Cyclobenzaprine HCl Sublingual Reduces Fibromyalgia Impact on Physical Symptoms & Functional Ability

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INTRODUCTION

- Fibromyalgia is a chronic nociplastic pain disorder that affects approximately 2% to 3% of US adults, occurs predominantly in women, and is characterized by widespread pain, nonrestorative sleep, fatigue, cognitive dysfunction, and functional impairment[1-3]
- Tonmya® (TNX-102 SL; cyclobenzaprine HCl sublingual tablets [CBP SL]) is US FDA-approved for the treatment of fibromyalgia in adults based on the results of two Phase 3 trials (RELIEF, NCT04172831; RESILIENT, NCT05273749)[4-6]
- CBP SL is the first FDA-approved treatment for adults with fibromyalgia in over 15 years
- Cyclobenzaprine antagonizes the 5-HT_{2A}-serotonergic, α_1-adrenergic, M_1-muscarinic, and H_1-histaminergic receptors, potentially influencing sleep architecture and alleviating core fibromyalgia symptoms[5]
- CBP SL is a rapidly disintegrating eutectic sublingual tablet designed for long-term daily bedtime use that enables rapid transmucosal absorption into the systemic circulation[7]
  - By largely bypassing first-pass hepatic metabolism, CBP SL administration results in reduced formation of the long half-life active metabolite norcyclobenzaprine (nCBP) relative to that formed after administration of oral immediate-release (IR) cyclobenzaprine, which may improve nonrestorative sleep, minimize next-day sedation, and enhance the durability of CBP SL's effects on pain[7]

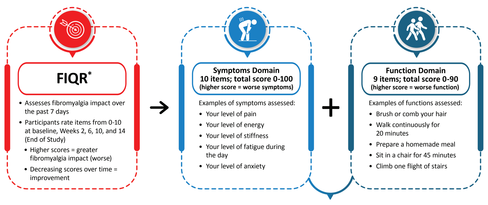
OBJECTIVE

- To evaluate the effect of CBP SL vs placebo on key fibromyalgia symptoms and function, as measured by the Fibromyalgia Impact Questionnaire – Revised (FIQR), using respective datasets from the RELIEF and RESILIENT trials

METHODS

- RELIEF and RESILIENT were randomized, placebo-controlled Phase 3 trials that assessed the efficacy and safety of CBP SL vs placebo in adults with fibromyalgia (2016 American College of Rheumatology [ACR] diagnostic criteria) over 14 weeks[4,5,8]
  - In both trials, participants were randomized 1:1 to receive either CBP SL (2.8 mg tablets at bedtime for 2 weeks, followed by 5.6 mg at bedtime through Week 14) or placebo for 14 weeks
- The two trials evaluated the same primary efficacy and key secondary endpoints
  - Primary efficacy endpoint: change from baseline in the weekly average of daily self-reported numeric rating scale (NRS) pain scores (0-10) at Week 14 for CBP SL vs placebo
  - Key secondary endpoints, all assessed at Week 14, included:
    - Proportion of subjects with a Patient Global Impression of Change (PGIC) rating of "very much improved" or "much improved"
    - **Change from baseline in the FIQR Symptoms domain score (Figure 1)**
    - **Change from baseline in the FIQR Function domain score (Figure 1)**
    - Change from baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance 8a score
    - Change from baseline in the PROMIS Fatigue 8a score
    - Change from baseline in the weekly average of the daily diary assessment of sleep quality

Figure 1. Fibromyalgia Impact Questionnaire – Revised Function and Symptoms Domains



*The FIQR also contains a 2-item Impact domain.
Figure contains examples of some of the items from the full measure.
FIQR, Fibromyalgia Impact Questionnaire – Revised.

- The RELIEF and RESILIENT trials used the same pre-specified statistical hierarchy for controlling for type 1 error and adjusting for multiplicity
  - Primary and continuous key secondary endpoints over multiple time points were analyzed using mixed model for repeated measures with multiple imputation for missing data
- Safety assessments included reporting of adverse events (AEs)

RESULTS

- A total of 959 adults with fibromyalgia from RELIEF (CBP SL, n=248; placebo, n=255) and RESILIENT (CBP SL, n=231; placebo, n=225) were included in this analysis; 417 (82.9%) completed the RELIEF study, and 366 (80.1%) completed the RESILIENT study (**Table 1**)

Table 1. Baseline Patient Demographics and Characteristics from RELIEF and RESILIENT Trials

