Time Since Trauma in PTSD: Phase 3 Multi-Center, Double-Blind, Placebo-Controlled Trial of TNX-102 SL*, a Sublingual Formulation of Cyclobenzaprine, in Military-Related PTSD (Study TNX-CY-P301)

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

INTRODUCTION

Trial P301 (the 'HONOR' study) was a Phase 3 randomized clinical trial of TNX-102 SL (TNX) in military-related PTSD. Participants who experienced index traumas during military service in 2001 or later, 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 ('AtEase'), in 2015-2016 with participants randomized 2:2:1 to placebo (N=92), TNX 2.8 mg (N=90), and TNX 5.6 mg (N=49) (topline reported 5/2016). The primary endpoint comparing the 2.8 mg dose and placebo at Week 12 was not met, but secondary analysis 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 continuation 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 trials 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(s) incurred during military service since 2001; free of antidepressants ≥ 2 months; free of or washed off other psychotropics. Excluded were severe suicide risk (intent or plan; attempt within 1 year); substance use disorders (SUDs) within 6 months; lifetime bipolar, psychotic, obsessive-compulsive, or antisocial personality disorders.

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 [standard error] difference -1.0 [1.88], p=0.60, MMRM with MI), yet, there was notable separation from placebo on the primary at Week 4 (-3.6 [1.51], p=0.019). Retrospective analyses were performed to better understand how to design future studies and identify the potential group of responders for enrichment design.

Table 1. Participant Demographics and Characteristics

Variable	P301 mITT Population	
	Placebo N=127	TNX-102 SL 5.6 mg N=125
Females, %	13.4%	8.0%
Avg age, yrs.	35.5	35.9
Body Mass Index, kg/m^2	29.3	29.9
Employment (current), %	63.0%	55.2%
Unable to work due to PTSD symptoms, %	12.6%	16.8%
Education, some college or higher, %	85.1%	82.4%
Tobacco Use (current), %	31.5%	33.6%
THC use (current), %	26.8%	26.4%
Alcohol use (current), %	75.6%	69.6%
Active Duty/Veterans (at time of study), No.	17/110	9/116
Time since trauma, mean years	9.2	9.1
Time since trauma, median years	9.3	9.5
Combat index trauma, %	77.2%	83.2%
Deployments, mean number	3.0	2.6
Baseline CAPS-5 Scores, mean	42.4	42.0
Baseline BDI-II Scores, mean	23.0	25.6

BDI-II=Beck Depression Inventory-II; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; THC=tetrahydrocannabinol

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

Visit / Statistic	Placebo N=127 CAPS-5 Value	Placebo N=127 MCFB	TNX-102 SL 5.6 mg N=125 CAPS-5 Value	TNX-102 SL 5.6 mg N=125 MCFB	Primary Analysis MMRM with MI Difference	Primary Analysis MMRM with MI p-value
Week 4						
LS Mean (SE)	31.0 (1.62)	-11.2 (1.62)	27.5 (1.73)	-14.7 (1.73)	-3.6 (1.51)	**0.019**
Week 8						
LS Mean (SE)	29.4 (1.76)	-12.8 (1.76)	27.6 (1.86)	-14.6 (1.86)	-1.8 (1.77)	0.321
Week 12						
LS Mean (SE)	28.0 (1.80)	-14.2 (1.80)	27.0 (1.90)	-15.2 (1.90)	-1.0 (1.88)	0.602

BOLD, p<0.05; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; LS=least squares; MCFB=mean change from baseline; MI=multiple imputation; mITT=modified Intent-to-Treat sample; MMRM=mixed model repeated measures; SE=standard error

Retrospective Analysis on Time-Since-Trauma (TST)

The median TST in P301 was approximately 9 years. When P301 participants are divided into two subgroups (**Table 3**), one with index trauma within 9 years of screening (≤9 year) and the other with index trauma >9 years prior to screening (>9 year), a treatment response is evident in the TST ≤9 year group (CAPS-5 improvement at Week 12 of -5.9 points, p=0.039). In contrast, in the TST >9 year group TNX 5.6 mg did not separate from placebo at Week 12 (numerical increase in CAPS-5 of +1.8 points, p=0.509). 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).

