Effect of Time Since Trauma on Response to TNX-102 SL* (Cyclobenzaprine Sublingual Tablets) in Military-Related PTSD: Results of Two Double-Blind Randomized Placebo-Controlled Studies

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

INTRODUCTION

Here we examine two multicenter registration quality studies of TNX-102 SL in military-related PTSD. Both studies involved participants who experienced index traumas during military service in 2001 or later, receiving TNX-102 SL ("TNX") or placebo ("PBO") for 12 weeks. TNX is a sublingual formulation of cyclobenzaprine designed for nightly bedtime use. It was first studied in a Phase 2 trial, P201 ('AtEase'), in 2015-2016 with participants randomized 2:2:1 to PBO (N=92), TNX 2.8 mg (N=90), and TNX 5.6 mg (N=49) (topline reported 5/2016). The primary endpoint comparing placebo and the 2.8 mg dose 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 second study was a Phase 3 trial, P301 ('HONOR'), conducted two years later in 2017-2018, comparing PBO and TNX 5.6 mg. P301 was stopped (July, 2018) after an interim analysis 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 P201 and P301 are compared and discussed.

METHODS

Both Phase 2 P201 and Phase 3 P301 were 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 PBO or TNX treatment groups. Primary efficacy analysis in P201 was CAPS-5 MCFB at Week 12 in TNX 2.8 mg v. PBO, and in P301 was TNX 5.6 mg v. PBO. Both trials required PTSD DSM-5 Criterion A trauma(s) incurred during military service since 2001; free of antidepressants ≥ 2 months; free of or washed off other psychotropics. Both excluded 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. Table 1 lists differences between P201 and P301.

Table 1. Differences in Methods Between P201 and P301

Categories	P201	P301
No. of US Sites Randomizing ≥ 1	24	43
No. of Treatment Arms	3	2
Baseline Entry CAPS-5 Threshold	≥ 29	≥33
Range of Includable Ages, years	18-65	18-75
Depression Rating Scale Employed	MADRS	BDI-II
Minimum Time Since No TFT	1 month	3 months
Primary Endpoint Analytic Method	MMRM	MMRM with MI
No. of In-Clinic Study Visits	9	5
No. of CAPS-5 Administrations	6	5
Key Secondary Endpoints	CGI-I, SDS, PROMIS SD	CGI-I, SDS

RESULTS

P201 enrolled 245 participants (modified Intent-To-Treat [mITT]= 231). In the primary analysis using MMRM, TNX 2.8 mg did not separate significantly from PBO at Week 12 (p=0.259). TNX 5.6 mg showed a strong trend for difference from PBO (MMRM, p=0.053; effect size [ES]=0.36), and in the sensitivity analysis MMRM with multiple imputation (MI), p=0.031. Also, at Week 12, TNX 5.6 mg had more Clinical Global Impressions – Improvement (CGI-I) responders (63%, p=0.041, logistic regression) compared to PBO (45%), and greater improvement on Patient Global Impression of Change and the social and work domains of the Sheehan Disability Scale (SDS) (MMRM, all p≤0.05). Retrospective subgroup analysis of P201 subjects with baseline CAPS-5 ≥33--a threshold comparable to that used in precedent studies with older CAPS versions and was the threshold used in the Phase 3 study P301, demonstrated improvement of TNX 5.6 mg over PBO at Week 12 by -6.8 points with ES=0.53 (MMRM, p=0.013).

P301 had 274 randomized participants (mITT=252) for the interim analysis. **Table 2** provides the demographic and baseline characteristics for both studies. The two studies were comparable on most characteristics, although it is notable that median time since index trauma in the P301 TNX 5.6 mg group was approximately 1.5 times **(Figure 1)** as long (9.5 years) as in the P201 TNX 5.6 mg group (6 years). As shown in **Table 3**, the P301 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). Several retrospective analyses were performed to better understand how to design future studies and identify the potential group of responders.

Retrospective Analysis on Time-since-Trauma

The median time since trauma in P301 was approximately 9 years. When P301 participants are divided into two subsamples (**Table 4**), 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 ≤9 year group (CAPS-5 improvement at Week 12 of -5.9 points, p=0.039). In contrast, those in the > 9 year group were treatment non-responsive, meaning no improvement on TNX-5.6 mg at Week 12 (numerical increase in CAPS-5 of +1.8 points, p=0.509). The lack of response to TNX in the > 9 year group was attributable to a high placebo response at Week 12 (least squares mean change from baseline -14.1 points).

In **Table 5**, the results of the P301 mITT population and the P301 ≤9 year subsample are presented for the key secondary measures of CGI-I and SDS, and the PGIC and PROMIS SD for Week 4 and Week 12. None of these fours measures differed from placebo at Week 8 in the ≤9 year subsample (data not shown). Note that for the ≤9 subsample, all four measures showed a p-value <0.05 at the Week 12 endpoint, indicating possible global recovery, functional recovery, and improved sleep quality after 12 weeks of treatment compared with placebo. Similar results were seen in P201 with the mITT TNX 5.6 mg group.

