Steady-state Pharmacokinetic Properties of a Sublingual Formulation of Cyclobenzaprine (CBP) HCl (TNX-102 SL): Comparison to Simulations of Oral immediate-release CBP

Poster #45

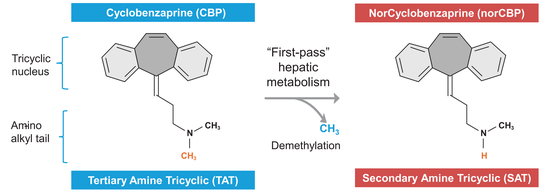
Gregory M. Sullivan, MD[1]; Bernd Meibohm, PhD, FCP, FAAPS[2]; Errol Gould, PhD[3]; Seth Lederman, MD[1]

[1]Tonix Pharmaceuticals, Inc., Chatham, NJ, USA; [2]The University of Tennessee Health Science Center, Memphis, Tennessee, USA; [3]Tonix Medicines, Inc., Chatham, NJ.

INTRODUCTION

- Fibromyalgia (FM) is a chronic condition characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive/somatic complaints[1,2]
- Cyclobenzaprine (CBP), a centrally acting skeletal muscle relaxant, has been widely prescribed off-label as a treatment for FM despite lack of approval by the FDA[3-8]
- CBP, a tertiary amine tricyclic (TAT), is metabolized in the liver via demethylation to norcyclobenzaprine (nCBP), an active secondary amine tricyclic metabolite (**Figure 1**)[9]
  - The pharmacokinetic (PK) profile of oral immediate release CBP is characterized by extensive hepatic metabolism with a relatively short plasma half-life ($t_{1/2}$)[10]
    - In contrast, the major active metabolite nCBP has a significantly longer $t_{1/2}$, leading to its accumulation, a flattened PK profile, and steady-state concentrations that exceed those of CBP
  - CBP exhibits antagonism at the 5-HT_{2A} serotonergic, α_1-adrenergic, M_1-muscarinic acetylcholine, and H_1-histaminergic receptors, each implicated in sleep regulation[9]
    - In contrast, nCBP may interfere with CBP's receptor activity and disrupt sleep through its potent inhibition of the norepinephrine transporter

Figure 1: Cyclobenzaprine Mechanism[9]



- Tonmya™ (TNX-102 SL, cyclobenzaprine HCl sublingual tablets) is designed for bedtime administration and is FDA approved for the treatment of FM in adults[9-14]
  - Compared to oral IR CBP, TNX-102 SL provides rapid transmucosal absorption, increased relative bioavailability (~50% higher), and reduced formation of the long half-life active metabolite nCBP by partially bypassing first-pass hepatic metabolism[10]
- Like other TATs (e.g., amitriptyline), oral CBP was poorly tolerated in clinical studies (i.e., increased frequency of systemic adverse events), potentially due to nCBP accumulation with daily dosing[10]
- Previous Phase 1 PK studies indicate that TNX-102 SL results in lower systemic exposure to nCBP relative to oral IR CBP (data on file, Tonix Pharmaceuticals, Inc.)

OBJECTIVE

- This post hoc analysis compares the steady-state PK profile of TNX-102 SL 5.6 mg with a simulated PK profile of oral IR CBP, focusing on the relative plasma concentrations of CBP and nCBP

METHODS

- A population pharmacokinetic (PopPK) modeling and simulation analysis was used to characterize and compare the PK of TNX-102 SL and oral IR CBP
  - Two separate PopPK models were developed for CBP and nCBP using pooled data from previously conducted single-dose (F104) and multiple-dose (F106) PK studies
    - The multiple-dose study was included to ensure reliable estimation of elimination parameters, especially for the active, long half-life metabolite, nCBP
  - Simulations were performed to compare steady-state exposure profiles (area under the curve [AUC] and maximum concentration [C_{max}]) of TNX-102 SL 5.6 mg once daily and oral IR CBP 5 mg and 10 mg once daily, calculating exposure ratios (nCBP-to-CBP for AUC and C_{max})
  - Nonlinear Mixed Effect Modeling Software (NONMEM®, version 7.5, Icon Plc, Dublin, Ireland) was used for model parameter estimation and for simulations
  - Exposures were calculated via non-compartmental analysis

RESULTS

- **Table 1** describes demographics and baseline characteristics for the TNX-102 SL group from the single-dose (F104) and multiple-dose (F106) PK studies

Table 1: Demographics and Other Baseline Characteristics

	Study F104		Study F106
	TNX-102 SL 2.8 mg (with potassium phosphate) (n=6)	Oral IR CBP (n=6)	TNX-102 SL 5.6 mg (n=30)
Age, years, mean (SD)	36.7 (15.0)	37.3 (15.4)	46.6 (13.9)
Female, n (%)	4 (67)	3 (50)	15 (50)
Race, n (%)			
White	5 (83)	6 (100)	27 (90)
Black	0 (0)	0 (0)	2 (7)
Asian	1 (17)	0 (0)	1 (3)

