Pharmacokinetic Characterization of Tonmya™ (TNX-102 SL), a Sublingual Formulation of Cyclobenzaprine (CBP SL) for the Treatment of Adults with Fibromyalgia

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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]
- Tonmya™ (TNX-102 SL; cyclobenzaprine HCl sublingual tablets [CBP SL]) is FDA-approved for the treatment of FM in adults based on two pivotal Phase 3 trials (RELIEF and RESILIENT)[3-5]
  - CBP SL is a sublingual eutectic formulation of CBP HCl and mannitol containing potassium phosphate dibasic that rapidly disintegrates and is absorbed transmucosally, resulting in rapid and efficient systemic exposure[6]
  - CBP SL tablets contain potassium phosphate dibasic as a basifying agent to increase local pH, shifting CBP to its un-ionized free base at the mucosal surface, thereby increasing membrane permeability and enabling rapid transmucosal absorption into systemic circulation[6,7]
  - Compared with oral immediate-release (IR) CBP, CBP SL largely bypasses first-pass hepatic metabolism, resulting in ~50% higher relative bioavailability of CBP and reduced formation of the long half-life active metabolite norcyclobenzaprine (nCBP)[6]

OBJECTIVE

To characterize the pharmacokinetic (PK) and clinical pharmacology profile of CBP SL in adults with FM

METHODS

Study 1: Single-Dose PK Study (CBP SL 2.8 mg vs oral IR CBP 5 mg)[6]

- Single-center, randomized, open-label, parallel-group study in healthy adults (N=24)
- Compared the rate and extent of absorption of CBP SL 2.8 mg (3 formulations: potassium phosphate dibasic, sodium phosphate dibasic, or trisodium citrate) with oral IR CBP 5 mg; safety and tolerability were also assessed
- Demographics: 58% female; 96% White; 13% Hispanic; aged 19–59 years (mean, 36.2 years)

Study 2: Food Effect Dose Proportionality Study[6]

- Single-center, randomized, open-label, single-dose, 3-period, 6-sequence crossover study in healthy adults (N=16)
- Evaluated CBP SL 2.8 vs 5.6 mg dose proportionality under fasting conditions, the effect of food on CBP SL 5.6 mg absorption, and safety and tolerability
- Demographics: 50% female; 100% white; 12.5% Hispanic; aged 36-62 years (mean, 52.7 years)

RESULTS

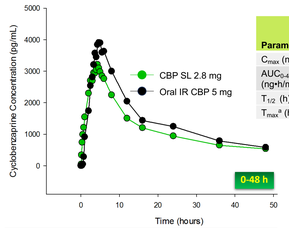
Safety and Tolerability, Studies 1 and 2

- CBP SL was well tolerated, with no serious treatment-emergent adverse events (TEAEs) and no clinically meaningful changes in laboratory parameters, vital signs, or ECG
- In Study 1 (including oral IR CBP), 16 TEAEs occurred, all mild, in 13 of 24 participants; oral hypoesthesia and somnolence were the only TEAEs reported in ≥2 participants taking CBP SL
- In Study 2 (CBP SL only), 61 TEAEs occurred in 14 of 16 participants, and 87% were mild; somnolence (44%), oral hypoesthesia (38%), nasopharyngitis (31%), abnormal product taste (31%), and headache (19%) were the most common TEAEs

Study 1 PK

- PK profiles of CBP SL 2.8 mg and oral IR CBP 5 mg were similar (**Figure 1**)
  - C_{max} and AUC_{0-48} were modestly lower with CBP SL 2.8 mg (20% and 17%, respectively) vs IR CBP 5 mg
  - Half-lives were similar between the two formulations

Figure 1: Single-Dose PK Profile of CBP SL 2.8 mg vs Oral IR CBP 5 mg in Healthy Adults

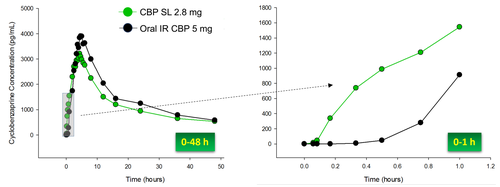


Parameter	CBP SL 2.8 mg mean (SD) (n=6)	Oral IR CBP 5 mg mean (SD) (n=6)
C_{max} (ng/mL)	3.4 (1.0)	4.3 (1.4)
AUC_{0-48} (ng•h/mL)	57.4 (10.7)	69.5 (18.8)
$T_{1/2}$ (h)	27.4 (3.3)	25.1 (9.2)
T_{max}[a] (h)	4.3 (2.0, 6.0)	4.0 (3.3, 6.0)

AUC_{0-48}, area under the plasma concentration–time curve from 0-48 h; CBP, cyclobenzaprine; C_{max}, maximum (peak) plasma concentration; IR, immediate-release; PK, pharmacokinetic; SD, standard deviation; SL, sublingual; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration. [a]median (minimum, maximum).

