Steady-State Pharmacokinetic Properties of a Sublingual Formulation of Cyclobenzaprine (CBP) HCl (TNX-102 SL*): Comparison to Simulations of Oral Immediate Release CBP

W29

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

INTRODUCTION

TNX-102 SL is a sublingual (SL) formulation of cyclobenzaprine (CBP) designed for bedtime dosing that is being developed for the indications of posttraumatic stress disorder (PTSD), fibromyalgia (FM) and agitation in Alzheimer's Disease (AAD). Each is a central nervous system (CNS) condition in which sleep disturbances in slow wave and/or rapid eye movement sleep play central roles in the illness expression, and TNX-102 SL targets improvement in sleep quality.

CBP is a tricyclic molecule that has a unique receptor binding profile with high potency binding to serotonin-2A (5-HT_{2A}), α_1-adreneric, H_1-histaminergic, and M_1-muscarinic cholinergic receptors. CBP acts as an antagonist on these receptors, and each have been suggested to have roles for enhancing different aspects of sleep quality. The primary metabolite, norcyclobenzaprine (nCBP), which has: (1) a long half-life of several days, (2) a binding profile similar to but less potent than CBP for these four receptors, except that nCBP has more potent binding and inhibitory activity at the norepinephrine transporter (NET), which enhances sympathetic activation and is disruptive to sleep quality. **Table 1.** shows the binding affinities (K_i) of CBP and nCBP on human receptors and transporters.

Table 1. Affinity (K_i in nM) of CBP and nCBP on Human Neuroreceptors & Transporters

	H_1	5-HT_{2A}	α_{1A}	α_{1B}	M_1	SERT	NET
Cyclobenzaprine (CBP)	1.2	5.4	7.1	8	8.4	29	39
Norcyclobenzaprine (nCBP)	17.8	38	82	71	155	461	12.8

TNX-102 SL was formulated to allow rapid sublingual absorption for bedtime dosing, which results in a CBP pharmacokinetic (PK) plasma concentration curve with maximal levels achieved during middle of the sleep phase and falling levels by the end. The oral mucosal absorption of TNX-102 SL largely bypasses hepatic first pass metabolism, resulting in a substantially lower levels of the long-lived and undesirable metabolite, nCBP. Previous Phase 1 PK studies comparing TNX-102 SL with immediate release (IR) oral CBP show TNX-102 SL provides sublingual transmucosal absorption, rapid systemic exposure, avoidance of first-pass metabolism, and lower exposure to the long-lived active major metabolite, nCBP, shown in Table 2.

Table 2. TNX-102 SL vs. Oral IR CBP: Single-Dose Pharmacokinetic Parameters

Parameter	TNX-102 SL 2.8 mg	Oral IR CBP 5 mg	TNX-102 SL Compared to Oral IR
	Cyclobenzaprine		
Absorption Lag Time	0.050 hr (3 min)	0.622 hr (37 min)	12x faster
Relative Bioavailability	154%	-	54% higher
C_{max}	3.41 ng/mL	4.26 ng/mL	20% lower
AUC_{0-48}	57.4 ng•hr/mL	69.5 ng•hr/mL	17% lower
	Norcyclobenzaprine		
C_{max}	0.81 ng/mL	1.71 ng/mL	53% lower
AUC_{0-48}	30.5 ng•hr/mL	58.6 ng•hr/mL	48% lower
	Cyclobenzaprine/Norcyclobenzaprine		
Ratio AUC_{0-48}	1.88	1.18	59% higher

In this pivotal multi-dose bridging PK and safety study (TNX-CY-F106/"F106"), TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) was compared with AMRIX® (CBP extended-release [ER] capsules) 30 mg at steady-state (SS) for CBP and major metabolite nCBP, and the overall profiles of metabolites were compared. Additionally, the PK profile of TNX-102 SL 5.6 mg at SS from this bridging study is also contrasted with a simulated SS PK profile of oral IR CBP 10 mg as modeled from a prior single dose PK study that included oral IR CBP arm (TNX-CY-F104) to assess the potential PK and pharmacodynamic (PD) differentiation of TNX-102 SL from the oral IR form of CBP.