- CBP and nCBP PK parameters after TNX-102 SL 5.6 mg on Day 20 are summarized in **Table 2**

Table 2: Summary of PK Parameters After TNX-102 SL 5.6 mg for CBP and nCBP on Day 20

	CBP (n=26)	nCBP (n=26)
AUC_{SS}, h*ng/mL, mean (SD)	175 (101)	205 (93)
C_{max}, ng/mL, mean (SD)	11.2 (5.7)	10.4 (4.6)
T_{max}, h, median (min, max)	5 (2, 9)	8 (6, 12)

AUC_{SS}, area under the curve at steady state; C_{max}, maximum concentration; CBP, cyclobenzaprine; max, maximum; min, minimum; nCBP, norcyclobenzaprine; SD, standard deviation; T_{max}, time to maximum concentration.

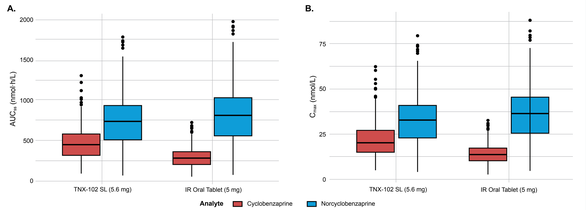
- Simulated steady-state exposure metrics are summarized in **Table 3**
  - For all regimens, nCBP exposure exceeded CBP exposure
  - The nCBP-to-CBP exposure ratios were lower for TNX-102 SL than for oral IR CBP, indicating a lower extent of metabolism to nCBP for TNX-102 SL
- Compared to oral IR CBP, TNX-102 SL produced higher and more consistent exposures to plasma CBP (**Figure 2**)
  - Conversely, oral IR CBP resulted in higher variability in plasma CBP and greater nCBP exposure vs TNX-102 SL
- Simulated concentration-time profiles for CBP and nCBP confirm that steady state is achieved within the dosing period for both analytes and formulations
  - TNX-102 SL produces a higher CBP profile with lower nCBP accumulation relative to the IR oral tablet, consistent with the observed formulation differences (**Figure 3**)

Table 3: Simulated Steady-State Exposure Metrics for CBP and nCBP After 21 Days of Once-Daily Dosing

Form	Analyte	$AUC_{0-\tau,SS}$ (nmol/L*h)	Ratio[a]	$C_{max,SS}$ (nmol/L)	Ratio[a]
TNX-102 SL 5.6 mg QD	CBP	446.77	1.67	21.72	1.52
	nCBP	745.98		33.05	
Oral IR CBP 5 mg QD	CBP	296.61	2.78	14.19	2.58
	nCBP	825.61		36.59	
Oral IR CBP 10 mg QD	CBP	593.22	2.78	28.38	2.58
	nCBP	1651.22		73.18	

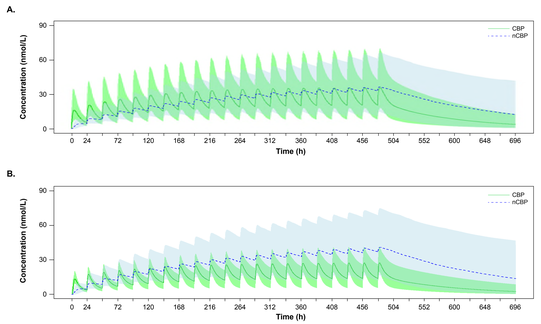
Simulations conducted for TNX-102 SL 5.6 mg and oral IR CBP (5 mg and 10 mg).
[a]Ratios were calculated as nCBP/CBP.
$AUC_{0-\tau,SS}$, area under the curve over the dosing interval at steady state; CBP, cyclobenzaprine; $C_{max,SS}$, maximum concentration at steady state; IR, immediate release; nCBP, norcyclobenzaprine; QD, once daily.

Figure 2: Boxplots of Simulated Steady-State $AUC_{0-\tau,SS}$ (A) and C_{max} (B) for CBP and nCBP by Formulation



Each box represents the interquartile range (IQR), with median values shown by horizontal lines and whiskers representing the 1.5×IQR range. TNX-102 SL shows higher CBP and lower nCBP exposures than oral IR CBP, consistent with reduced metabolic formation.
$AUC_{0-\tau,SS}$, area under the curve over the dosing interval at steady state; CBP, cyclobenzaprine; C_{max}, maximum concentration; IR, immediate release; nCBP, norcyclobenzaprine.

Figure 3: Simulated Concentration-Time Profiles for CBP and nCBP Following 21 Days of Once-Daily Dosing of TNX-102 SL 5.6 mg (A) and Oral IR CBP 5 mg (B)



Solid lines represent the median concentration; shaded areas depict the 95% prediction interval for each analyte.
CBP, cyclobenzaprine; h, hour; IR, immediate release; nCBP, norcyclobenzaprine.

