Optimizing Acute Stress Reaction (ASR) Interventions with TNX-102 SL* (Sublingual Cyclobenzaprine HCl) – The OASIS Trial: Sustaining Civilian Performance Post-Trauma by Reduction of ASR and Prevention of ASD/PTSD

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*TNX-102 SL is an investigational new drug and has not been approved for any indication

BACKGROUND

U.S. military personnel exposed to life-threatening traumatic events (e.g., intense firefights with multiple casualties, witnessing death) can experience **acute stress reactions (ASRs)** in the war theater, adversely affecting warfighter performance and safety and predisposing to chronic psychopathological outcomes. Symptoms of ASR include intrusions, dissociation, avoidance, arousal (including poor sleep), and negative mood. When symptoms persists >72 hours after the event, **acute stress disorder (ASD)** may be diagnosed, and when they persist for ≥ 1 month, **posttraumatic stress disorder (PTSD)** may be diagnosed. **To reduce the persistence of ASR symptoms and the rate and severity of ASD and PTSD, it may be critical to intervene in the immediate aftermath of trauma (Fig 1).** Currently, there are no medications available at or near the point of care to treat patients suffering from acute trauma and to support long-term health.

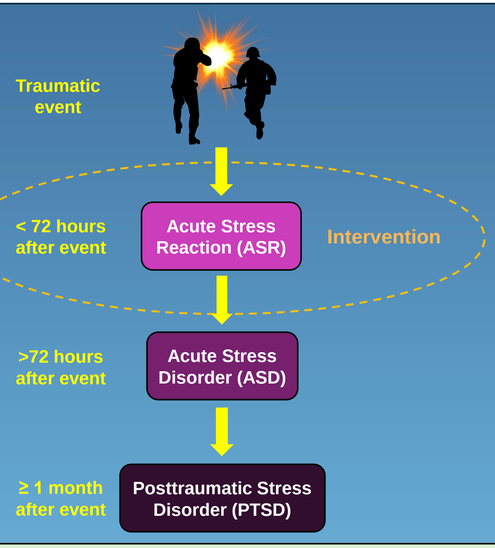


Fig. 1. Early intervention may be a critical strategy to reduce ASR symptoms and the rate and severity of ASD and PTSD.

TNX-102 SL (sublingual cyclobenzaprine HCl) is in development by Tonix Pharmaceuticals Inc., for treating fibromyalgia and PTSD. Cyclobenzaprine HCl **(Fig 2)** is the active ingredient in TNX-102 SL **(Fig. 3)**.

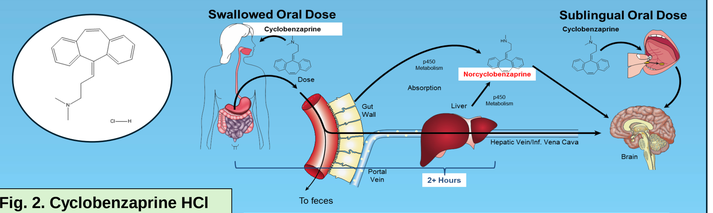


Fig. 2. Cyclobenzaprine HCl

- Potent binding and antagonist activities at postsynaptic receptors:
  - serotonin-5-HT_{2A}
  - α_1-adrenergic
  - histaminergic-H_1
  - muscarinic-M_1
- Improves sleep quality but is not a traditional hypnotic or sedative

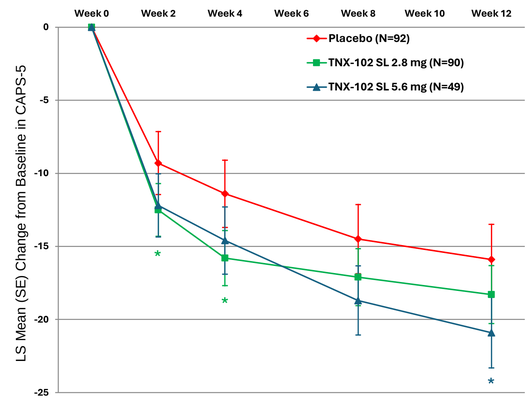
Fig. 3. TNX-102 SL (Sublingual Cyclobenzaprine HCl)

Advantages of the sublingual route:

- Faster absorption provides PK that is ideal for bedtime dosing, minimizing morning somnolence
- Bypasses "first-pass" hepatic metabolism.
  - Reduced metabolism of parent CBP to active metabolite norcyclobenzaprine (nCBP); increased CBP to nCBP ratio in blood

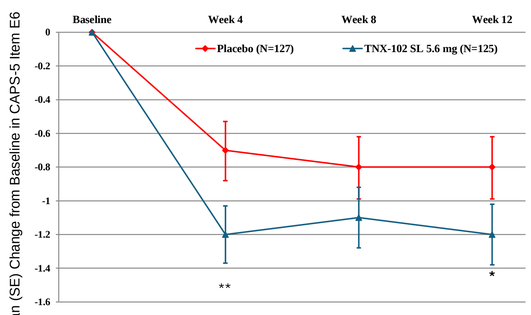
TNX-102 SL was previously studied in military PTSD in randomized, double-blind, placebo-controlled Phase 2 and Phase 3 trials. TNX-102 SL reduced PTSD symptom severity (3) **(Fig. 4)** and reduced sleep disturbance **(Fig. 5)**, which is a significant factor in stress recovery. Importantly, TNX-102 SL has favorable tolerability with low rates and low severity of systemic side effects. Local effects, such as numbness/tingling under the tongue and/or awareness of bitter taste are common but generally mild.

