A Randomized Placebo-Controlled Multicenter Trial of a Low-Dose Bedtime Sublingual Formulation of Cyclobenzaprine (TNX-102 SL) for the Treatment of Military-Related PTSD

Results from the "AtEase" Study

Presented by
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at
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The AtEase Study
Why We Studied Military PTSD

- **Characteristics of military-related PTSD population**
  - Combat traumas but could include non-combat traumas during service (e.g. sexual assault)
  - Male-predominant (85:15) vs. civilian female-predominant (67:33)[1]
  - More commonly repeated traumas during deployments vs. discrete traumas
  - Both military and civilian PTSD diagnosed using DSM-5/CAPS-5[2]

- **Unmet need treating military-related PTSD**
  - No treatment response observed in US military population with the two FDA-approved therapies for PTSD
    - Sertraline – negative large multicenter trial in US military veterans[3]
      - Placebo numerically superior on CAPS-2
    - Paroxetine – not studied in military population
  - Inconsistent treatment response observed in males
    - Sertraline – FDA-conducted post-hoc analysis concluded no effect for male civilian subgroup[4]
    - Paroxetine – no sex-related difference in treatment outcomes in civilian population[5]
  - Important tolerability issues with SSRIs in this population
    - Sexual dysfunction
    - Insomnia

[1] Tolin & Foa. Psychol Bull 2006;132:959-92. [2] Weathers FW et al. The Clinician-Administered PTSD Scale for DSM-5 (CAP-5), National Center for PTSD at ptsd.va.gov. [3] Friedman MJ et al. J Clin Psychiatry 2007;68:711-20.
[4] Zoloft® Package Insert, Pfizer, NY, NY; August 2014. [5] Paxil® Package Insert, Glaxo, June 2014

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The AtEase Study
Rational for TNX-102 SL for PTSD

- **TNX-102 SL is a sublingual formulation of cyclobenzaprine (CBP)**
  - Transmucosal absorption
  - Tricyclic molecule – not antidepressant
  - Targets receptors believed to play key roles in sleep physiology
    - functional studies show antagonism at each of[1]
      - 5-HT_{2A}
      - α_1-adrenergic
      - Histamine-H_1
- **TNX-102 SL is designed for bedtime administration and nighttime pharmacokinetic and pharmacodynamics effects**
  - Rapid sublingual transmucosal absorption (reduced lag-time)
  - Avoidance of first-pass metabolism
    - reduces exposure to active metabolite, norcyclobenzaprine (nCBP)
      - Long-lived active metabolite ($t_{1/2}$~72 hours)
      - Distinct receptor binding profile less selective for target receptors
      - Potentially 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 form[2]

[1] Daugherty et al. Society of Biological Psychiatry 70th Annual Scientific Convention, May 14-16, 2015 Toronto, Ontario, Canada.
[2] Lederman et al. European Congress of Rheumatology, Rome, June 2015
TNX-102 SL (cyclobenzaprine HCl sublingual tablets, 2.8 mg) is an Investigational New Drug and is not approved for any indication.

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The AtEase Study
Rational for Targeting of Sleep for Treatment of PTSD

- **Previous work of TNX-102 SL in a bedtime, nightly regimen improved fibromyalgia symptoms and supported a mechanism in which TNX-102 SL improved sleep quality**
  - PTSD has clinical overlap with fibromyalgia
  - PTSD has comorbidity with fibromyalgia

- **PTSD patients complain of sleep disturbance as a core symptom**
  - Distressing dreams (nightmares) are part of "re-experiencing"
  - Sleep disturbance is part of the hyperarousal cluster of PTSD diagnostic criteria
    - Altered autonomic and neurohormonal balance
    - May interfere with processing of emotionally charged memories[2]
      - i.e. attenuated extinction consolidation

- **Sleep disturbance also correlates with depression, substance abuse and suicidal behaviors in PTSD[3]**