- Assuming linear pharmacokinetics as previously reported for IR CBP HCl[15], these simulations suggest that 10 mg once-daily oral IR CBP results in only a 40% higher AUC for CBP but a 128% higher AUC for nCBP than would be seen with TNX-102 SL 5.6 mg
  - This result implies a higher ratio of CBP-to-nCBP exposure with sublingual administration of TNX-102 SL compared with CBP IR administered orally

Safety

- The most frequent TEAEs reported were mild and transient oral administration site reactions (**Table 4**)
  - No unexpected TEAEs were observed
  - Most TEAEs were mild in severity, and the majority resolved without treatment

Table 4: Most Frequently Reported (≥5 Participants in Any Treatment Arm) TEAEs by Preferred Term (Study F104 and F106)

	Study F104		Study F106
MedDRA Preferred Term	TNX-102 SL 2.8 mg (with potassium phosphate) n (%) (n=6)	Oral IR CBP n (%) (n=6)	TNX-102 SL 5.6 mg n (%) (n=30)
Hypoesthesia oral	2 (33)	0 (0)	15 (50)
Abnormal product taste	0 (0)	0 (0)	13 (43)
Somnolence	0 (0)	0 (0)	10 (33)
Increased heart rate	0 (0)	0 (0)	9 (30)
Constipation	0 (0)	0 (0)	8 (27)
Increased blood pressure	0 (0)	0 (0)	5 (17)
Back pain	0 (0)	0 (0)	5 (17)
Fatigue	0 (0)	0 (0)	5 (17)

MedDRA®, Medical Dictionary for Regulatory Activities, Version 21.0.

CONCLUSIONS

- Daily administration of TNX-102 SL 5.6 mg for 20 days was well-tolerated in healthy participants
- For the intended therapeutic daily bedtime administration, during typical hours of sleep (0-8 h post-dose), CBP steady-state concentration and AUC were higher than nCBP post-TNX-102 SL administration, optimizing the effects of CBP on the sleeping brain
  - In contrast, simulation of oral IR CBP predicted that steady-state concentration and AUC were higher for nCBP than CBP during sleep
- It is reasonable to expect that during waking hours (8-24 h post-dose), TNX-102 SL provides lower CBP levels than nCBP
- The dynamic changes in CBP over 24 hours are believed to optimize the effects on the brain, and these changes are magnified by the predicted occupancy of relevant receptors, since CBP has higher affinities for the 5-HT_{2A}, α_1, H_1 and M_1 receptors than nCBP
  - In contrast, nCBP has higher affinity for the norepinephrine transporter, which would be expected to impair sleep due to higher synaptic norepinephrine availability during the period in which optimal sleep quality is associated with lower noradrenergic sympathetic nervous system activity
- Together, these data support the use of TNX-102 SL as a chronic bedtime treatment for FM

References

1. Kang JH, et al. *J Rheum Dis.* 2022;29(1):4-13.
2. Theadom A, et al. *J Psychosom Res.* 2007;62(2):145-51.
3. Bennett RM, et al. *Arthritis Rheum.* 1988;31(12):1535-42.
4. Carette S, et al. *Arthritis Rheum.* 1994;37(1):32-40.
5. Fossaluzza V, De Vita S. *Int J Clin Pharmacol Res.* 1992;12(2):99-102.
6. Quimby LG, et al. *J Rheumatol Suppl.* 1989;19:140-3.
7. Reynolds WJ, et al. *J Rheumatol.* 1991;18(3):452-4.
8. Santandrea S, et al. *J Int Med Res.* 1993;21(2):74-80.
9. Gould E, et al. International Symposium on Pediatric Pain, June 17-20, 2025, Glasgow, UK. Poster 195.
10. Lederman S, et al. *PainConnect* 2025, April 3-6, 2025, Austin, TX.
11. Iglehart III I, et al. EULAR Annual Meeting, June 11-14, 2025, Barcelona, Spain. Poster POS0216.
12. Lederman S, et al. *Arthritis Care Res* (Hoboken). 2023;75(11):2359-68.
13. Lederman S, et al. *Pain Med.* 2025:pnaf089.
14. TONMYA™ (cyclobenzaprine hydrochloride sublingual tablets) [prescribing information]. Chatham, NJ: Tonix Medicines, Inc.; 2025.
15. Winchell GA, et al. *J Clin Pharmacol.* 2002;42(1):61-9.

Disclosures

BM: Nothing to disclose. **EG:** Employee of Tonix Medicines, Inc. **GMS, SL:** Employee of and stock ownership in Tonix Pharmaceuticals, Inc.

Acknowledgements

This study was supported by Tonix Pharmaceuticals, Inc. (Chatham, NJ). Medical writing and editorial assistance were provided by Elizabeth Schoelwer, PharmD, and Anthony DiLauro, PhD, of the Sensified Division of Woven Health Collective, LLC (New York, NY), and were funded by Tonix Pharmaceuticals, Inc.
Population pharmacokinetic modeling and simulation were performed by CTI Clinical Trial & Consulting.

Contact info

Errol Gould, PhD, Tonix Medicines, Inc. 26 Main Street – Suite 101, Chatham, NJ 07928

Presented at the PAINWeek Conference 2025, September 2-5, 2025, Las Vegas, NV