Figure 2 shows the levels of remission (CAPS-5 <11) in P301 that was sustained at both Weeks 8 and 12 in the P301 ≤ 9 year subsample next to the comparable subsample in P201 with same CAPS-5 entry baseline threshold (>33) as P301. The sustained remission rates appeared similar in the subsamples of these two studies although formal comparisons between studies may not be feasible.

Table 2. Participant Demographics and Characteristics

Variable	P201 Placebo N=92	P201 TNX 2.8 mg N=90	P201 TNX 5.6 mg N=49	P301 Placebo N=127	P301 TNX 5.6 mg N=125
Females, %	6.50%	6.70%	8.20%	13.40%	8.00%
Age, yrs. (SD)	32.0	34.5	34.8	35.5	35.9
Body Mass Index, kg/m^2	28.9	29.0	29.0	29.3	29.9
Employment (current), %	58.7%	62.2%	67.3%	63.0%	55.2%
Unable to work due to PTSD, %	9.8%	11.1%	14.3%	12.6%	16.8%
Active Duty/Reservists/Veterans, No.	8/4/79	9/5/71	5/7/37	17/0/110	9/0/116
Time since trauma, mean years	7.1	7.3	6.2	9.2	9.2
Time since trauma, median years	7.0	7.2	6.0	9.3	9.5
Combat index trauma, %	80.4%	85.6%	93.8%	77.2%	83.2%
Number of deployments	2.2	2.3	2.6	3.0	2.6
Baseline CAPS-5 Scores	39.5	39.5	39.3	42.4	42.0
Baseline BDI-II Scores	NA	NA	NA	23.0	25.6
Baseline MADRS Scores	17.3	17.6	16.1	NA	NA

BDI-II=Beck Depression Inventory-II; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; MADRS= Montgomery-Åsberg Depression Rating Scale; NA=not applicable – scale not administered in designated study

Table 3. P301 Study Primary Analysis in mITT Population

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	Difference
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)
95% CI	(27.8,34.2)	(-14.4,-8.0)	(24.1,30.9)	(-18.1,-11.4)	(-6.5,-0.6)
p-value					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)
95% CI	(25.9,32.8)	(-16.3,-9.4)	(24.0,31.3)	(-18.2,-10.9)	(-5.2,1.7)
p-value					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)
95% CI	(24.5,31.5)	(-17.7,-10.7)	(23.3,30.8)	(-18.9,-11.4)	(-4.7,2.7)
p-value					0.602

CAPS-5=Clinician-Administered PTSD Scale; LS=least squares; MCFB=mean change from baseline; SE=standard error

Table 4. P301 Study Subsamples on CAPS-5 - ≤9 & >9 Years Since Trauma

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	Diff	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	Diff
Week 4										
LS Mean	34.2	-7.8	27.3	-14.7	-6.9	33.1	-9.3	30.7	-11.7	-2.4
p-value					0.004					0.300
Week 8										
LS Mean	32.4	-9.6	27.2	-14.8	-5.2	31.5	-10.9	31.3	-11.1	-0.2
p-value					0.069					0.940
Week 12										
LS Mean	33.2	-8.8	27.3	-14.7	-5.9	28.3	-14.1	30.1	-12.3	1.8
p-value					0.039					0.509

CAPS-5=Clinician-Administered PTSD Scale; Diff=least squares mean difference; LS=least squares; MCFB=mean change from baseline

Figure 1. Comparison of Time Since Traumatic Event P201 versus P301 (TNX 5.6 mg Groups)

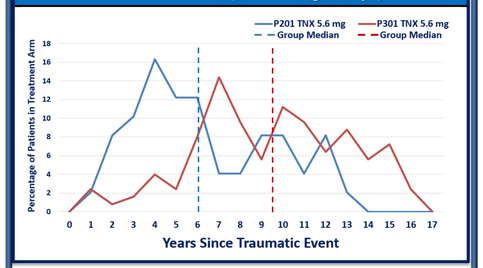


Table 5. P301 CGI-I, PGIC, SDS & PROMIS SD Results for Weeks 4 and 12 in mITT Population and ≤9 Year Subsample

		P301 mITT: PBO (N=127) v. TNX 5.6 mg (N=125)				P301 ≤9 Year Subsample: PBO (N=60) v. TNX 5.6 mg (N=61)			
		Week 4		Week 12		Week 4		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
PGIC	MMRM	-0.2	0.238	-0.3	0.020	-0.4	0.045	-0.6	0.007
SDS	MMRM	-0.2	0.785	-1.6	0.101	-1.8	0.167	-4.3	0.007
PROMIS SD	MMRM	-3.1	0.015	-2.7	0.082	-4.5	0.029	-5.0	0.042