[1] Moldofsky et al, J Rheumatol 2011, 38:2653-63; Lederman et al. European Congress of Rheumatology, Rome, June 2015.
[2] Pace-Schott et al. Biology of Mood & Anxiety Disorders 2015;5(3):1-19.
[3] Germain, Am J Psychiary 2013;170:372-382; McHugh et al, J Traumatic Stress 2014:27:82-89; Betts et al, Journal of Anxiety Disorders 2013;27:735-41.
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The AtEase Study
Phase 2 Trial of TNX-102 SL in PTSD

TNX-CY-P201 Began Enrolling in 1Q 2015; Finished Enrolling in Q4 of 2015

TNX-102 SL at bedtime once-daily
5.6 mg — *N = 49**

TNX-102 SL at bedtime once-daily
2.8 mg — *N = 90**

Placebo at bedtime once-daily
0 mg — *N = 92**

Randomized, double-blind, placebo-controlled trial in **military-related PTSD**

N=231*; 24 U.S. clinical sites (2 VA; 2 University; 20 private)

Primary efficacy endpoint:
Difference in Clinician-Administered PTSD Scale for DSM-5 (**CAPS-5**) score between TNX-102 SL 2.8 mg and placebo at 12 weeks

* modified Intent-to-Treat (mITT) population

TNX-102 SL (cyclobenzaprine HCl sublingual tablet) 2.8 mg is an Investigational New Drug and is not approved for any indication.

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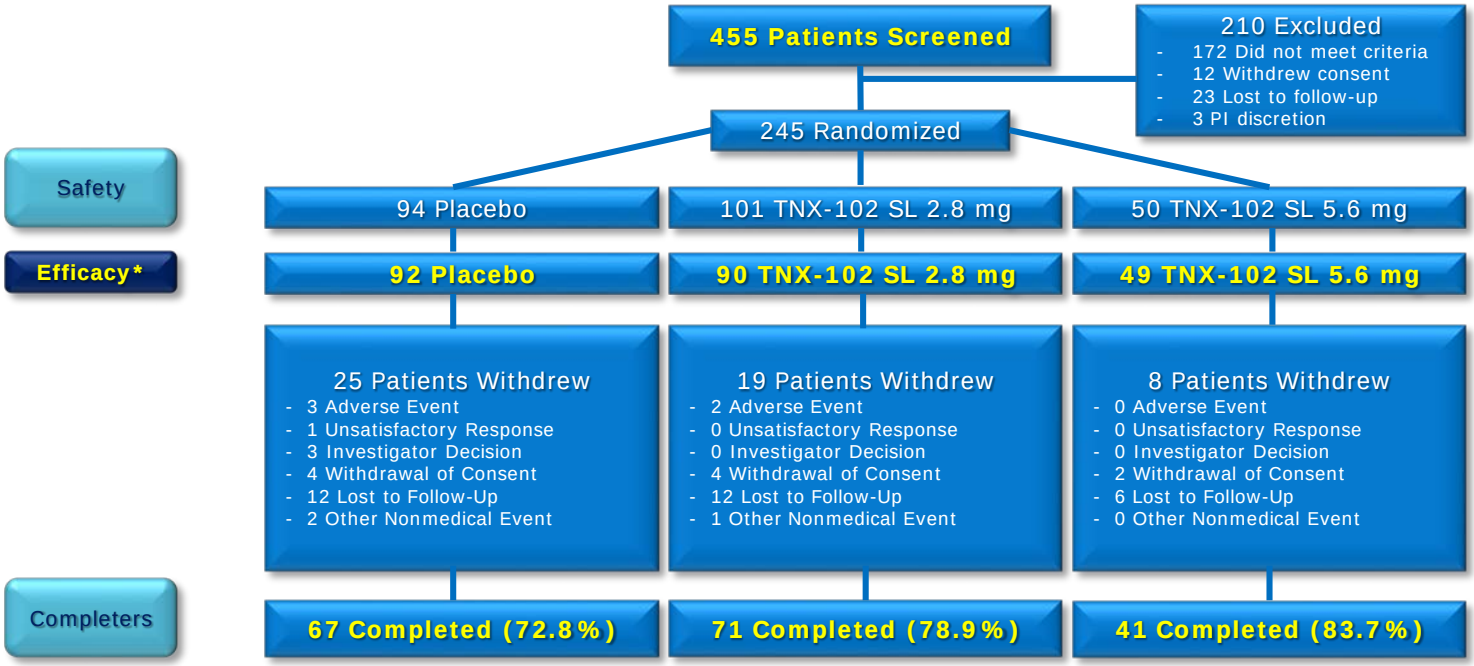
The AtEase Study
Consort Diagram of TNX-CY-P201



