL and Placebo; #p=0.08, Odds Ratio 3.01 (0.89, 10.18)
*p=0.02, Odds Ratio 4.60 (1.27, 16.66); logistic regression

Phase 3 HONOR Study in PTSD Enrolling

- **To confirm Phase 2 AtEase findings in military-related PTSD:**
  - Larger adaptive design study
  - Enrollment started in 1Q 2017

TNX-102 SL once-daily at bedtime

5.6 mg *N ~ 275 (140*)*

Placebo once-daily at bedtime

N ~ 275 (140)*

- **General study characteristics:**
- Randomized, double-blind, placebo-controlled, entrance CAPS-5 ≥ 33
- One unblinded interim analysis (IA) by an independent data monitoring committee at 50% randomized
- IA (N ~275) for efficacy stop, continuation as planned or sample size adjustment
- Potential to enroll 550 patients
- Approximately 35 U.S. clinical sites
- **Primary efficacy endpoint:**
- Mean change from baseline in total CAPS-5 at Week 12 compared between TNX-102 SL 5.6 mg and placebo

12 weeks ····· ***open-label extension***

* *Interim analysis*

1H 2018 - IA outcome anticipated
2H 2018 – topline data anticipated, if 550 patients are studied

Conclusions

- Phase 2 clinical investigation established that **TNX-102 SL 5.6 mg is the potential efficacious and safe dose to treat PTSD** in a military-related PTSD population (TNX-102 SL 5.6 mg, N=49 v. placebo, N=92)
  - Established CAPS-5 ≥33 as entry threshold for Phase 3 studies to confirm AtEase findings
- Relationship between early sleep improvement and Week 12 PTSD recovery supports mechanistic hypothesis that **improved sleep quality is a mediator of TNX-102 SL treatment response**
- **TNX-102 SL 5.6 mg treatment resulted in sustained remission** between Weeks 8 and 12 in 21% of participants that was statistically significant relative to placebo and approximately 4X the rate in placebo in the CAPS-5 ≥33 subgroup (TNX-102 SL, N=38 v. placebo, N=77)
- **Phase 3 clinical investigation of TNX-102 SL 5.6 mg in military-related PTSD is ongoing**

TONIX PHARMACEUTICALS

NASDAQ: TNXP

Thank you!