Efficacy and Safety of a Low Dose, Bedtime, Proprietary, Sublingual Formulation of Cyclobenzaprine (TNX-102 SL®) for the Treatment of Military-Related PTSD: Study Protocol of a Phase 3 Randomized Placebo-Controlled Trial (P001)

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

INTRODUCTION

Posttraumatic stress disorder (PTSD) is one of the most prevalent and disabling psychiatric conditions affecting US Warfighters and is associated with symptoms of hyperarousal, re-experiencing (intrusion) phenomena, blunted mood and negative cognitions, and behavioral avoidance. Only two medications, intranasal sustained release (naltrexone) antiserotonergic antidepressants, have received Food and Drug Administration (FDA) approval for treatment of PTSD, in 1999 and 2001, respectively. A crisis has been declared by experts in the field in the development of evidence-based pharmacotherapies for PTSD, because to date there has been no new pharmaceutical treatment approved by the FDA for PTSD. In the same period between 2001 and present, over 2.7 million military personnel served tours of duty in Iraq and Afghanistan.

In recent years, Tonix Pharmaceuticals has made substantial progress towards developing TNX-102 SL or Tomnya®, a proprietary sublingual formulation of the tricyclic molecule cyclobenzaprine or TNX-102, as a bedtime medicine for the treatment of PTSD. TNX-102 potently binds to and antagonizes 5-HT₄, α₁-adrenergic, and histamine-1 (H₁) receptors, each of which play rules in sleep regulation and nocturnal memory processing. The sublingual route results in rapid transdermal absorption of the drug and avoids first pass hepatic metabolism, reducing exposure to its active long-lived major metabolite, nortylobenzaprine.

PTSD has come to be understood as a “disorder of recovery” in which new learning is impaired due to insufficient sleep-dependent memory processing, e.g. consolidation of extinction memory.1 Vulnerability to memory intrusions and trauma-associated triggers progresses even if new extinction consolidation does not complete. Sleep via slow–period blockade of 5-HT₄, α₁-adrenergic, and H₁ receptors, TNX-102 is hypothesized to enhance the sleep quality necessary for sleep-dependent processes to occur (Figure 1).

Figure 1: Mechanistic Hypothesis for TNX-102 Action in PTSD

To assure both the efficacy and safety of TNX-102 SL in PTSD patients with military-related PTSD (See Figure 3).

METHODS

HONOR is a 12-week, multicenter, randomized, double-blind, placebo-controlled trial, investigating a fixed-dose of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken at bedtime for the treatment of the military-related PTSD at 35 U.S. sites.

Eligible participants (males/females) ages 18-75 years, experienced DSM-5 PTSD Criteria A qualifying trauma(s) during military service since 2001, meet PTSD criteria as diagnosed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), have an entry CAPS-5 severity score ≥ 33, not on antidepressants, and free or washed off other psychotropic medications.

CONCLUSIONS

The “HONOR” study is an ongoing, FDA-registration quality, randomized placebo-controlled Phase 3 trial to confirm the efficacy and safety of TNX-102 SL 5.6 mg taken at bedtime as a potential pharmacotherapy for the treatment of PTSD.

In addition to centralizing rater administration, to ensure proper administration of TNX-102 SL interview, ensuring confidentiality, understanding the barriers to seeking treatment and unique demographics, and appreciating the differences in military from civilian culture are essential for recruiting the TNX-102 SL study participants.

Results of the interim analysis are expected in the first half of 2018, and results from complete enrollment, if necessary, are expected in the second half of 2018.

CITATIONS


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