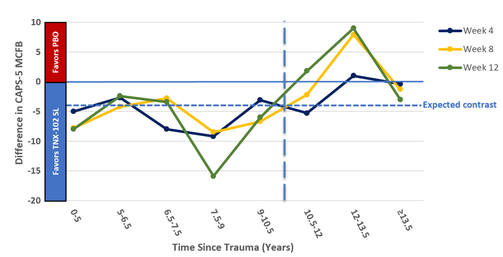
Table 3. CAPS-5 – TST ≤9 & >9 Years in P301

Visit / Statistic	Time Since Index Trauma ≤9 Years: Placebo (N=60) Value	Placebo (N=60) MCFB	TNX-5.6 mg (N=61) Value	TNX-5.6 mg (N=61) MCFB	MMRM with MI Diff	MMRM with MI p-value	Time Since Index Trauma >9 Years: Placebo (N=67) Value	Placebo (N=67) MCFB	TNX-5.6 mg (N=64) Value	TNX-5.6 mg (N=64) MCFB	MMRM with MI Diff	MMRM with MI p-value
Week 4												
LS Mean	34.2	-7.8	27.3	-14.7	-6.9	**0.004**	33.1	-9.3	30.7	-11.7	-2.4	0.300
Week 8												
LS Mean	32.4	-9.6	27.2	-14.8	-5.2	0.069	31.5	-10.9	31.3	-11.1	-0.2	0.940
Week 12												
LS Mean	33.2	-8.8	27.3	-14.7	-5.9	**0.039**	28.3	-14.1	30.1	-12.3	1.8	0.509

BOLD, p<0.05; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; Diff=difference; LS=least squares; MCFB=mean change from baseline; MI=multiple imputation; MMRM=mixed model repeated measures; SE=standard error; TNX-5.6=TNX-102 SL 5.6 mg

Dividing the mITT sample into groups based on TST (1.5-2 years each as well as 0-5 years and ≥13.5 years groups), the CAPS-5 differences in MCFB between TNX 5.6 mg and PBO are displayed in **Figure 1** for Weeks 4, 8, and 12 post-baseline timepoints. The figure shows that for TST <10.5 years, TNX 5.6 mg showed good separation from PBO (left side of vertical 10.5 year line). "Expected contrast" dashed line indicates observed effect from Phase 2. Separation of TNX 5.6 mg from PBO in TST >10.5 years group was either small or worked in the favor of PBO (right side of vertical 10.5 year line).

Figure 1. CAPS-5 Mean Change from Baseline Difference from Placebo of TNX-102 SL 5.6 mg in TST Subgroupings

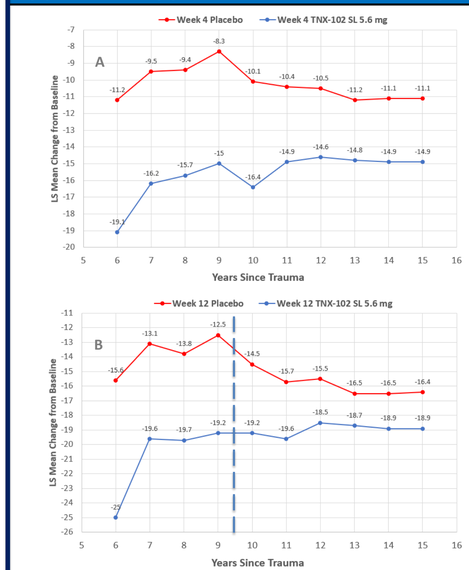


Group TST (yrs)	0-5	5-6.5	6.5-7.5	7.5-9	9-10.5	10.5-12	12-13.5	≥ 13.5
Placebo 'N'	12	23	11	13	21	18	13	18
TNX-5.6 mg 'N'	14	17	16	12	22	10	17	18

MCFB=mean change from baseline; 'N'=number of participants in group; TST=time since trauma

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 ≤6 years TST, through to ≤15 years TST. The results of this exploratory analysis are presented in **Figure 2A and 2B** for the Week 4 and Week 12 timepoints, respectively. 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** for Week 12 the increasing response to PBO with the additions of 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 improvement) with the additions of participants >6 years TST.

Figure 2A & 2B. CAPS-5 Total Score Change from Baseline at Week 4 (A) and Week 12 (B) by Cumulative Years Since Trauma (MMRM)



Time Since Trauma (years)	6	7	8	9	10	11	12	13	14	15
Number of Participants in Model	53	83	105	121	147	172	196	214	228	243

Secondary Efficacy Evaluations in mITT Population and ≤9 Year Subgroup

In **Table 4**, the results of the mITT population and the TST ≤9 years subgroup are presented for the key secondary endpoints of CGI-I and SDS, and the other secondaries of PGIC, PROMIS SD, and BDI-II for Week 4 and Week 12. Of these five secondary endpoints, only in BDI-II did TNX differ from PBO at Week 8 in the TST ≤9 year subgroup (data not shown). Note that for TST ≤9 subgroup, all five secondary endpoints showed a p-value <0.05 at Week 12, indicating possible global and functional recovery, and improved sleep quality and mood after 12 weeks of TNX 5.6 mg compared with PBO.