* at least one post-baseline assessment in modified Intent-to-Treat population (mITT)

AtEase Study
Selected Demographics and Characteristics

- **93% of the sample was male**
- **98% had trauma during military service**
  - Deployed an average of 2.3 times
- **Mean time since index trauma was 7 years**
- **Race and ethnicity generally consistent with US military distribution**
- **Fibromyalgia 7% by ACR 2010 criteria**
- **Current Major Depression Disorder 14% by MINI 7.0**
- **Similar baseline CAPS-5 scores and MADRS scores across treatment arms**
  - Entry criteria included a CAPS-5 score ≥ 29

Variable	Placebo N=92	TNX-102 SL 2.8 mg N=90	TNX-102 SL 5.6 mg N=49	Overall N=231
Baseline CAPS-5 Scores (SD)	39.5 (7.7)	39.5 (8.0)	39.3 (8.1)	39.5 (7.85)
Baseline MADRS Scores (SD)	17.3 (6.5)	17.6 (5.2)	16.1 (5.5)	17.1 (5.83)

CAPS-5, Clinician Administered PTSD Scale for DSM-5
MADRS, Montgomery-Åsberg Depression Rating Scale
MINI, Mini-International Neuropsychiatric Interview

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AtEase Study
Severity of Baseline CAPS-5 Scores

CAPS-5 PTSD Severity*	Score
Asymptomatic/few symptoms	0 – 10
Mild PTSD/subthreshold	11 - 22
Moderate PTSD/threshold	23 - 34
Severe PTSD symptomatology	35 - 46
Extreme PTSD symptomatology	≥ 47

Mean CAPS-5 Score at Baseline (SD)

39.5 (7.85)

CAPS-5: 20 severity items
0-4 rating for *combined* intensity and frequency
maximum score = 80

*personal communication – Frank Weathers PhD, National Center for PTSD

AtEase Study
Index Traumas During Military Service

Index Traumas During Military Service Related to Dx of PTSD (Categories with >5 Patients)	Patient Count
Being involved in an IED explosion or suicide bombing	35
Being attacked or ambushed	33
Witnessing death or injury of fellow soldiers	30
Witnessing IED explosion	29
Receiving incoming artillery, rocket, or mortar fire	10
Being wounded or injured	9
Being responsible for the death of a noncombatant	9
Witness suicide-related deaths or injury	9
Seeing ill or injured women or children you were unable to help	8
Witnessing death or injury of civilians	7
Handling or uncovering human remains	6
Sexual assault	6
Involved in serious vehicular accident (Humvee, helicopter, plane)	6

