POS0927

Steady-state Pharmacokinetic Properties of a Sublingual Formulation of Cyclobenzaprine (CBP) HCl: Comparison to Simulations of Oral Immediate-Release CBP

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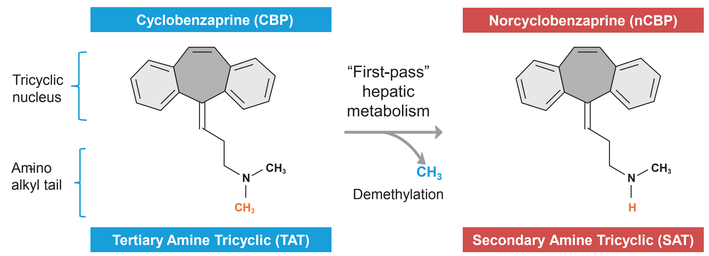
INTRODUCTION

- 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]
- 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 (IR) 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[10]
  - 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[11]
    - 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

Figure 1: Cyclobenzaprine Metabolism[9]



- Cyclobenzaprine HCl sublingual tablets (CBP SL; TNX-102 SL) is designed for bedtime administration and is US FDA approved for the treatment of FM in adults[11-13]
  - Compared to oral IR CBP, CBP SL provides rapid transmucosal absorption, increased relative bioavailability (~50% higher), and reduced formation of the long half-life active metabolite nCBP by largely 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[12]
- Previous Phase 1 PK studies indicate that CBP SL results in lower systemic exposure to nCBP relative to oral IR CBP[10]

OBJECTIVE

- By 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 long half-life active metabolite nCBP
  - 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** describes demographics and baseline characteristics for the CBP SL group from the single-dose (F104) and multiple-dose (F106) PK studies

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; SL, sublingual.

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

Table 2: Summary of PK Parameters After CBP 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; SL, sublingual; T_{max}, time to maximum concentration.

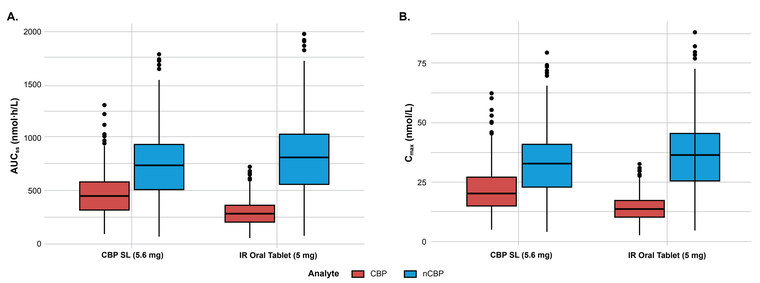
- Simulated steady-state exposure metrics for CBP SL and oral IR CBP are summarized in **Table 3**
  - For all regimens, nCBP exposure exceeded CBP exposure
  - The nCBP-to-CBP exposure ratios were lower for CBP SL than for oral IR CBP, indicating a lower extent of metabolism to nCBP for CBP SL
- CBP SL produced higher and more consistent exposures to plasma CBP than oral IR CBP 5 mg (**Figure 2**)
  - Oral IR CBP simulations resulted in greater variability in CBP exposure and greater nCBP exposure than 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
  - CBP SL produced a higher CBP profile with lower nCBP accumulation relative to oral IR CBP, consistent with the observed formulation differences (**Figure 3**)

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	

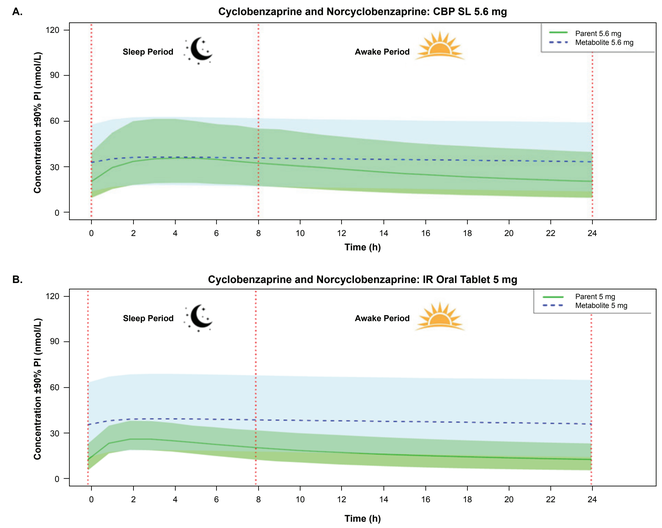
Simulations conducted for CBP SL 5.6 mg and oral IR CBP (5 mg and 10 mg).
[a]Ratios were calculated as nCBP/CBP.
$AUC_{0-\tau,SS}$, area under the curve over the dosing interval at steady state; CBP, cyclobenzaprine; $C_{max,SS}$, maximum concentration at steady state; IR, immediate-release; nCBP, norcyclobenzaprine;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

Figure 2: Boxplots of Simulated Steady-State $AUC_{0-T,SS}$ (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.
CBP SL shows higher CBP and lower nCBP exposures than oral IR CBP, consistent with reduced metabolic formation.
$AUC_{0-T,SS}$, area under the curve over the dosing interval at steady state; CBP, cyclobenzaprine; C_{max}, maximum concentration; IR, immediate-release; nCBP, norcyclobenzaprine; SL, sublingual.

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.
CBP SL, cyclobenzaprine sublingual tablets; h, hour; IR, immediate release; PI, prediction interval.

- Assuming linear pharmacokinetics as previously reported for oral IR CBP HCl[14], 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 CBP SL 5.6 mg
  - This result implies a higher ratio of CBP-to-nCBP exposure with sublingual administration of CBP SL compared with CBP IR administered orally

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
MedDRA Preferred Term, n(%)	CBP SL 2.8 mg (with potassium phosphate) (n=6)	Oral IR CBP 5 mg (n=6)	CBP SL 5.6 mg (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; SL, sublingual; 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 in the first 8 hours and decreased very little for the rest of the 24 hours, whereas CBP 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
- Daily administration of CBP SL 5.6 mg for 20 days was well-tolerated in healthy participants
- The dynamic changes in CBP plasma concentrations over 24 hours following CBP SL administration are believed to optimize CBP 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 CBP SL as a chronic bedtime treatment for FM

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Disclosures

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

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