METHODS

Study F106 was a single-center, comparative PK, open-label, randomized, multiple-dose, 2-arm, parallel study conducted to support the registration of TNX-102 SL 5.6 mg. This pivotal exposure/safety bridging study compared the PK of TNX-102 SL at its potential therapeutic daily dose, 5.6 mg (2 x 2.8 mg tablets) with the reference listed drug (RLD), AMRIX ER capsules at the maximum recommended daily dose, 30 mg. F106 compared (1) the rate and extent of absorption, (2) the safety and tolerability, (3) the systemic exposure, and (4) the metabolic profile of the two drug products after reaching steady state exposure in 60 healthy adult volunteers under fasting conditions. The study included a 30-day screening period, 21-day confinement period with a 20-day daily dosing to reach steady state PK blood collections up to 648 hours (27 days) post-last dose. Fifty-six (56) healthy volunteers ages ≥18 and ≤65 years were assigned to one of the two treatments:

Treatment A (N=26): 2 x TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 2.8 mg once daily for 20 consecutive days

Treatment B (N=30): 1 x cyclobenzaprine HCl ER capsule (AMRIX) 30 mg once daily for 20 consecutive days.

Four (4) volunteers ages >65 and ≤75 years old were enrolled and assigned to **Treatment A**, but PK parameters for these four were analyzed separately and are not included in the displayed tables and figures.

The following PK parameters were calculated by standard non-compartmental methods for CBP and nCBP:

Day 1: $AUC_{0\text{-}24}$, C_{max}, T_{max}

Day 20: $AUC_{0\text{-}t\ ss}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $C_{max\ ss}$, $C_{min\ ss}$, Residual area, T_{max}, $T_{½\ el}$, K_{el}, Fl(%)

Safety variables include adverse events, clinical lab tests, vital signs, electrocardiogram and physical exam

The F106 TNX-102 SL 5.6 mg PK data also served as the comparator with PK simulations of steady state oral IR CBP 10 mg. The concentration-time profiles of CBP and nCBP during multiple dosing at steady state for oral IR CBP 10 mg once daily dosing were simulated from single-dose oral IR CBP 5 mg data from previous Phase 1 study TNX-CY-F104 ('F104') using nonparametric superposition methodology under the assumption of linear pharmacokinetics for CBP and nCBP. The adequacy of this methodology and assumption is supported by the good agreement between the predicted CBP and nCBP concentrations during multiple dosing of TNX-102 SL 5.6 mg once daily based on the TNX-102 SL 2.8 mg single dose administration in study F104 and the actually observed concentration-time profiles in study F106 (see Figure 3).

RESULTS

F106 Pharmacokinetic Results:

PK results show that following the first dose of TNX-102 SL 5.6 mg on Day 1 and the last dose on Day 20, exposure levels of CBP and its long-lasting major metabolite, nCBP, from TNX-102 SL 5.6 mg were less than AMRIX ER 30 mg.

Table 3 and **Table 4** show **Day 1** PK parameters for CBP for nCBP, respectively, for TNX-102 SL 5.6 mg and AMRIX ER 30 mg.

Table 3. Day 1 Plasma Cyclobenzaprine PK Parameters for TNX-102 SL 5.6 mg vs. AMRIX 30 mg

	TNX-102 SL 5.6 mg (2 x 2.8 mg Tablets) (Treatment A)				AMRIX 30 mg (1 x 30 mg ER Capsule) (Treatment B)			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}24}$ (h*pg/mL)	26	69115	26441	38.3	30	182587	50115	27.5
C_{max} (pg/mL)	26	5378	2122	39.5	30	12805	3398	26.5
Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	26	5.0	2.0	9.0	30	8.0	5.0	14.0

$AUC_{0\text{-}24}$=Area under the concentration-time curve from time zero to 24 hours; C_{max}=Maximum observed concentration; T_{max}=Time of observed Cmax

Table 4. Day 1 Plasma Norcyclobenzaprine PK Parameters for TNX-102 SL 5.6 mg vs. AMRIX 30 mg