- CBP SL 2.8 mg administration resulted in rapid systemic CBP exposure (**Figure 2**)
  - In the first hour after CBP SL 2.8 mg administration, CBP AUC was 338% higher than that observed after oral IR CBP 5 mg (P<0.01)
  - CBP absorption was 12 times faster after CBP SL 2.8 mg administration

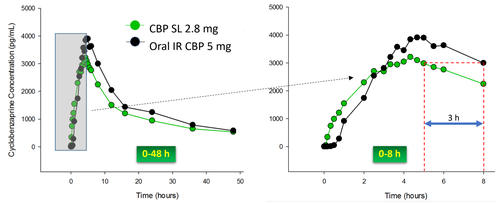
Figure 2: Absorption of CBP SL 2.8 mg vs Oral IR CBP 5 mg



CBP, cyclobenzaprine; IR, immediate-release; SL, sublingual.

- CBP SL is designed to align CBP exposure with the sleep period[6]
- In the 0-8 h after CBP SL 2.8 mg administration, CBP exposure increased and then declined (**Figure 3**)
  - Total CBP AUC was 10% lower with CBP SL 2.8 mg vs oral IR CBP 5 mg

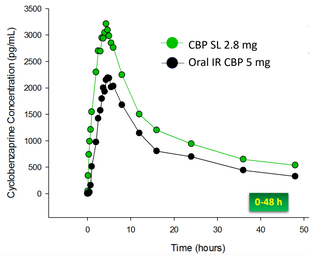
Figure 3: CBP SL Provides a Targeted Systemic Exposure Pattern of CBP During Sleep



CBP, cyclobenzaprine; IR, immediate-release; SL, sublingual.

- Upon dose normalization, the bioavailability of CBP SL 2.8 mg was 154% greater than that of oral IR CBP 5 mg (**Figure 4**)

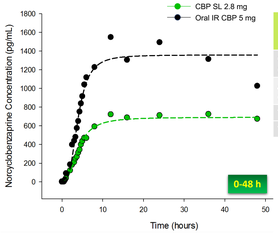
Figure 4: Dose-Normalized PK Comparison of CBP SL 2.8 mg vs Oral IR CBP 5 mg



CBP, cyclobenzaprine; IR, immediate-release; SL, sublingual.

- After single-dose administration, nCBP exposure was lower (C_{max} 53%; AUC 48%) with CBP SL 2.8 mg vs oral IR CBP 5 mg (**Figure 5**)
  - Compared with parent CBP, nCBP had a prolonged half-life (~70 h)
  - The CBP:nCBP ratio was 59% higher for CBP SL 2.8 mg vs oral IR CBP 5 mg (AUC ratio, 1.88 vs 1.18, respectively)

Figure 5: nCBP PK Profile After Single-Dose Administration of CBP SL 2.8 mg vs Oral IR CBP 5 mg



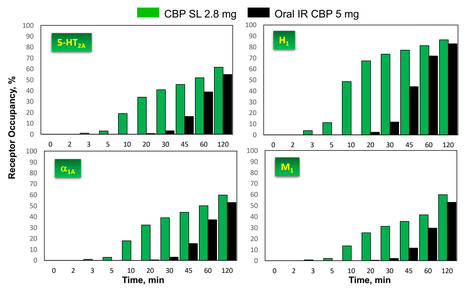
Parameter	CBP SL 2.8 mg, mean (SD) (n=6)	Oral IR CBP 5 mg, mean (SD) (n=6)
C_{max} (ng/mL)	0.81 (0.25)	1.71 (0.91)
AUC_{0-48} (ng•h/mL)	30.5 (10.7)	58.6 (25.7)
$T_{1/2}$ (h)	72.0 (31.0)	66.7 (35.1)
T_{max}[a] (h)	24 (8, 48)	18 (8, 36)

AUC_{0-48}, area under the plasma concentration–time curve from 0-48 h; CBP, cyclobenzaprine; C_{max}, maximum (peak) plasma concentration; IR, immediate-release; nCBP, norcyclobenzaprine; PK, pharmacokinetic; SD, standard deviation; SL, sublingual; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration. [a]median (minimum, maximum).

