Rapid Sublingual Absorption of Cyclobenzaprine (CBP) with Basifying Agents: Prospect for Bedtime Treatment of Fibromyalgia Syndrome (FM)

Bruce Daugherty, Nunzia Ceppi Monti, Valentina Panzeri, Roberto Marelli, Enrico Magnocavallo, Giorgio Reiner and Seth Lederman
Tonix Pharmaceuticals, Inc., New York, NY and APR Applied Pharma Research s.a., Balerna, Switzerland

Funded by Tonix Pharmaceuticals, Inc.

Presentation Number LB-026

Background

Cyclobenzaprine (CBP) exposure during sleep improves daytime fibromyalgia (FM) symptoms and sleep quality[1]. CBP absorption into plasma is delayed after ingesting immediate release (IR) tablets. To speed absorption, TNX-102 SL*, a sublingual (SL) formulation of 2.8 mg CBP was developed for transmucosal absorption.

Methods

Plasma CBP was measured in healthy subjects (N=6/group) after a single tablet of TNX-102 SL 2.8 mg or CBP IR 5 mg, and PK parameters were calculated.

Results

TNX-102 SL is a eutectic CBP formulation which contains potassium phosphate dibasic as a basifying agent that disintegrates in saliva and rapidly dissolves. The addition of a basifying agent results in a higher pH, thereby rendering CBP in an un-ionized state at the mucosal membrane, thus rapidly driving CBP across the mucosa into the bloodstream. For TNX-102 SL 2.8 mg v. ingested CBP IR 5 mg, plasma CBP levels were: at 10 min 338 pg/ml v. below limit of detection (BLD); at 20 min 739 pg/mL v. BLD; at 30 min 988 pg/mL v. BLD; at 45 min 1209 v. 280 pg/mL (p=0.001); at 60 min 1545 v. 913 pg/mL (p=0.062); and at 120 min 2296 v. 1737 pg/mL (p=0.043). For TNX-102 SL 2.8 mg v. CBP IR 5 mg tablets, the mean exposure was 338% (p=0.009) higher at 1h, and 83% (p=0.034) higher at 2h. TNX-102 SL 2.8 mg had C_{max} = 3.4 ng/mL and $AUC_{0\text{-}8}$ = 79 ng hr/mL while CBP IR 5 mg had C_{max} = 4.3 ng/mL and $AUC_{0\text{-}8}$= 92 ng hr/mL showing more efficient dose-adjusted absorption for TNX-102 SL. The plasma levels of norcyclobenzaprine (nCBP), the major metabolite of CBP, were lower with TNX-102 SL consistent with bypassing first pass hepatic metabolism. TNX-102 SL was well tolerated and side effects were similar to those of oral CBP although some subjects experienced numbness in the mouth that was transient and self-limited.

Conclusions

TNX-102 SL delivers CBP rapidly across the sublingual mucosal membrane into plasma resulting in 12 times faster onset of absorption relative to oral CBP IR, and provides significantly increased plasma CBP levels during the first 2 hours. The relative bioavailability was 154% when compared to the CBP IR tablet. The SL formulation had no effect on T_{max}. Sublingual administration of CBP via TNX-102 SL bypasses "first-pass" metabolism reducing C_{max} and AUC to nCBP, the active metabolite. The pharmacokinetic properties of TNX-102 SL appear to be well suited for its development as a potential bedtime medication for FM in a long-term treatment regimen.

[1] Moldofsky H et al, (2011) J Rheum 38: 2653-2663

* TNX-102 SL is being investigated in the US for FM under a US IND and is not approved for any indication

Table 1. Demographic Data

Category	TNX-102 SL 2.8 mg N=6	CBP IR 5 mg N=6
Age (years)		
Mean (SD)	36.7 (15.0)	37.3 (15.4)
Gender, N (%)		
Female	4 (66.7%)	3 (50.0%)
Male	2 (33.3%)	3 (50.0%)
Ethnicity, N (%)		
Not Hispanic	5 (83.3%)	5 (83.3%)
Hispanic	1 (16.7%)	1 (16.7%)
BMI (kg/m^2)		
Mean (SD)	26.160 (2.821)	25.873 (2.456)

Abbreviations: SL: sublingual; IR: immediate release; CBP: cyclobenzaprine; SD: standard deviation; BMI: body-mass index

Table 2. Treatment-Emergent Adverse Events

System Organ Class/ Preferred Term	TNX-102 SL 2.8 mg N (%)	CBP IR 5 mg N (%)
Gastrointestinal disorders	3 (50.0)	0
Hypoaesthesia oral	2 (33.3)	0
Oral mucosal erythema	1 (16.7)	0