CGI-I=Clinical Global Impressions – Improvement scale; PGIC, Patient Global Impression of Change scale; PROMIS SD=Patient-Reported Outcome Measures Information System Sleep Disturbance; SDS=Sheehan Disability Scale

Table 6. Adverse Events in P201 & P301 (at ≥5% in TNX Groups)

Category of Adverse Reaction Preferred Term	P201 Placebo (N=94)	P201 TNX 2.8 mg (N=93)	P201 TNX 5.6 mg (N=50)	P301 Placebo (N=134)	P301 TNX 5.6 mg (N=134)
Systemic Adverse Events					
Somnolence	6.4%	11.8%	16.0%	9.0%	15.7%
Dry mouth*	10.6%	4.3%	16.0%		
Headache*	4.3%	5.4%	12.0%		
Insomnia*	8.5%	7.5%	6.0%		
Sedation*	1.1%	2.2%	12.0%		
Local Administration Site Reaction					
Hypoaesthesia oral	2.1%	38.7%	36.0%	1.5%	37.3%
Paraesthesia oral	3.2%	16.1%	4.0%	0.7%	9.7%
Glossodynia*	1.1%	3.2%	6.0%		
Product Taste Abnormal*				3.0%	11.9%

*no values in a row for either study means the AE in the active group(s) in the study at a rate of <5%

Safety

There were no serious and unexpected adverse events (AEs) in P301 or P201. The AEs observed in both studies (**Table 6**) were comparable and also consistent with the experience in prior studies in fibromyalgia. Observed systemic AEs were consistent with those described in approved oral cyclobenzaprine product labels. Similar severity and incidence of oral hypoaesthesia (tongue/mouth numbness) is reported across studies (37% in P301; 36% in P201) for TNX 5.6 mg.

Retrospective Analyses of Participants with Administration Site Reactions

TNX is a sublingual tablet that rapidly disintegrates in the mouth and results in transmucosal absorption of cyclobenzaprine. Some local administration site reactions that occurred in TNX treated groups more than placebo include oral numbness (ON, oral hypoaesthesia), oral tingling (OT, oral paraesthesia) and noticeable taste (NT). ON events are typically mild and transient (typically <60 min) and rarely lead to discontinuation. ON/OT/NT experiences were not elicited systematically and may have had variable reporting. ON/OT/NT events are episodic and observed infrequently. ON adverse event rate also has been consistent across studies.

To investigate the possibility of ON/OT/NT events for potential unblinding, individuals were grouped as either having experienced ON/OT/NT event or not (+ or -). In P201 and P301, experiencing ON/OT/NT event(s) seems to correlate with treatment effect based on some *post hoc* analyses, but not others. In P201, the TNX 5.6 mg ON/OT/NT+ subgroup had an improvement of -6.9 points (p=0.037) relative to the improvement seen in the TNX 5.6 mg mITT population of -4.5 points (p=0.053).

Figure 2. Sustained Remission in P301 and P201

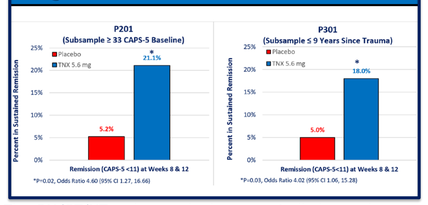
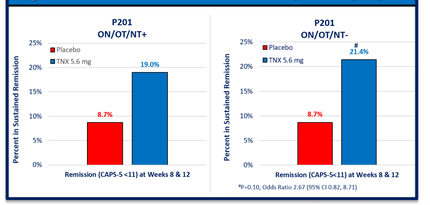
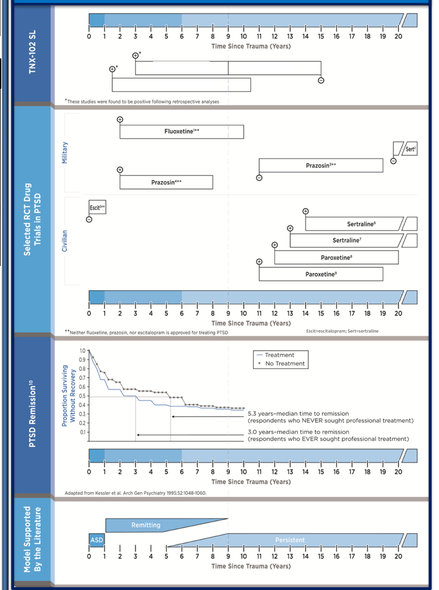