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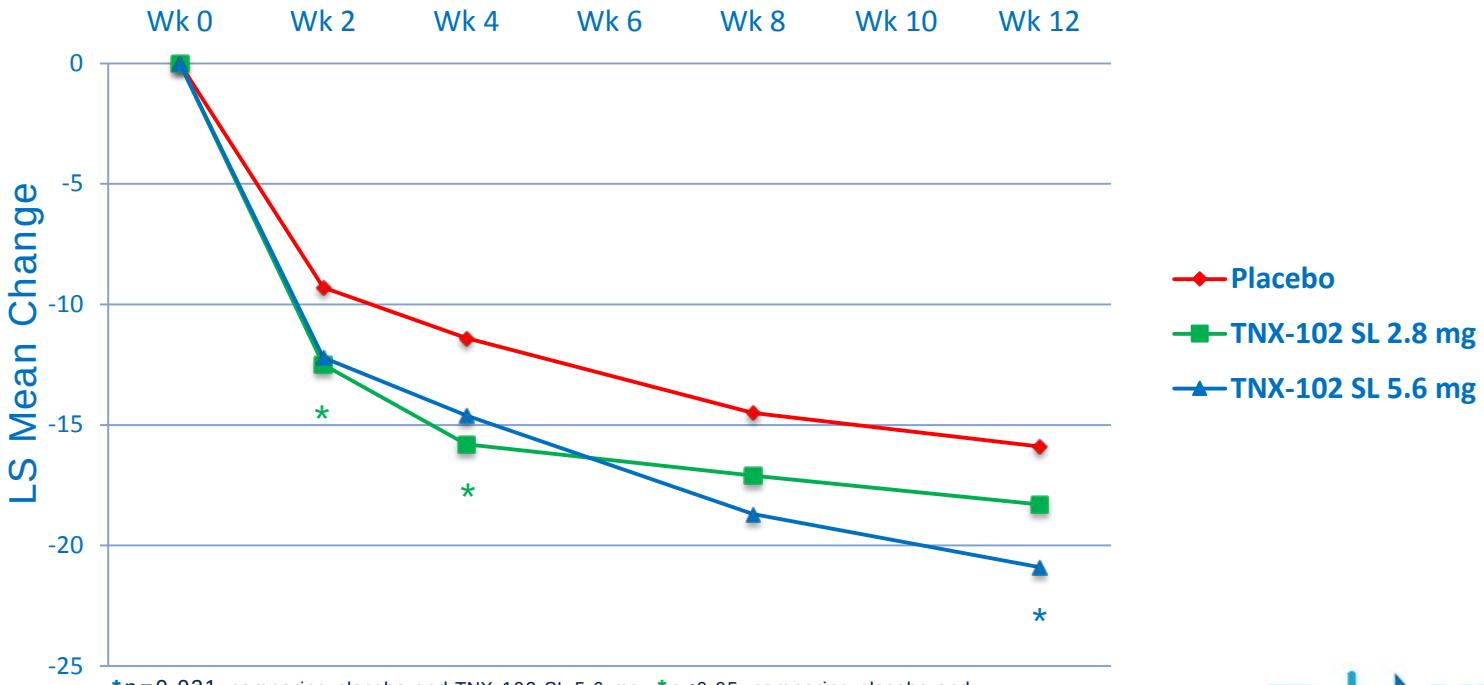
AtEase Study Results
CAPS-5 Total Score Mean Change from Baseline



*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

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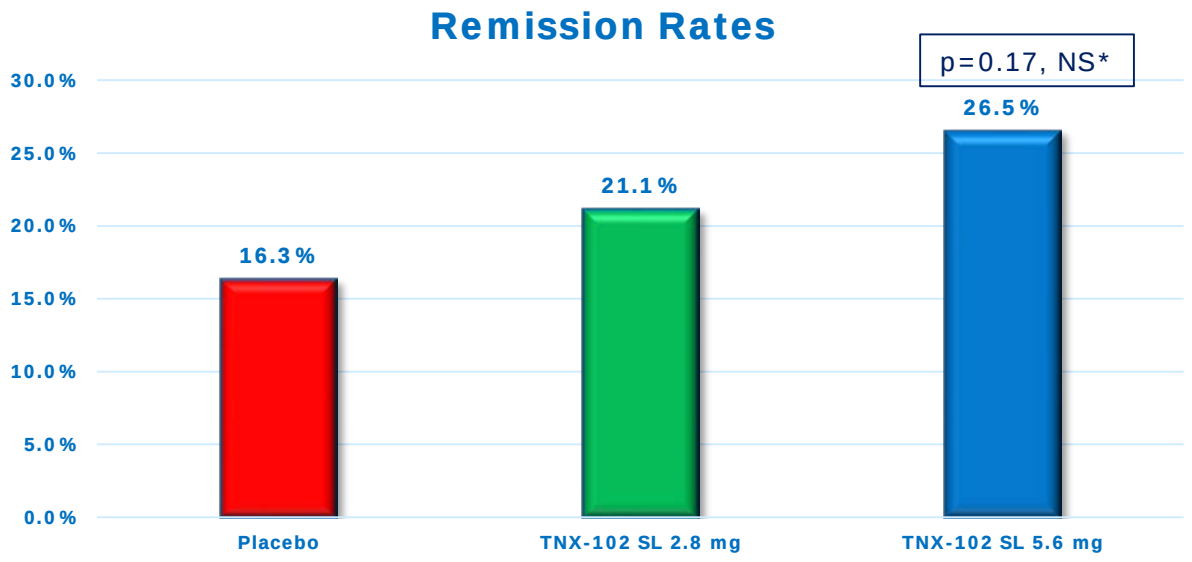
AtEase Study Results
Remission Rates (CAPS-5 Score <11)