Abbreviations: SL: sublingual; IR: immediate-release; CBP: cyclobenzaprine

Figure 1. TNX-102 SL 2.8 mg: Sublingual CBP Tablet

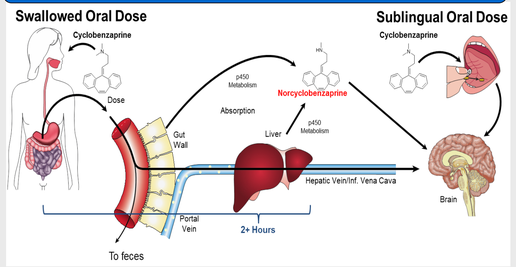

Figure 2. Proprietary CBP-HCl Eutectic Mixture Stabilizes Tablet Formulation

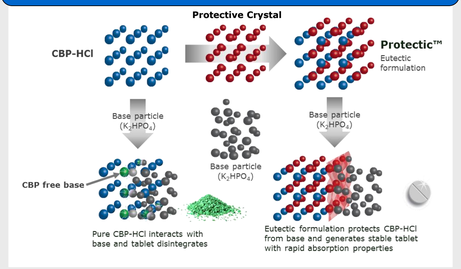

Figure 3. Formulation with Base Increases Systemic Absorption of Sublingual CBP

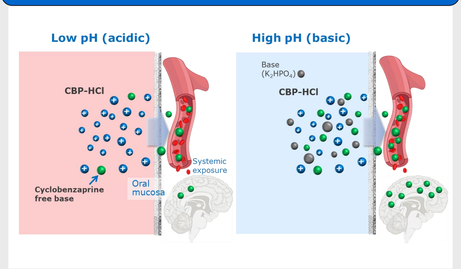

Figure 4. Pharmacokinetic Profile of TNX-102 SL 2.8 mg Tablet vs CBP IR 5 mg Tablet Plasma Levels of CBP

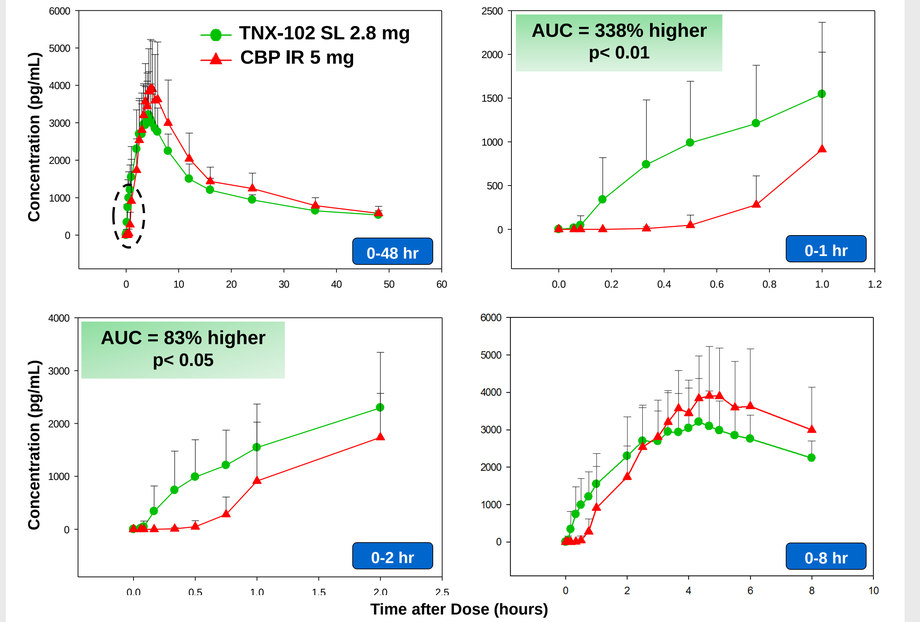

Figure 5. Pharmacokinetic Profile of TNX-102 SL 2.8 mg vs CBP IR 5 mg Plasma Levels of CBP and its Metabolite, nCBP

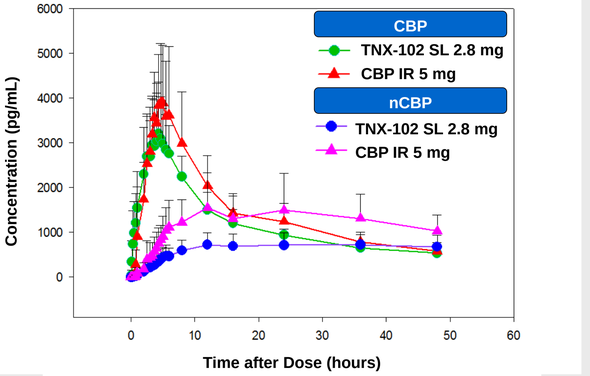

Table 3. Pharmacokinetic Parameters

	TNX-102 SL 2.8 mg N=6	CBP IR 5 mg N=6
Parameter	**Cyclobenzaprine**	
Absorption Lag Time (T_{lag})	0.050 hr (3 min)	0.622 hr (37 min)
Relative Bioavailability (F_{rel}), %	154	-
T_{max}*, hours	4.33 (1.99-6.00)	4.00 (3.33-5.99)
C_{max}, ng/mL	3.41 ± 0.99	4.26 ± 1.40
$AUC_{0\text{-}48}$, ng•hr/mL	57.4 ± 10.7	69.5 ± 18.8
$t_{1/2}$, hours	27.44 ± 3.32	25.06 ± 9.17
Parameter	**Norcyclobenzaprine**	
T_{max}*, hours	24.0 (8.00-48.00)	18.0 (8.01-36.00)
C_{max}, ng/mL	0.81 ± 0.25	1.71 ± 0.91
$AUC_{0\text{-}48}$, ng•hr/mL	30.5 ± 10.7	58.6 ± 25.7
$t_{1/2}$, hours	71.95 ± 30.97	66.70 ± 35.11

T_{lag} is defined at the first nominal sampling time after administration from which onward the CBP concentrations consistently exceed the limit of quantitation; Relative Bioavailability (F_{rel}) was calculated using the formula, F_{rel}= 100 x [Dose (IR) x AUC (SL)/Dose (SL) x AUC (IR)]; Mean ± SD; *Median (Min-Max)