An Evaluation of the Efficacy of a Low Dose, Bedtime, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL†) in Military-Related PTSD

Gregory M. Sullivan[1], Judy F. Gendreau[1], R. Michael Gendreau[2], Amy Schaberg[3], Bruce L. Daugherty[1], Heather Jividen[1], Ashild Peters[1], Perry Peters[1], Seth Lederman[1]

[1]Tonix Pharmaceuticals, Inc., New York, NY 10022; [2]Gendreau Consulting, Poway, CA 92064; [3]Schaberg Consulting, Cary, NC 27513

Introduction

- There is an urgent unmet need for efficacious pharmacotherapy interventions for military-related posttraumatic stress disorder (PTSD)
- TNX-102 SL† is a proprietary formulation of low dose cyclobenzaprine (CBP) HCl, a tricyclic molecule, administered by sublingual (SL) route nightly at bedtime
- Efficacy of tricyclic class in PTSD is supported by clinical data[1]
- In a Phase 2b trial in fibromyalgia, TNX-102 SL demonstrated significant improvement on sleep disturbance (*P*=.005), and anxiety (*P*=.015) and sensory sensitivity (*P*=.017) item scores, potentially relevant to PTSD; while being well tolerated over 12 weeks of treatment[2] *
- TNX-102 SL is also being investigated to improve global symptoms of PTSD by targeting sleep disturbance and hyperarousal
- The 'AtEase Study' (TNX-CY-P201) is evaluating the potential clinical benefit of TNX-102 SL in the treatment of military-related PTSD

Investigational Product

- TNX-102 SL
  - is more rapidly absorbed into the circulation **(Fig 1)** compared with oral cyclobenzaprine
  - bypasses "first pass" metabolism to norcyclobenzaprine (nCBP), a long half-life (72 hr) active metabolite, by liver **(Fig 2)**; $AUC_{0\text{-}48}$ ratio for CBP/nCBP of 1.9 vs. 1.2 for oral IR form[2]
  - CBP is a multifunctional agent with potent 5-HT_{2A}, α1-adrenergic, and H1-receptor blocking properties **(Fig 3 & 4)**[3]

Methods

- Randomized, double blind, placebo-controlled 12-week trial testing 3 groups in 2:2:1 ratio: (1) placebo, (2) TNX-102 SL 2.8 mg, and (3) TNX-102 SL 5.6 mg
- Total N=220
- 25 private trial clinics within the continental United States (US)
- Male and female US military personnel and veterans age 18-65 with PTSD DSM-5 Criterion A trauma(s) that occurred during military service in last 14 years

†TNX-102 SL is an Investigational New Drug and has not been approved for any indication
*Most common adverse event: oral hypoaesthesia, 42% in TNX-102 SL vs. 1% in placebo

Figure 1–Plasma concentration vs. time for TNX-102 SL & CBP IR

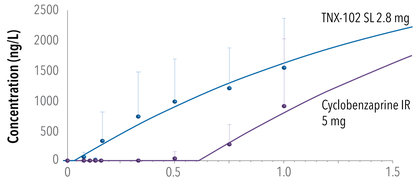


Figure 2–Hepatic metabolism of CBP to active metabolite

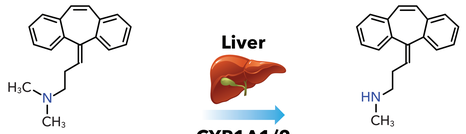


Figure 3–Schematic of inhibitory activities of CBP & nCBP

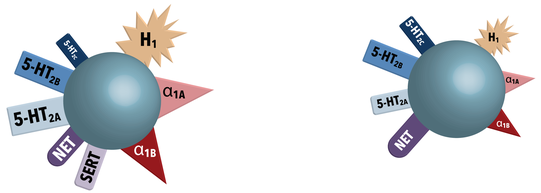
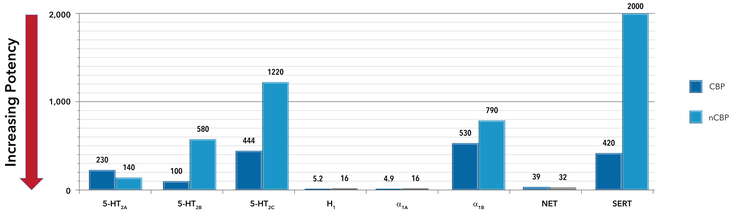


Figure 4–Functional antagonism (IC_{50}) of CBP and nCBP



ClinicalTrials.gov Identifier: NCT02277704

- Primary Outcome Measure: The Clinician Administered PTSD Scale for DSM-5 (CAPS-5), which is a standardized structured clinical interview that is the gold standard in research for measuring PTSD symptom severity
- Inclusion criteria include:
  - PTSD diagnosed by CAPS-5; severity ≥ 29
  - No antidepressant treatment within 2 months
  - Willing and able to discontinue medications including opioids, α-adrenergic agents, mood stabilizers, antipsychotics, stimulants, benzodiazepines, non-benzodiazepine hypnotics for period of the study
  - No trauma-focused psychotherapy during study
- Exclusion criteria include:
  - Greatly increased suicidal risk (based on C-SSRS & MINI 7.0 criteria, and/or history of attempt within prior 12 months)
  - Moderate or severe traumatic brain injury (TBI)
  - Severe depression based on MADRS score of ≥ 30
  - Unstable medical conditions; BMI > 40
  - Lifetime diagnosis bipolar disorder, psychotic disorder, OCD, or antisocial personality disorder by MINI 7.0
  - Alcohol or substance use disorder in remission <6 months
- Efficacy Assessments
  - Primary outcome: change in PTSD severity on the CAPS-5
  - Secondary efficacy assessments include PTSD Checklist-5 (PCL-5), CGI-I, PGIC, PROMIS Sleep Disturbance, Pain Questionnaire, Sheehan Disability Scale (SDS)

Current Study Status

- Over 50% enrolled as of August 2015
- Recruitment information found at AtEaseStudy.com

Conclusions

- Prior clinical studies of TNX-102 SL in fibromyalgia suggest evidence of broad activity potentially relevant to PTSD treatment in concert with good systemic tolerability
- The AtEase Study, a registration quality clinical trial of TNX-102 SL for the treatment of military-related PTSD, is currently enrolling across the US

References

1. Davidson J. *J Psychopharm.* 29(3):264-9, 2015.
2. Lederman et al. European Congress of Rheumatology, Rome, June 2015.
3. Daugherty BL, Sullivan GM, Gershell L, Lederman S. Comparative Neuropharmacology of Therapeutic Agents Targeting Posttraumatic Stress Disorder, Poster presented at the NEI Psychopharmacology Congress; November 12-15, 2015; Orlando, FL.