

# The AtEase Study: An Evaluation of the Efficacy of a Low Dose, Bedtime, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL) for the Treatment of Military-Related PTSD

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## INTRODUCTION

- There is an urgent unmet need for efficacious pharmacotherapy interventions for military-related posttraumatic stress disorder (PTSD)
- TNX-102 SL<sup>#</sup> 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<sup>1</sup>
- 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, relevant to PTSD; while being well tolerated over 12 weeks of treatment<sup>2</sup> \*
- TNX-102 SL is intended to target sleep disturbance and hyperarousal in order to improve global symptoms of PTSD
- 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: a proprietary formulation of low dose cyclobenzaprine 2.8 mg tablets for sublingual administration
  - more rapid absorption into the circulation (**Fig 1**)
  - Bypasses "first pass" metabolism to norcyclobenzaprine (nCBP), a long half-life (72 hr) active metabolite, by liver (**Fig 2**); AUC<sub>0-48</sub> for CBP/nCBP of 1.9 vs. 1.2 for oral IR form<sup>2</sup>
  - CBP is a multifunctional agent with potent 5-HT<sub>2A</sub>, α<sub>1</sub>-adrenergic, and H<sub>1</sub>-receptor blocking properties (**Fig 3 & 4**)

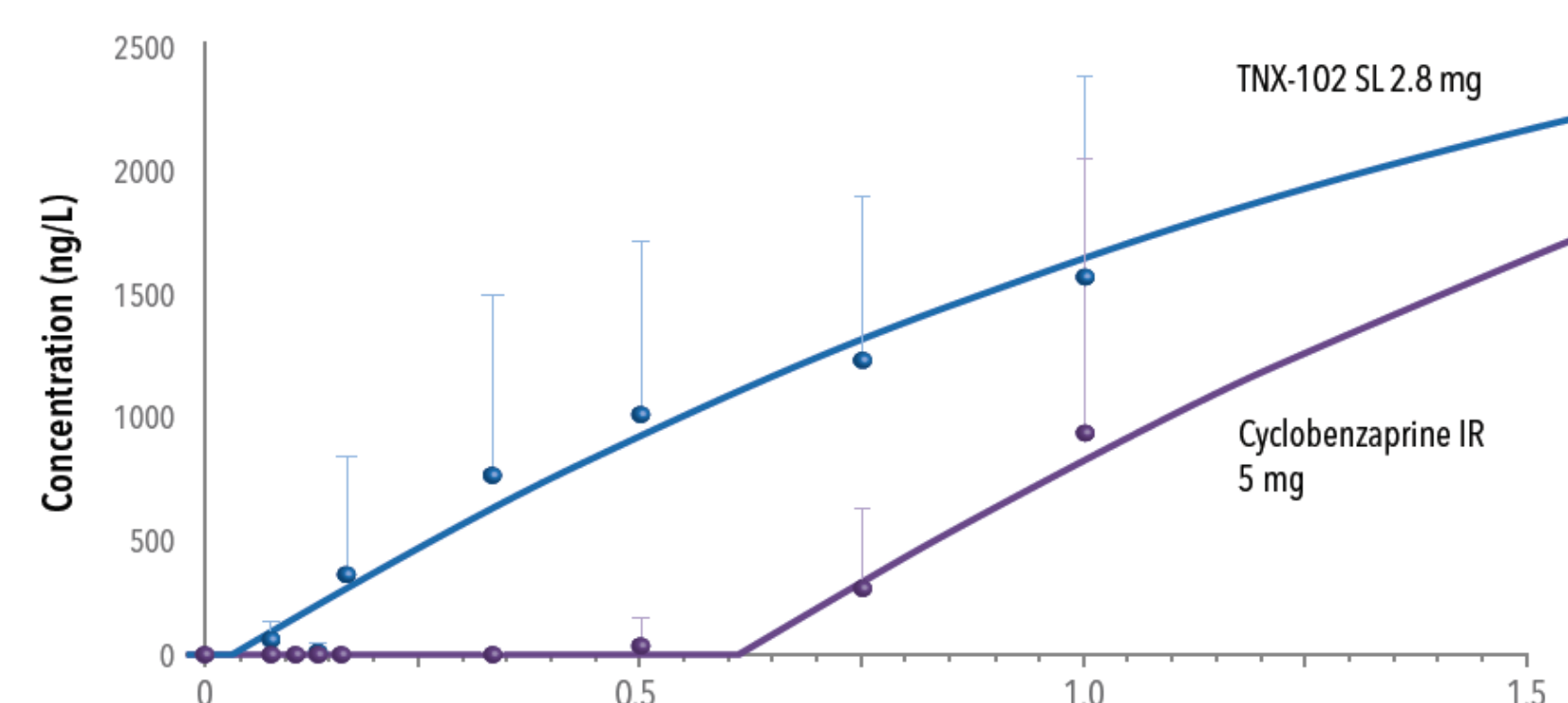
## METHODS

- 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

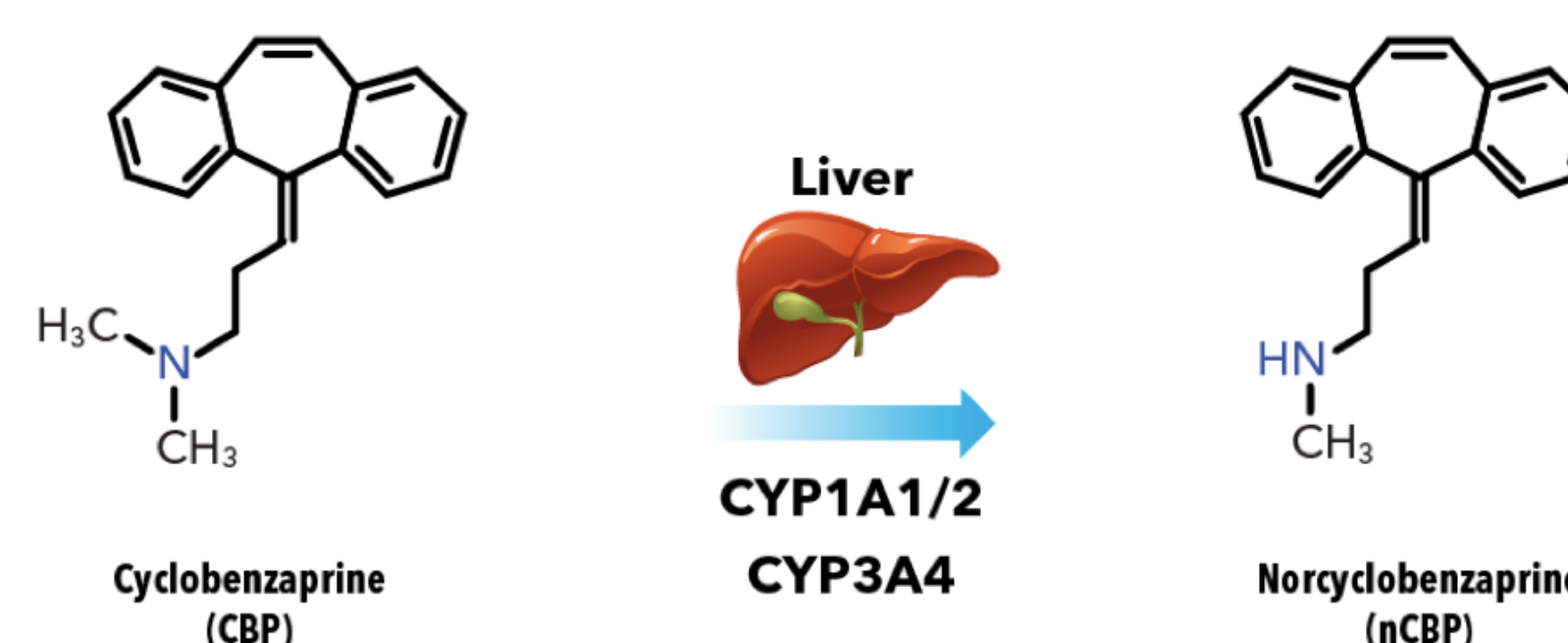
<sup>#</sup>TNX-102 SL is an Investigational New Drug and has not been approved for any indication

\*Most common adverse event: oral hypoesthesia, 42% in TNX-102 SL vs. 1% in placebo

