An Evaluation of the Efficacy of a Low Dose, Bedtime, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL) in 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 is a proprietary formulation of dose cyclobenzaprine (CBP) HCl, a tricyclic molecule, administered by sublingual (SL) route nightly at bedtime
- Efficacy of tricyclic class is supported by clinical data
- 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
- 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); AUCIR:6 ratio for CBP/nCBP of 1.9 vs. 1.2 for oral IR form
  - CBP is a multifunctional agent with potent 5-HT2A, 5-HT2B, and 5-HT2C receptors, targeting sleep disturbance and hyperarousal
  - TNX-102 SL is a proprietary formulation of low dose cyclobenzaprine (CBP) HCl, a tricyclic molecule, administered by sublingual (SL) route nightly at bedtime

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 tril 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
- There is an urgent unmet need for efficacious pharmacotherapy interventions for military-related posttraumatic stress disorder (PTSD)
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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 (IC50) of CBP and nCBP

Figure 5–Activity of CBP & nCBP on various receptors

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. et al. ClinicalTrials.gov Identifier: NCT02277704