*NS, Not significant, Logistic Regression, comparing Placebo and TNX-102 SL 5.6 mg

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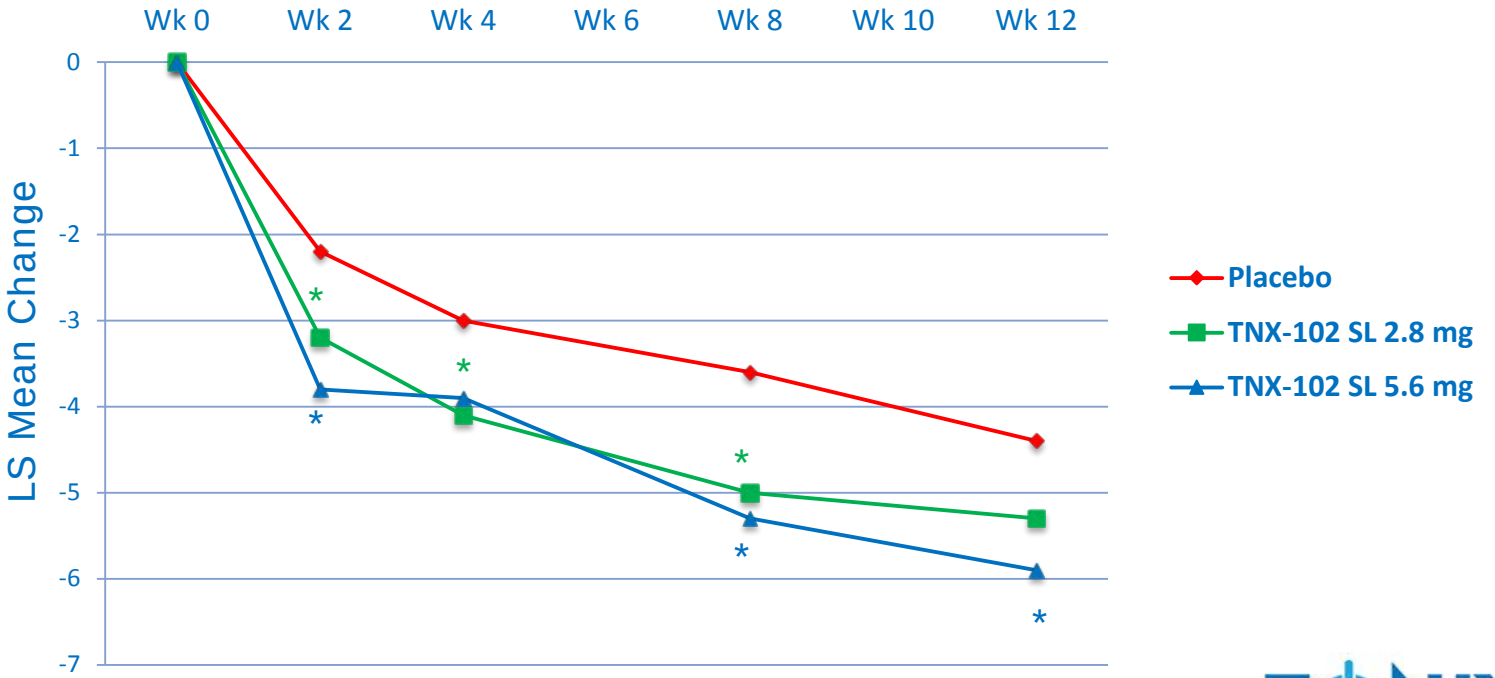
AtEase Study Results
CAPS-5 Arousal and Reactivity Cluster Score Mean Change



*p<0.05, comparing TNX-102 SL 5.6 mg to placebo, mixed-effect model repeated measures
*p<0.05, comparing TNX-102 SL 2.8 mg to placebo, mixed-effect model repeated measures

