Tonmya™ (TNX-102 SL; CBP SL) steady-state pharmacokinetics compared to oral simulations

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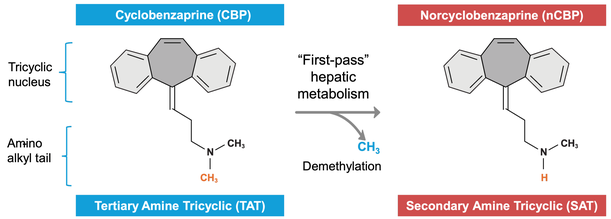
INTRODUCTION

- Fibromyalgia (FM) is a chronic nociplastic pain disorder 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 not being approved by the FDA[3-8]
- Oral immediate-release (IR) CBP has a short half-life (t1/2) and is extensively metabolized; in contrast, its major active metabolite norcyclobenzaprine (nCBP) has a long half life, accumulating over time with nCBP predominating at steady state[9]
- High daytime blood levels of nCBP may add to daytime side effect burden, and nCBP's uniquely potent inhibition of the norepinephrine transporter may disrupt sleep in opposition to the sleep quality-enhancing effects of the parent molecule
- CBP antagonizes the 5-HT_{2A} serotonergic, α_1-adrenergic, M_1-muscarinic acetylcholine, and H_1-histaminergic receptors, each implicated in sleep regulation[10]

Figure 1: Cyclobenzaprine Metabolism



- Tonmya™ (TNX-102 SL; cyclobenzaprine HCl sublingual tablets [CBP SL]) is approved for the treatment of FM in adults and is designed for bedtime administration[11-13]
- CBP SL provides rapid transmucosal absorption, has increased bioavailability, and reduces the formation of nCBP relative to oral IR CBP[10]

OBJECTIVE

- Employing advanced population pharmacokinetic modeling techniques, this post hoc analysis compares the steady-state PK profile of CBP 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 CBP 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, where the single-dose study data were inadequate
- Simulations were performed to compare steady-state exposure profiles (area under the curve [AUC] and maximum concentration [C_{max}]) of CBP 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: Demographics and Other Baseline Characteristics

	Study F104		Study F106
	CBP SL 2.8 mg (with potassium phosphate) (n=6)	Oral IR CBP 5 mg (n=6)	CBP 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, cyclobenzaprine; IR, immediate-release; SD, standard deviation.

Table 2: Summary of PK Parameters After CBP SL 5.6 mg Administration on Day 20 at Steady State

	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.

- nCBP exposure exceeded CBP exposure in each simulated regimen (**Table 3**)
- nCBP-to-CBP exposure ratios were lower for CBP SL than for oral IR CBP, indicating a lower extent of metabolism to nCBP with CBP SL

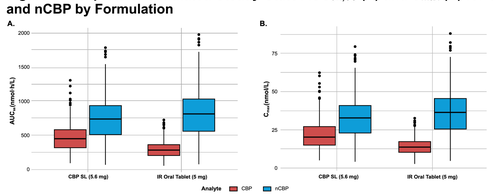
Table 3: Simulated Steady-State Exposure Metrics for CBP and nCBP After 20 Days of Once-Daily Dosing

Form	Analyte	$AUC_{0-\tau,SS}$ (nmol/L*h)	Ratio[a]	$C_{max,SS}$ (nmol/L)	Ratio[a]
CBP SL 5.6 mg QD	CBP	447	1.67	21.7	1.52
	nCBP	746		33.1	
Oral IR CBP 5 mg QD	CBP	297	2.78	14.2	2.58
	nCBP	826		36.6	
Oral IR CBP 10 mg QD	CBP	593	2.78	28.4	2.58
	nCBP	1650		73.2	

Simulations conducted for CBP 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.

- Assuming linear pharmacokinetics for oral IR CBP, these simulations suggest that once-daily oral IR CBP 10 mg results in only a 40% higher AUC for CBP but a 128% higher AUC for nCBP than with CBP SL 5.6 mg
- This result implies a higher ratio of CBP-to-nCBP exposure with sublingual administration of CBP SL compared with oral IR CBP
- CBP SL produced higher and more consistent exposures to plasma CBP compared with oral IR CBP 5 mg (**Figure 2**)
- Oral IR CBP simulations resulted in greater variability in CBP exposure and greater nCBP exposure compared with CBP SL
- Simulated concentration-time profiles for CBP and nCBP confirm that steady state was achieved within the dosing period for both analytes and formulations
- At steady state, CBP SL was associated with higher CBP exposure and lower nCBP accumulation relative to oral IR CBP, consistent with the observed formulation differences (**Figure 2**)

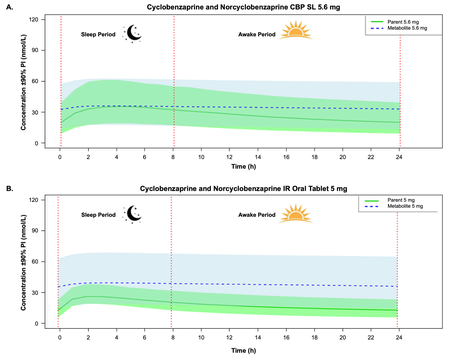
Figure 2: Boxplots of Simulated Steady-State $AUC_{0-\tau,SS}$ (A) and C_{max} (B) for CBP and nCBP by Formulation



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

CBP SL 5.6 mg optimizes CBP exposure in the first 8 hours after administration to facilitate restorative sleep whereas with oral IR CBP administration, nCBP predominates and accumulates over time potentially leading to next-day somnolence, sedation and cognitive dysfunction (**Figure 3**)

Figure 3: Simulated Concentration-Time Profiles for CBP and nCBP Following 20 Days of Once-Daily Dosing of CBP SL 5.6 mg (A) and Oral IR CBP 5 mg (B)



Solid lines represent the median concentration; shaded areas depict the 90% prediction interval for each analyte.
h, hour; IR, immediate release; PI, prediction interval; SL, sublingual.

Safety

- The most frequent treatment-emergent adverse events (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
	CBP SL 2.8 mg (with potassium phosphate) n (%) (n=6)	Oral IR CBP 5 mg n (%) (n=6)	CBP 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)

CBP, cyclobenzaprine; IR, immediate-release; MedDRA®, Medical Dictionary for Regulatory Activities, Version 21.0; TEAE, treatment-emergent adverse event

CONCLUSIONS

- After CBP SL 5.6 mg administration at Day 20 (i.e., steady state), nCBP concentration was similar to peak CBP concentration in the first 8 hours and decreased very little for the rest of the 24 hours, whereas CBP concentration kept falling to about one-half its peak
- After oral IR 5 mg CBP administration at steady state, nCBP peak concentration was ~75% higher than the peak CBP concentration and remained similarly high for the rest of the 24 hours while CBP concentration fell; at the end of 24 hours, nCBP concentration was >2 times higher than that of CBP
- 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
- Daily administration of CBP SL 5.6 mg for 20 days was well-tolerated in healthy participants
- Together, these data support the use of CBP SL as a chronic bedtime treatment for FM

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DISCLOSURES

MC: Employee of Tonix Medicines, Inc. and owns stock and/or stock options in Tonix Pharmaceuticals Holding Corp.
GMS: Employee of Tonix Pharmaceuticals, Inc. and owns stock and/or stock options in Tonix Pharmaceuticals Holding Corp.
BM: Paid consultant of Tonix Pharmaceuticals.