Fig. 4. Effect of TNX-102 SL on CAPS-5 in military PTSD.



*P < 0.05, TNX-102 SL 2.8 mg group vs. placebo; *P = 0.031, TNX-102 SL 5.6 mg group vs. placebo; mixed model repeated measures with multiple imputation. LS = least squares; SE = standard error; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5

Fig. 5. Mean change from baseline in CAPS-5 Sleep Disturbance Item (E6) at all post-baseline assessments by MMRM Analysis in military PTSD.

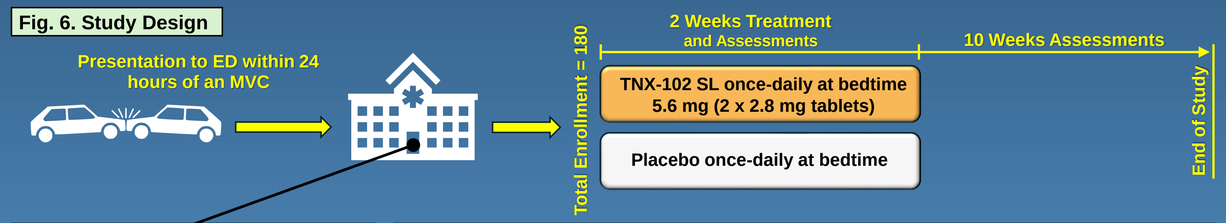


**P= 0.002, *P = 0.026, comparing TNX-102 SL 5.6 mg group vs. placebo, mixed model repeated measures. LS = least squares; SE = standard error; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5

METHODS

The present study, the OASIS trial (**O**ptimizing **A**cute **S**tress Reaction **I**nterventions with TNX-102 **SL**), will be conducted under an investigator-initiated IND by the University of North Carolina Institute for Trauma Recovery, the sponsor of the study, in their emergency department (ED) research network. This randomized, double-blind placebo-controlled multicenter trial will evaluate the efficacy and safety of TNX-102 SL in civilians presenting to the ED after a motor vehicle collision (MVC) **(Fig 6)**. MVC is one of the most common traumatic events for which individuals seek ED care. The AURORA study (1) of more than 3,800 civilians showed that in the early aftermath of an MVC, the same ASR/ASD/PTSD symptoms occur as in servicemembers exposed to traumatic events in the war theater. Thus, civilians in a recent MVC are an optimal population to test interventions for evidence of efficacy, which could benefit both service members and civilians.

Fig. 6. Study Design



Emergency Department Visit

- Key inclusion criteria
  - ✓ ≥ 18 years and ≤ 55 years of age
  - ✓ Admitted to ED within 24 hours of MVC
  - ✓ Anticipated to be discharged home
  - ✓ PTSD prediction tool risk score ≥16; pain severity ≥4 (0-10 rating scale) (2)
- Key exclusion criteria
  - ✓ Substantial comorbid injury
  - ✓ Pregnant females
  - ✓ Chronic opioid use prior to MVC
  - ✓ Active psychosis, suicidal ideation, or homicidal ideation
- Consent, baseline surveys, and lab assessments
- Randomization to TNX-102 SL 5.6 mg (n = 90) or placebo (n = 90)
- 1st dose of study drug, and initial post-study drug assessments

Objective

Investigate the potential of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) to reduce the frequency and severity of the adverse effects of traumatic exposure, including ASR, ASD, and PTSD.

Primary Outcome Measure

- Acute Stress Disorder Scale (14-item self report inventory that indexes ASD and predicts PTSD) assessed at 7 and 21 days post MVC

Secondary Outcome Measures

- Posttraumatic stress symptom severity assessed at 6 and 12 weeks post MVC using the PTSD Checklist for DSM-5 (PCL-5)
- Standardized survey instruments of sleep disturbances, anxiety and depression symptoms, general physical and mental health, and clinical global improvement
- Detailed and brief neurocognitive assessments (e.g., generalized cognitive function, psychomotor vigilance, procedural reaction, response inhibition/control, visuospatial processing, and visuospatial attention tasks) performed from baseline to 12 weeks after MVC at specific timepoints throughout study participation period

Safety Assessments

In person or text/email adverse event assessments at 30 minutes, 1 hour, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 5 weeks, 6 weeks, 8 weeks, 11 weeks, and 12 weeks after drug administration. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be used to assess AE severity.

CONCLUSIONS

- According to the National Center for PTSD, about 60% of men and 50% of women in the US are exposed to at least one traumatic experience in their lives (4). In the US alone, one-third of ED visits (40-50 million patients per year) are for evaluation after trauma exposure (5). No medications are currently available at or near the point of care to treat patients suffering from acute trauma and support long-term health.
- Previous trials showed that TNX-102 SL reduced military PTS symptoms, in as early as 2 weeks, with favorable tolerability.
- TNX-102 SL is hypothesized to reduce ASR symptoms in the immediate aftermath of an MVC.
- The first participant for the OASIS trial is expected to enroll in Q3 2024.
- The results may ultimately provide military personnel, veterans, and civilians with a new treatment option that, when administered in the early aftermath of a traumatic event, improves recovery, job performance, and quality of life.

ACKNOWLEDGEMENTS

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DISCLOSURES

DTH, SL, and GS are employees of Tonix Pharmaceuticals, Inc., and own stock and/or have stock options in the company. CWJ, LG, XA, CM, CB, RS, and SAM declare no conflicts of interest related to this work.

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