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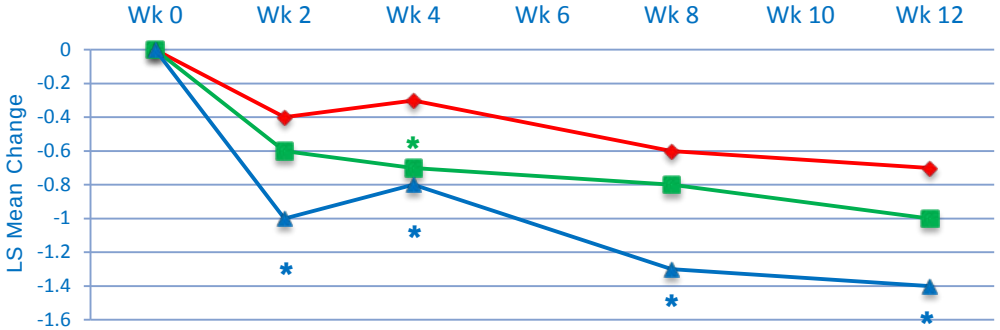
AtEase Study Results

CAPS-5: Sleep Disturbance and Exaggerated Startle Items

Sleep Disturbance



Placebo

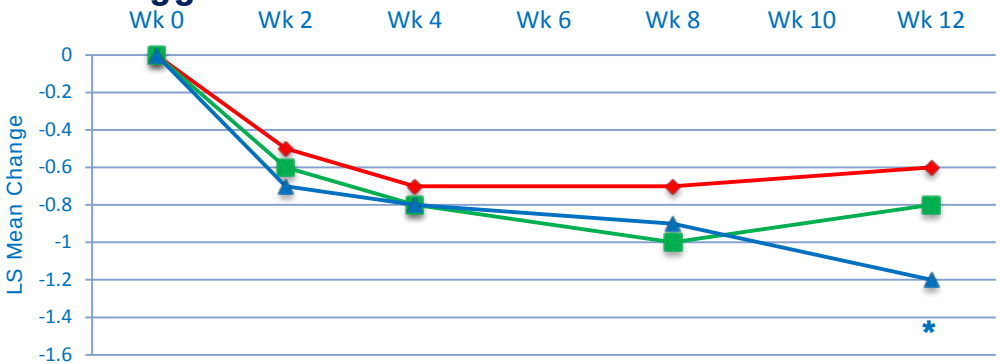
TNX-102 SL 2.8 mg

TNX-102 SL 5.6 mg

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

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

Exaggerated Startle



Placebo

TNX-102 SL 2.8 mg

TNX-102 SL 5.6 mg

*p=0.015, Placebo v. TNX-102 SL 5.6 mg, MMRM