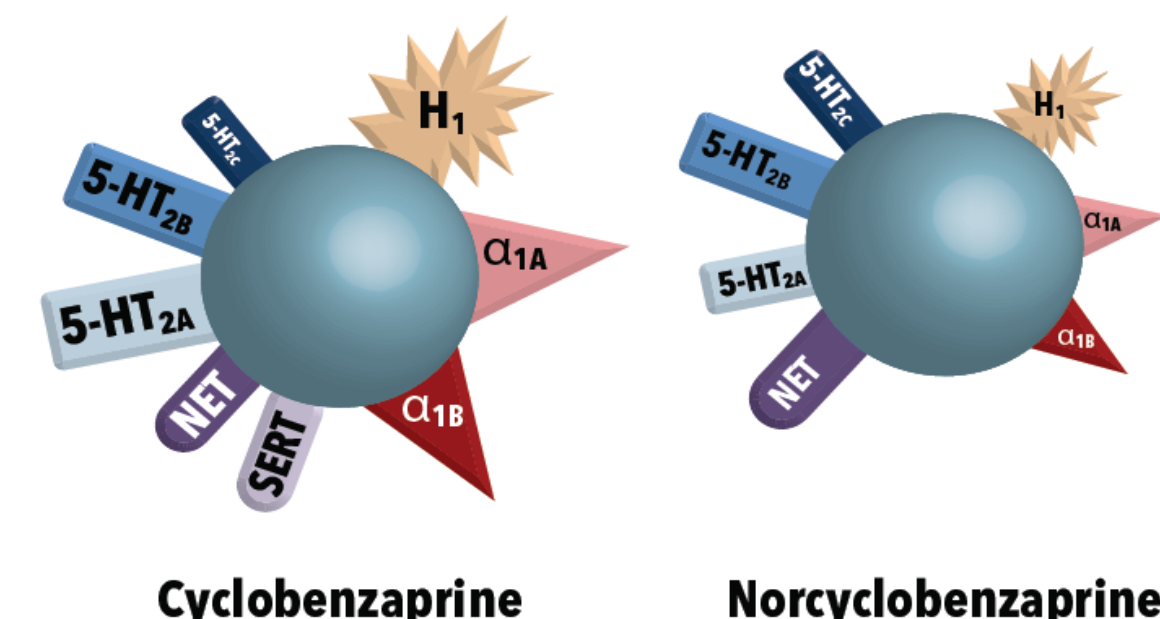
**Figure 1 – Plasma concentration vs. time for TNX-102 SL & CBP IR**



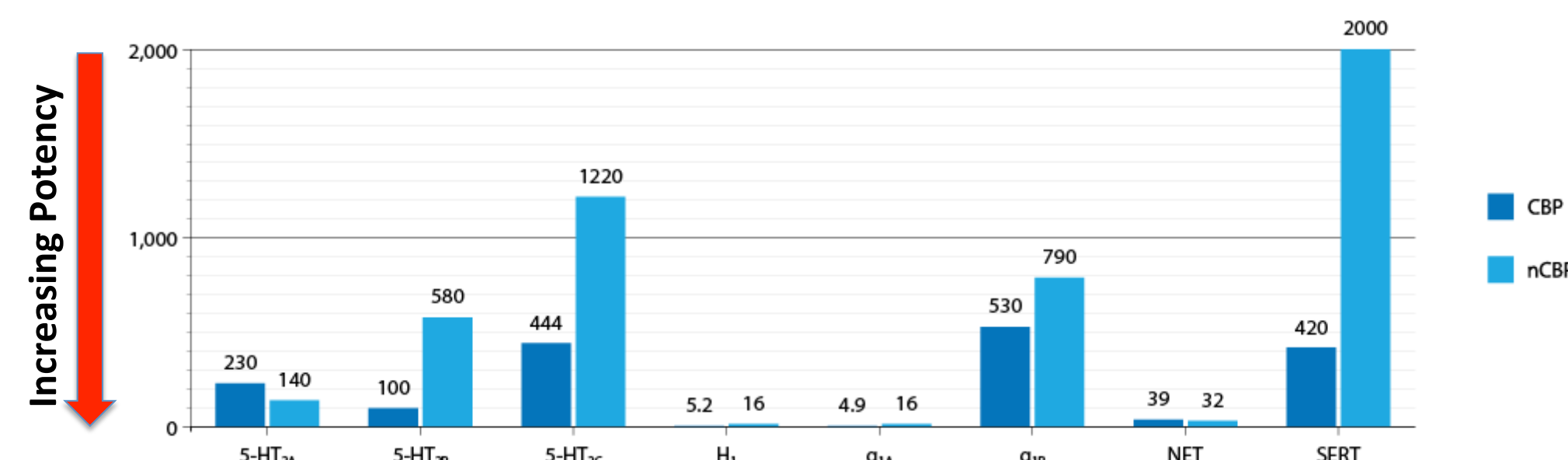
**Figure 2 – Hepatic metabolism of CBP to active metabolite**



**Figure 3 – Schematic of inhibitory activities of CBP & nCBP**



**Figure 4 – Functional antagonism (IC<sub>50</sub>) 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

- Currently enrolling; over 50% enrolled to date
- Recruitment information found at [AtEaseStudy.com](http://AtEaseStudy.com)

## CONCLUSIONS

- Prior clinical studies of TNX-102 SL in fibromyalgia suggest evidence of broad activity 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

<sup>1</sup>Davidson J. J Psychopharm 29(3):264-9, 2015; <sup>2</sup>Lederman et al., European Congress of Rheumatology, Rome, June 2015