	TNX-102 SL 5.6 mg (2 x 2.8 mg Tablets) (Treatment A)				AMRIX 30 mg (1 x 30 mg ER Capsule) (Treatment B)			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}24}$ (h*pg/mL)	26	22436	5628	25.1	30	72528	20484	28.2
C_{max} (pg/mL)	26	1331	330	24.8	30	4694	1239	26.4
Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	26	14.0	8.0	23.9	30	23.9	11.0	24.0

$AUC_{0\text{-}24}$=Area under the concentration-time curve from time zero to 24 hours; C_{max}=Maximum observed concentration; T_{max}=Time of observed Cmax

Table 5 and **Table 6** show **Day 20** steady state PK parameters for CBP for nCBP, respectively, for TNX-102 SL 5.6 mg and AMRIX ER 30 mg.

Table 5. Day 20 Plasma Cyclobenzaprine PK Parameters for TNX-102 SL 5.6 mg vs. AMRIX 30 mg

	TNX-102 SL 2 x 2.8 mg Tablets (Treatment A)				AMRIX® 1 x 30 mg ER Capsule (Treatment B)			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}t\ ss}$ (h*pg/mL)	26	174712	101480	58.1	30	669739	204457	30.5
$AUC_{0\text{-}t}$ (h*pg/mL)	26	498862	492177	98.7	30	2064790	909970	44.1
$AUC_{0\text{-}inf}$ (h*pg/mL)	26	508080	494870	97.4	30	2072921	910721	43.9
Residual Area (%)	26	2.37	1.03	43.4	30	0.46	0.22	48.7
$C_{max\ ss}$ (pg/mL)	26	11206	5659	50.5	30	39603	11862	30.0
$C_{min\ ss}$ (pg/mL)	26	4910	3531	71.9	30	20504	7448	36.3
Fl (%)	26	92.9	23.2	24.9	30	70.4	12.3	17.5
K_{el} (/h)	26	0.018	0.005	24.4	30	0.021	0.005	25.4
$T_{½\ el}$ (h)	26	40.3	10.4	25.7	30	35.6	8.2	23.2
Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
$T_{max\ ss}$ (h)	26	5.0	2.0	9.0	30	7.0	5.0	9.0

$AUC_{0\text{-}t\ ss}$ = Area under the concentration-time curve for one dosing interval (t) at steady-state; $AUC_{0\text{-}t}$ = Area under the concentration-time curve from time zero to the last non-zero concentration; $AUC_{0\text{-}inf}$ = Area under the curve from time zero to infinity (extrapolated); $C_{max\ ss}$ = Maximum observed concentration at steady state; $C_{min\ ss}$ = Minimum observed concentration at steady state; T_{max} = Time of observed C_{max}; Fl (%) = Percentage of fluctuation; K_{el} = Elimination rate constant; $T_{½\ el}$ = Elimination half-life (equivalent to $t_{1/2}$); Tmax ss = Time of observed C_{max} at steady state.

Table 6. Day 20 Plasma Norcyclobenzaprine PK Parameters for TNX-102 SL 5.6 mg vs. AMRIX 30 mg

	TNX-102 SL 2 x 2.8 mg Tablets (Treatment A)				AMRIX 1 x 30 mg ER Capsule (Treatment B)			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}t\ ss}$ (h*pg/mL)	26	204882	92984	45.4	30	812843	336032	41.3
$AUC_{0\text{-}t}$ (h*pg/mL)	26	1272429	980634	77.1	30	4705126	3366756	71.6
$AUC_{0\text{-}inf}$ (h*pg/mL)	26	1285031	998324	77.7	30	4721586	3396773	71.9
Residual Area (%)	26	0.95	0.59	61.5	30	0.26	0.20	77.5
$C_{max\ ss}$ (pg/mL)	26	10370	4601	44.4	30	40159	16864	42.0
$C_{min\ ss}$ (pg/mL)	26	6950	3202	46.1	30	27700	12216	44.1
Fl (%)	26	40.9	9.2	22.4	30	37.1	9.7	26.0
K_{el} (/h)	26	0.011	0.003	27.0	30	0.012	0.004	31.1
$T_{½\ el}$ (h)	26	66.7	18.1	27.1	30	64.0	17.4	27.2
Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
$T_{max\ ss}$ (h)	26	8.0	6.0	12.0	30	8.0	5.0	24.1