Figure 6: Receptor Occupancy and Binding Affinities of CBP SL 2.8 mg vs Oral IR CBP 5 mg

	Receptors believed to have a role in sleep quality							
	H_1	5-HT_{2A}	α_{1A}	M_1	α_{1B}	D_1	SERT	NET
Cyclobenzaprine	1.3	5.2	5.6	7.9	9.1	12	29	35
Norcyclobenzaprine	5.6	13	34	30	11	57	91	2.6
CBP/nCBP Activity	Antagonist						Inhibitor	

- Rapid engagement of sleep modulation receptors with CBP SL 2.8 mg aligns with the sleep initiation window and facilitates restorative sleep



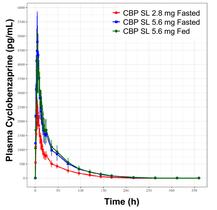
5-HT_{2A}, 5-hydroxytryptamine-2A; $_{\alpha1}$A, alpha$_{1A}$ adrenergic; CBP, cyclobenzaprine; D_1, dopamine-1; H_1, histamine-1; IR, immediate-release; M_1, muscarinic acetylcholine-1; nCBP, norcyclobenzaprine; NET, norepinephrine transporter; SERT, serotonin transporter; SL, sublingual.

- CBP SL 2.8 mg achieved more rapid and higher receptor occupancy across key receptors implicated in sleep modulation and arousal (5-HT_{2A}, H_1, $_{\alpha1}$A, and M_1) vs oral IR CBP 5 mg (**Figure 6**)
- Differences were greatest in the 0–60 min post-administration window
- While H_1 and 5-HT_{2A} antagonism from the metabolic conversion of CBP to nCBP after oral IR CBP administration supports sleep, the long half-life and flat circadian profile of nCBP increase the likelihood of sedative and psychomotor effects persisting into daytime, increasing the risk of residual drowsiness, fatigue, and impaired alertness
  - As nCBP has a high affinity for the NE transporter, the resulting increase in synaptic NE, which is activating, may impair sleep quality when nCBP predominates

Study 2 PK

- CBP SL demonstrated dose-proportional increases in exposure when administered at 2.8 mg and 5.6 mg doses under fasting conditions (AUC and C_{max} almost doubled)
  - Food had no clinically meaningful effect on CBP exposure when administered as CBP SL 5.6 mg, with an $AUC_{0-\infty}$: 128.1 (fasting) vs 133.1 ng*h/mL (fed); C_{max}: 5.1 (fasting) vs 4.5 ng/mL (fed)
  - T_{max} and $t_{½}$ were comparable between conditions
- Plasma concentration-time profiles were similar under fed and fasting conditions (**Figure 7**)

Figure 7. Dose Proportionality and Food Effect on CBP SL PK Profile (2.8 mg and 5.6 mg)



Parameter	CBP SL, mean (SD) 2.8 mg Fasted (n=15)	5.6 mg Fasted (n=16)	5.6 mg Fed (n=16)
AUC_{0-t} (ng•h/mL)	64.4 (14.1)	128.1 (27.6)	133.1 (27.6)
C_{max} (ng/mL)	2.5 (0.4)	5.1 (1.0)	4.5 (1.0)
$T_{1/2}$ (h)	35.4 (7.2)	36.4 (7.6)	37.9 (7.1)
T_{max} (h)	4.3 (1.0, 5.7)	4.3 (1.0, 5.7)	4.7 (4.0, 10.0)

AUC_{0-t}, area under the plasma concentration–time curve; CBP, cyclobenzaprine; C_{max}, maximum (peak) plasma concentration; PK, pharmacokinetic; SD, standard deviation; SL, sublingual; $T_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration.

CONCLUSIONS

- Following CBP SL 5.6 mg administration at steady state, nCBP concentration stayed near peak for 8 hours, decreasing little over hours 8-24; CBP concentration declined to about half its peak at 24 hours
- After administration of oral IR 5 mg CBP at steady state, nCBP peak concentration was ~75% higher than CBP and remained >2-fold higher at 24 hours
- CBP SL 5.6 mg once daily for 20 days was well tolerated in healthy participants
- Dynamic changes in CBP exposure over 24 hours may optimize restorative sleep, since CBP has higher 5-HT_{2A}, α_1, H_1 and M_1 receptor affinity than nCBP
- In contrast, nCBP's higher norepinephrine transporter affinity is expected to impair sleep by increasing synaptic norepinephrine when optimal sleep depends on lower noradrenergic sympathetic activity
- Together, these data support CBP SL as a chronic bedtime treatment for FM

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DISCLOSURES

BD, GMS: Employee of Tonix Pharmaceuticals, Inc. and owns stock and/or stock options in Tonix Pharmaceuticals Holding Corp. **SF:** Employee of Tonix Pharma Limited and owns stock and/or stock options in Tonix Pharmaceuticals Holding Corp.