Figure 3. Sustained Remission P201 w/wo ON/OT/NT



The ON/OT/NT- subgroup had a numerically lower decrease (-1.8 points; p=0.523). However, as seen in **Figure 3**, in P201 sustained remission rates (CAPS-5 total <11 at both Week 8 & 12), were similar between the ON/OT/NT+ and - subgroups. In P301, the ON/OT/NT+ subgroup had an improvement in CAPS-5 of -5.5 points (p=0.010), relative to the mITT population change of -1.0 point (p=0.602). The P301 ON/OT/NT- subgroup did not improve, with a change in CAPS-5 of +1.5 points (p=0.505). In P301 the ON/OT/NT+ group appears to correlate with treatment response in the ≤ 9 year subsample (-13.4 points), but not in the > 9 year subsample (-0.6 points). The lack of response in the > 9 year subsample that was ON/OT/NT+ indicates treatment response could not simply be due to an unblinding effect (caused by the sublingual formulation) as this subgroup would be expected to show a treatment response. Together, these findings support the interpretation that ON/OT/NT events did not account for the observed responses to TNX 5.6 mg in the P201 mITT population or the P301 ≤ 9 year subgroup.

Figure 4. Time Since Trauma



DISCUSSION AND CONCLUSIONS

Posttraumatic stress disorder (PTSD) is complex with clear evidence that it has a dynamic pathophysiology which changes over time. Treatment responsiveness over the course of the disease may vary with different pharmacological classes, and may also differ between PTSD from combat versus other types of trauma (**Figure 4**). US epidemiologic study suggests a quarter to a third of PTSD remits within 1st year of symptom onset, another third remits over the next 4-5 years, and, in over a third, PTSD persists for many years.[10] A comparable pattern of PTSD persistence beyond 6 years is observed in OEF/OIF service members.[11] Several longitudinal studies of diverse PTSD samples have defined a similar trajectory pattern of early rapid remitters, slower remitters, and a non-remitting group with persistent PTSD in 17-40%.[12-15] SSRIs have been shown to be effective in civilian samples with mean times since trauma of 15 years or more,[6-8] and one trial reported a treatment by time-since-trauma interaction suggesting greater response to paroxetine in those with index trauma *greater* than 5 years prior.[9] In contrast, a similar pattern as seen with TNX may be extrapolated from prazosin studies, which improved sleep and global measures in active duty military close to combat trauma,[4] but had no effect in veterans mostly >9 years out (~70%)[3] Comparison of the P301 and P201 studies points to a differential treatment effect with TNX in a military sample based on time since trauma, with greater effect within 9 years of the index trauma. It is not clear how SSRIs would behave in military sample closer to trauma, although one study described a better response to fluoxetine among combat veterans in Europe with relatively short time since trauma.[1]

- The Phase 3 P301 study differed from the Phase 2 P201 study because median time since index trauma in the P301 TNX 5.6 mg group was 9.5 years, whereas it was only 6 years in P201
- The ≤9 year subgroup of the P301 study essentially replicated the results of the P201 mITT TNX 5.6 mg group
- Time since index trauma is important in the treatment response, as in is more difficult to demonstrate a response in those with >9 years since trauma
- The TNX treatment-responsive phase of PTSD may correspond to the "remitting" phase of Kessler et al.[10] (see **Figure 4**).
- The P301 and P201 studies help to advance the clinical development of TNX-102 SL, i.e. future studies will focus on participants with more recent trauma (≤9 years)
- Treatment response with TNX in P301 decreases over time since trauma (lack of separation from PBO), suggesting military service members and veterans with PTSD >9 years are transitioning from a treatment responsive state to a non-responsive state and emphasizes the urgency for early diagnosis and treatment for PTSD, especially military-related PTSD

Citations: [1]Martenyi et al. *J Clin Psychiatry* 2002;63:199-206.[2]Friedman et al. *J Clin Psychiatry* 2007;68:711-720. [3]Raskind et al. *NEJM* 2018;378:507-517. [4]Raskind et al. *Am J Psychiatry* 2013;170:1003-1010. [5]Shalev et al. *Arch Gen Psychiatry* 2012;69:166-176. [6]Davidson et al. *Arch Gen Psychiatry* 2001;58:485-492. [7]Brady et al. *JAMA* 2000;283:1837-1844. [8]Marshall et al. *Am J Psychiatry* 2001;158:1982-1988. [9]Tucker et al. *J Clin Psychiatry* 2001;62:860-868. [10]Kessler et al. *Arch Gen Psychiatry* 1995;52:1048-1060. [11]Armenta et al. *BMC Psychiatry* 2018;18:48. [12]Galatzer-Levy et al. *PLOS ONE* 2013;8:e70084. [13]Perkonigg et al. *Am J Psychiatry* 2005;162:1320-1327. [14]Santiago et al. *PLOS ONE* 2013;8:e59236. [15]Davidson & Connor. *Eur Neuropsychopharmacol* 2001;11(Supp3):S148-S149.

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