Table 4. Weeks 4 & 12 Secondary Endpoints for mITT & TST ≤9 Years Subgroup

		P301 mITT: PBO (N=127) v. TNX-5.6 (N=125) Week 4				P301 ≤9 Year Subsample: PBO (N=60) v. TNX-5.6 (N=61) Week 4			
				Week 12				Week 12	
	Analysis	LSMD	p-value	LSMD	p-value	LSMD	p-value	LSMD	p-value
CGI-I	MMRM	-0.3	**0.015**	-0.1	0.403	-0.6	**0.002**	-0.5	**0.021**
SDS	MMRM	-0.2	0.785	-1.6	0.101	-1.8	0.167	-4.3	**0.007**
PGIC	MMRM	-0.2	0.238	-0.3	**0.020**	-0.4	**0.045**	-0.6	**0.007**
PROMIS SD	MMRM	-3.1	**0.015**	-2.7	0.082	-4.5	**0.029**	-5.0	**0.042**
BDI-II	MMRM	-1.1	0.330	-1.4	0.255	-5.2	**0.008**	-6.6	**0.001**

BOLD, p<0.05; BDI-II=Beck Depression Inventory-2; CGI-I=Clinical Global Impressions – Improvement scale; MMRM=mixed model repeated measures; PBO=placebo; PGIC, Patient Global Impression of Change scale; PROMIS SD=Patient-Reported Outcome Measures Information System Sleep Disturbance; SDS=Sheehan Disability Scale; TNX-5.6=TNX-102 SL 5.6 mg

Supported by P301 TNX 5.6 mg Response in Female and Non-Combat Subgroups and Clinically Meaningful Week 4 CAPS-5 Score Reduction, Next Phase 3 Trial Will Study Mixed Civilian and Military Population with Week 4 Primary:

Based on preliminary agreement received at a recent Breakthrough Therapy Clinical Guidance meeting with the US Food and Drug Administration, Tonix plans to study a mixed civilian and military-related PTSD population in the upcoming Phase 3, potential pivotal study of TNX 5.6 mg for PTSD. The primary endpoint will be Week 4 change from baseline in CAPS-5 in TNX 5.6 mg compared with placebo, with one of the key secondary endpoints of Week 12 CAPS-5 change from baseline. As shown in **Table 5**, in P301, although groups are small, females and participants with non-combat traumas (males and females) in the TST ≤9 years subgroup trended for clinically-meaningful reductions in CAPS-5 for TNX 5.6 mg relative to placebo.

Table 5. Weeks 4 & 12 CAPS-5 MCFB in P301 Female & Non-Combat Subsamples

Subsample	Numbers Per Arm	Difference in CAPS-5 MCFB from Placebo: Week 4	Week 12
Females (mITT)	PBO N= 17; TNX-5.6 N=10	-11.5	-9.1
Non-combat (≤9 yr TST)	PBO N=14; TNX-5.6 N=10	-4.8	-4.4

CAPS-5=Clinician-Administered PTSD Scale for DSM-5; MCBF=mean change from baseline; mITT=modified Intent-to-Treat sample; PBO=placebo; TNX-5.6=TNX-102 SL 5.6 mg; TST=time since trauma

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 AE was oral hypoaesthesia (tongue/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, also 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.

Table 6. Adverse Events in P301 at Rate ≥5% in TNX 5.6 mg Group

Category of Adverse Reaction / Preferred Term	Placebo (N=134*)	TNX-102 SL 5.6 mg (N=134*)
Systemic Adverse Events		
Somnolence	9.0%	15.7%
Local Administration Site Reactions		
Hypoaesthesia oral	1.5%	37.3%
Product Taste Abnormal	3.0%	11.9%
Paraesthesia oral	0.7%	9.7%

* Safety Population

DISCUSSION AND CONCLUSIONS

- Study P301 was discontinued at a pre-planned unblinded interim analysis after a pre-specified Week 12 continuation threshold was not met.
- TNX 5.6 mg improved CAPS-5 at Week 4 (p=0.019) in the mITT population which was a pre-specified secondary endpoint.
- Retrospective analyses identified a subgroup based on TST ≤9 years in which TNX 5.6 mg separated from PBO showing a strong treatment effect.
- The lack of separation in the >9 years TST subgroup appeared to be due to a high placebo response in this subgroup.
- In the TST ≤9 years subgroup, secondary endpoints including CGI-I, PGIC, PROMIS SD and BDI-II were all p<0.05 at Weeks 4 and 12; and SDS was p=0.007 at Week 12.
- Results informed design of a new Phase 3 study with a primary endpoint at Week 4 in a mix of civilian and military PTSD.
- Analysis of subgroup of female participants and of non-combat traumas in the TST ≤9 years subgroup suggests clinically meaningful separation from PBO at Weeks 4 and 12 in these subgroups, although the numbers are small in these subgroups

ClinicalTrials.gov Identifier: NCT03062540

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