**INTRODUCTION**

Trial P301 (the ‘HONOR’ study) was a Phase 3 randomized clinical trial of TNX-102 SL* in military-related PTSD. Participants who experienced index trauma during military service in 2001 or later, or received TNX 5.6 mg or placebo (PBO) for 12 weeks. TNX is a sublingual formulation of cyclobenzaprine designed for nightly bedtime use. TNX was previously studied in a Phase 2 trial, P201 (ExElate), in 2015-2016 with participants randomized 2:1 to placebo (N=92), TNX 2.8 mg (N=90), and TNX 5.6 mg (N=49) (Table 2). In P201, criteria for the index trauma were different and 2.8 mg dose and placebo at Week 12 was not met, but secondary analyses showed the 5.6 mg dose had a strong trend for difference from PBO in mean change from baseline (MCFB) on CAPS-5 mixed model repeated measures (MMRM), p=0.053. The present Phase 3 trial, P301, was conducted two years later in 2017-2018 and compared TNX 5.6 mg and placebo. P301 was stopped (7/2018) after an interim analysis (IA) of the first 274 randomized participants showed the primary endpoint did not meet a pre-specified significance threshold at Week 12. The results of pre-planned and retrospective analyses of P301 are presented, and relevant analyses supporting the design of the upcoming Phase 3 trial are discussed.

**METHODS**

The Phase 3 P301 study was a multicenter, double-blind, placebo-controlled, 12-week trial conducted in the US. Participants meeting PTSD diagnosis, assessed by Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), were randomized to TNX 5.6 mg or PBO treatment groups. Study P301 required PTSD DSM-5 Criterion A-qualifying trauma incurred during military service since 2001, free of antidepressants ≥1 year; and a baseline PTSD symptom severity of ≥30 on the CAPS-5 within 90 days of randomization.

**RESULTS**

At the time of IA, there were 274 randomized participants (mITT=252) in P301. Table 1 provides the demographic and baseline characteristics. As shown in Table 2, the primary analysis at Week 12 was not significant (LS mean change from baseline of -14.1 in the TNX 5.6 mg compared to PBO). Dividing the mITT sample into groups based on TST (1.5-2 years each as shown in Figure 1), the CAPS-5 improvement at Week 12 of -0.9 was not significant (p=0.339). In contrast, in the TST ≤9 year subgroup, the CAPS-5 improvement at Week 12 was -18.5 compared to PBO (p=0.003). The lack of separation between TNX 5.6 mg and PBO in the TST 9 year group was in large part attributable to a high placebo response at Week 12 (least squares mean change from baseline of -14.1 points).

**DISCUSSION AND CONCLUSIONS**

An alternate way to look at the efficacy of TNX 5.6 mg is CAPS-5 change from baseline for TNX 5.6 mg and PBO as a function of cumulative years since index trauma within each time range, starting with ≤9 years TST, through to ≥15 years TST. The results of this exploratory analyses are presented in Table 6 and Figure 1. At Week 12, the increasing response to PBO with the additions of ≥10 years TST was notable separation from placebo on the primary at Week 4 (-3.6 points, p=0.019). Retrospective analyses were performed to better support the design of the upcoming Phase 3 trial are discussed. Relevant analyses of P301 are presented, and relevant analyses supporting the design of the upcoming Phase 3 trial are discussed. The total number of participants included in the model for each time range is provided in the table following the figure. Note in Figure 2B that CAPS-5 for the Week 4 and Week 12 timepoints, respectively. The post hoc analysis compared participants >9 years TST (see vertical dashed line). In contrast, the response to TNX 5.6 mg is relatively constant (in range of -19.5 to -18.5 CAPS-5 post-baseline improvement) with the additions of ≥10 years TST (p=0.003).

Table 2. P301 Study Primary Analysis in mITT Population in P301

| Variable | Placebo | TNX 5.6 mg | p-Value
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<tr>
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</thead>
<tbody>
<tr>
<td>TST (years)</td>
<td>1.5-2</td>
<td>&lt;0.05</td>
<td>0.039</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.6</td>
<td>-0.9</td>
<td>0.339</td>
</tr>
</tbody>
</table>

**SAFETY**

There were no serious and unexpected adverse events (AEs) in P301. The AEs observed (Table 6) in P301 were comparable to prior studies with TNX 5.6 mg. Most frequent AEs were generally mild, non-specific (e.g., rhinitis/mouth numbness), related to the site of administration of TNX, which was transient (<60 min post administration) and never rated as severe. The most common systemic AE was somnolence, which was never rated as severe. Two participants on PBO and 8 participants on TNX 5.6 mg had at least one AE leading to study discontinuation. There were no serious and unexpected adverse events (AEs) in P301. The AEs observed (Table 6) in P301 were comparable to prior studies with TNX 5.6 mg. Most frequent AEs were generally mild, non-specific (e.g., rhinitis/mouth numbness), related to the site of administration of TNX, which was transient (<60 min post administration) and never rated as severe. The most common systemic AE was somnolence, which was never rated as severe. Two participants on PBO and 8 participants on TNX 5.6 mg had at least one AE leading to study discontinuation.

**REFERENCES**


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