$AUC_{0\text{-}t\ ss}$ = Area under the concentration-time curve for one dosing interval (t) at steady-state; $AUC_{0\text{-}t}$ = Area under the concentration-time curve from time zero to the last non-zero concentration; $AUC_{0\text{-}inf}$ = Area under the curve from time zero to infinity (extrapolated); $C_{max\ ss}$ = Maximum observed concentration at steady state; $C_{min\ ss}$ = Minimum observed concentration at steady state; T_{max} = Time of observed Cmax; Fl (%) = Percentage of fluctuation; K_{el} = Elimination rate constant; $T_{½\ el}$ = Elimination half-life (equivalent to $t_{1/2}$); Tmax ss = Time of observed C_{max} at steady state.

Figures 1 shows Day 1 and Day 20 mean concentration-time profiles for plasma cyclobenzaprine for TNX-102 SL 5.6 mg and AMRIX ER 30 mg. **Figures 2** shows Day 1 and Day 20 mean concentration-time profiles for norcyclobenzaprine for TNX-102 SL 5.6 mg and AMRIX ER 30 mg.

Figure 1. Day 1 & Day 20 Cyclobenzaprine Levels for TNX-102 SL 5.6 mg vs. AMRIX 30 mg

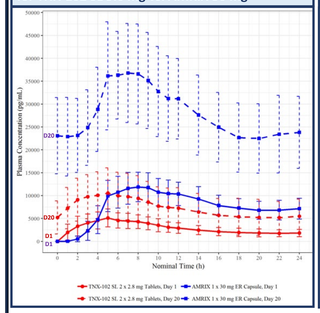
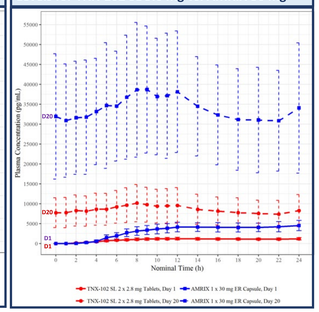


Figure 2. Day 1 & Day 20 Norcyclobenzaprine Levels for TNX-102 SL 5.6 mg vs. AMRIX 30 mg



F106 Metabolite Profiles for TNX-102 SL and AMRIX ER Tablets: A total of nine (9) phase I metabolites and eight (8) phase II metabolites were detected in human plasma dosed with CBP. All metabolites detected in the human plasma dosed with TNX-102 SL 5.6 mg were also detected in the samples dosed with AMRIX 30 mg ER capsules. Higher responses of the phase I and II (glucuronide conjugates) metabolites were detected in the volunteers dosed with AMRIX 30 mg ER capsules. In light of these results, it is reasonable to assume that the metabolic profiles are comparable in human plasma for both TNX-102 SL 5.6 mg and AMRIX 30 mg ER capsules. Moreover, the volunteers dosed with AMRIX 30 mg ER capsules were exposed to a higher concentration of each metabolite compared to the volunteers dosed with TNX-102 SL 5.6 mg.

F106 Safety Results and Prior Phase 1 Safety Results from Same Center:

In F106 the most commonly reported treatment-emergent adverse event (TEAE) reported by 30 subjects receiving 20 days of TNX-102 SL 5.6 mg were hypoesthesia oral (HO)(50.0%), product taste abnormal (43.3%), somnolence (33.3%), heart rate increase (30.0%), constipation (26.7%), blood pressure increase (16.7%), nausea (13.3%), paresthesia oral (10.0%), and dry mouth (10.0%). HO and/or paraesthesia oral (PO) was reported 3 days or less in 26.7%, and 7 days or more in 23.3% of subjects receiving TNX-102 SL 5.6 mg (**Figure 6**). All reports were rated as mild and were transient (lasting an average of ~60 minutes or less).

For the 30 receiving 20 days of AMRIX 30 mg, most commonly reported TEAEs were heart rate increase (53.3%), constipation (40%), dry mouth (36.7%), headache (16.7%), blood pressure increase (13.3%), palpitations 13.3%, alanine aminotransferase increase (13.3%), dizziness (10.0%) and product taste abnormal (10.0%).