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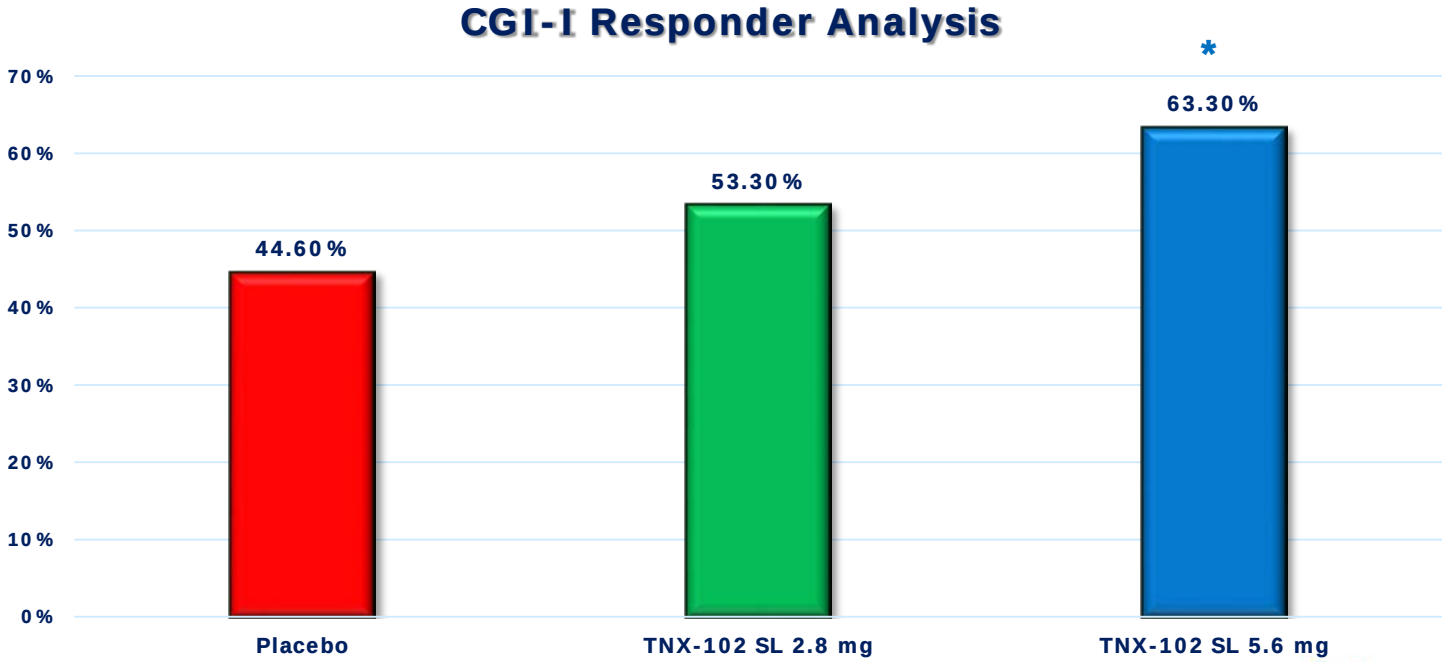
AtEase Study Results
Clinician Global Impression – Improvement Scale Responders

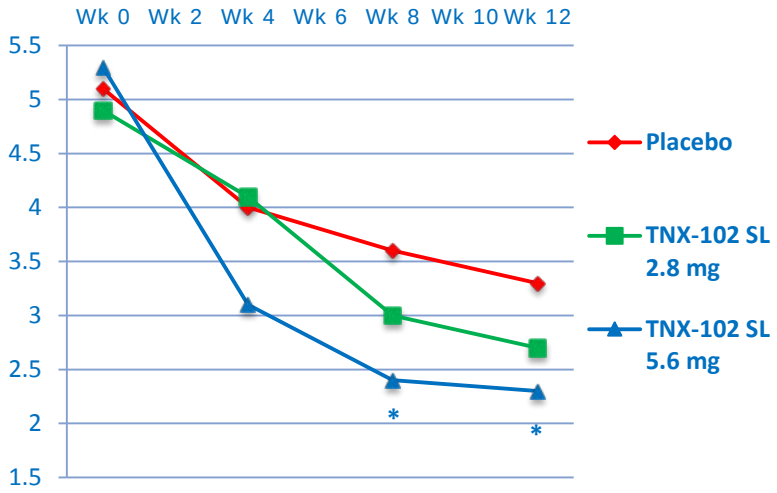


*p=0.041, Logistic regression comparing placebo and TNX-102 SL 5.6 mg
Responders are those rated as “much improved” or “very much improved”

AtEase Study Results

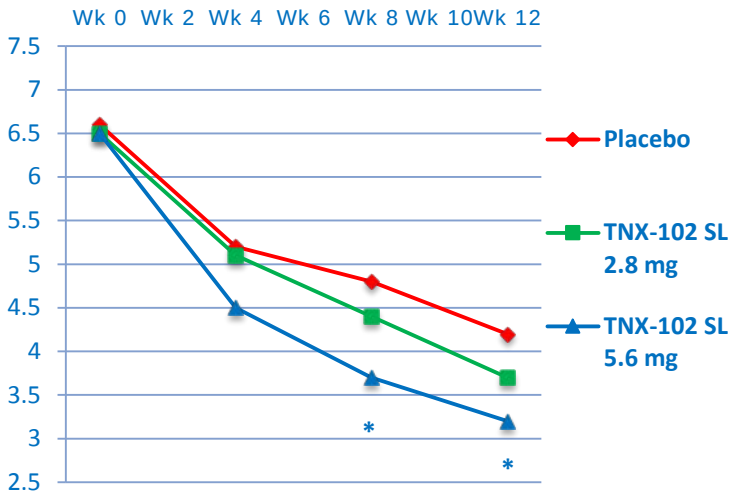
Sheehan Disability Scale – Work/School & Social/Leisure Domains