No deaths, serious, or significant AEs were reported during the study.

Figure 3. Day 20 Concentration-Time Profiles of TNX-102 SL 5.6 mg Observed (F106) vs. Simulated (F104)

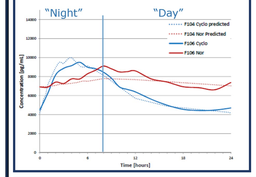


Figure 3 shows the observed concentration-time profile for TNX-102 SL 5.6 mg from study F106 for CBP and nCBP and the simulated profile based on single dose data for TNX-102 SL 2.8 mg from F104. The good agreement between the observed and predicted data support the adequacy of this methodology and assumption employed (nonparametric superposition methodology under assumption of linear pharmacokinetics for CBP and nCBP).

Figures 4 & 5 below show the Day 20 concentration-time profiles of CBP and nCBP for TNX-102 SL 5.6 mg and simulated oral IR CBP at 5 mg & 10 mg, respectively. During sleep hours (0-8 hrs post-dose), CBP steady-state levels and AUC are higher than nCBP post TNX-102 SL, unlike the pattern observed with simulated oral IR CBP, with nCBP higher.

Figure 4. Day 20 Concentration-Time Profiles for TNX-102 SL 5.6 mg vs. Simulated Oral IR Cyclobenzaprine 5 mg

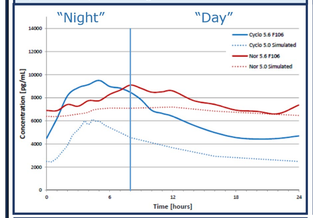


Figure 5. Day 20 Concentration-Time Profiles for TNX-102 SL 5.6 mg vs. Simulated Oral IR Cyclobenzaprine 10 mg

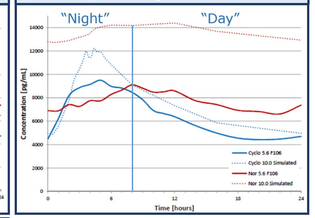


Figure 6. AEs of Hypoaesthesia Oral and/or Paraesthesia Oral in F106: No. of Days Reported

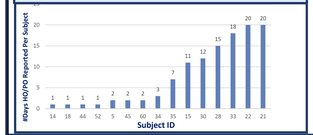


Figure 6 shows the total number of days per subject receiving TNX-102 SL 5.6 mg in which either hypoaesthesia oral (HO) or paraesthesia oral (PO) was reported. Of the 30 subjects, 50% reported at least occurrence on one day, and all occurrences were temporally related to dosing. Of the 30, 23.3% reported occurrence on a total of 7-20 days, and 26.7% reported occurrence on 3 or less days. All were rated as mild, lasted an average of 60 minutes, and never were associated with an oral lesion.

CONCLUSION

- At steady-state, exposure to CBP and nCBP from TNX-102 SL were less than from AMRIX.
- Overall, TNX-102 SL 5.6 mg or AMRIX 30 mg taken for 20 days were well tolerated.
- For the intended therapeutic daily bedtime administration, these data show during typical sleep hours (0-8 hours post-dose), CBP steady-state levels and AUC are higher than nCBP post TNX-102 SL administration, which optimizes the effects of CBP on the sleeping brain.
- In contrast, a simulation of oral IR CBP 5 mg (Figure 4) and 10 mg (Figure 5) predicts nCBP steady-state levels and AUC *higher* than CBP during sleep.
- The dynamic changes in CBP over 24 hours are believed to optimize the effects on the brain, and these changes are magnified in the higher predicted occupancy of relevant receptors, 5-HT_{2A}, α_1, H_1 and M_1, during the typical sleep hours.
- In contrast, nCBP has a higher affinity for the norepinephrine (NE) transporter, which would be expected to impair sleep due to higher synaptic NE availability during period in which optimal sleep quality is associated with lower NE activity. Therefore, TNX-102 SL is predicted to be differentiated from oral IR CBP due to lower nCBP levels than CBP during the typical sleep hours.
- Together these data support the use of TNX-102 SL as a potential chronic bedtime treatment for PTSD, FM and AAD.

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