The symptoms have disrupted your work/school work



*p≤0.05, TNX-102 SL 5.6 mg v. Placebo, MMRM, MMRM, mixed-effects model repeated measure

The symptoms have disrupted your social/leisure activities



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

AtEase Study Results
Adverse Events (≥5% rate in any group)

Preferred Term	Placebo N=94*	TNX-102 SL 2.8 mg N=93*	TNX-102 SL 5.6 mg N=50*	Overall N=237*
Local Administration Site Conditions				
Hypoaesthesia oral	2 (2.1%)	36 (38.7%)	18 (36.0%)	54 (37.8%)
Paraesthesia oral	3 (3.2%)	15 (16.1%)	2 (4.0%)	17 (11.9%)
Glossodynia	1 (1.1%)	3 (3.2%)	3 (6.0%)	6 (4.2%)
Systemic Adverse Events				
Somnolence	6 (6.4%)	11 (11.8%)	8 (16.0%)	19 (13.3%)
Dry mouth	10 (10.6%)	4 (4.3%)	8 (16.0%)	12 (8.4%)
Headache	4 (4.3%)	5 (5.4%)	6 (12.0%)	11 (7.7%)
Insomnia	8 (8.5%)	7 (7.5%)	3 (6.0%)	10 (7.0%)
Sedation	1 (1.1%)	2 (2.2%)	6 (12.0%)	8 (5.6%)
Upper respiratory tract infection	5 (5.3%)	3 (3.2%)	2 (4.0%)	5 (3.5%)
Abnormal dreams	5 (5.3%)	1 (1.1%)	1 (2.0%)	2 (1.4%)
Weight increased	5 (5.3%)	1 (1.1%)	1 (2.0%)	2 (1.4%)

* safety population

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The AtEase Study
Results Summary

- **Recruited a population with severe military-related PTSD, almost exclusively combat traumas incurred during OIF/OEF/OND deployments:**
  - Predominantly male

- **TNX-102 SL at 5.6 mg daily at bedtime for 12 weeks:**
  - Reduced severity of PTSD (CAPS-5, p=0.031, Effect Size=0.39)
  - 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 only one discontinuation for AE (increased nightmares)

- **TNX-102 SL at 2.8 mg daily at bedtime for 12 weeks:**
  - Reduced PTSD symptoms (CAPS-5) at weeks 2 and 4
  - Reduced hyperarousal at weeks 2, 4 and 8
  - Non-significant intermediate effects at week 12 on PTSD symptoms, global and functional improvement (CAPS-5 total, sleep and startle items, CGI-I, SDS)

OIF/OEF/OND, Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn
CGI-I, Clinician Global Impression – Improvement scale; CAPS-5, Clinician Administered PTSD Scale for DSM-5;
SDS, Sheehan Disability Scale

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AtEase Study
Conclusions: TNX-102 SL in Military-Related PTSD

- **This is the first multicenter randomized clinical trial of any medication that has demonstrated efficacy in a population with military-related PTSD**
  - Male predominant (93%)
  - Low incidence of comorbid fibromyalgia (7%)
  - Low incidence of current major depression (14%)

- **Early effects on sleep and hyperarousal are consistent with the mechanistic hypothesis that TNX-102 SL's primary actions on sleep architecture and autonomic balance underlie the observed PTSD treatment effect**
  - Late effect of TNX-102 SL 5.6 mg on exaggerated startle consistent with longer time of recovery of sleep-related memory processing (consolidation)

- **Next steps**
  - Phase 3 trial in military-related PTSD
  - Phase 3 trial in civilian PTSD

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AtEase Study
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AtEase Study
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