	RELIEF		RESILIENT	
	CBP SL 5.6 mg (n=248)	Placebo (n=255)	CBP SL 5.6 mg (n=231)	Placebo (n=226)
Age, years, mean (SD)	50.0 (9.4)	49.3 (10.2)	49.3 (10.5)	49.5 (11.3)
Female, n (%)	232 (93.5)	247 (96.9)	224 (97.0)	212 (93.8)
Race, n (%)				
White	222 (89.5)	216 (84.7)	194 (84.0)	192 (85.0)
Black/African American	19 (7.7)	20 (7.8)	32 (13.9)	27 (11.9)
Asian	2 (0.8)	5 (2.0)	1 (0.4)	5 (2.2)
Multiple	3 (1.2)	9 (3.5)	2 (0.9)	1 (0.4)
Other	1 (0.4)	3 (1.2)	2 (0.9)	1 (0.4)
Ethnicity, n (%)				
Not Hispanic or Latino	205 (82.7)	213 (83.5)	195 (84.4)	190 (84.1)
BMI, kg/m², mean (SD)	32.43 (6.58)	31.63 (6.29)	31.14 (6.34)	31.14 (6.32)
Duration of FM, years, mean (SD)	9.2 (8.4)	9.0 (8.1)	8.6 (8.4)	9.9 (9.5)
NRS pain score, mean (SD)	6.1 (1.1)	6.0 (1.1)	5.9 (1.1)	5.9 (1.1)
FIQR Symptoms domain score, mean (SD)	52.3 (14.2)	54.2 (14.5)	53.1 (14.9)	54.1 (14.6)
FIQR Function domain score, mean (SD)	35.6 (20.5)	37.1 (20.0)	38.5 (19.9)	37.9 (19.1)

Data shown for the Safety population in each study.
BMI, body mass index; CBP SL, cyclobenzaprine HCl sublingual tablets; FIQR, Fibromyalgia Impact Questionnaire – Revised; FM, fibromyalgia; ITT, intention-to-treat; NRS, numeric rating scale; SD, standard deviation.

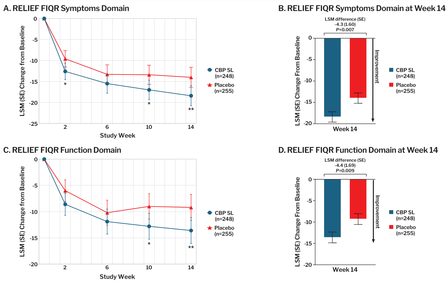
Primary Endpoint

- CBP SL treatment provided statistically significant improvements over placebo in the change from baseline in the weekly average of daily self-reported NRS pain scores at Week 14 in both the RELIEF (P=0.010) and RESILIENT (P<0.001) trials

FIQR Symptoms and Function Domains

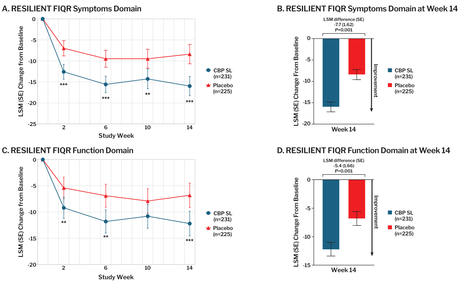
- In RELIEF, CBP SL treatment provided significant improvements vs placebo in the FIQR Symptoms domain at Weeks 2, 10, and 14 and in the FIQR Function domain at Weeks 10 and 14 (**Figure 2**)
- In RESILIENT, CBP SL treatment provided significant improvements vs placebo in the FIQR Symptoms domain at each assessment point and in the FIQR Function domain at Weeks 2, 6, and 14 (**Figure 3**)

Figure 2. RELIEF FIQR Symptoms and Function Scores: Mean Change From Baseline by Study Week (A and C)[a] and Mean Change from Baseline at Week 14 (B and D)[a]



[a]Due to hierarchical testing to adjust for multiplicity and control for type I error, all P values were considered nominal for FIQR outcomes.
*P<0.0452; **P<0.01.
CBP SL, cyclobenzaprine HCl sublingual tablets; FIQR, Fibromyalgia Impact Questionnaire – Revised; LSM, least-squares mean; SE, standard error.

Figure 3. RESILIENT FIQR Symptoms and Function Scores: Mean Change From Baseline by Study Week (A and C)[a] and Mean Change From Baseline at Week 14 (B and D)



[a]P-values at Weeks 2, 6, and 10 are unadjusted for multiplicity.
**P<0.01, ***P<0.001.
CBP SL, cyclobenzaprine HCl sublingual tablets; FIQR, Fibromyalgia Impact Questionnaire – Revised; LSM, least-squares mean; SE, standard error.

- Nearly all other key secondary endpoints showed statistically significant improvement with CBP SL vs placebo, favoring CBP SL at Week 14 (**Table 2**)

Table 2. Other Key Secondary Endpoint Results in RELIEF and RESILIENT at Week 14

	RELIEF			RESILIENT		
	CBP SL 5.6 mg (n=248)	Placebo (n=255)	Treatment Difference vs Placebo (*P* value)	CBP SL 5.6 mg (n=231)	Placebo (n=225)	Treatment Difference vs Placebo (*P* value)
PGIC responders[a], n (%)	93 (37.5)	75 (29.4)	1.44 (0.99, 2.10) (P=0.058)[b]	81 (35.1)	43 (19.1)	16.0 (7.9, 24.0) (P<0.001)[c]
PROMIS Sleep Disturbance, LSM (SE)[d]	-9.5 (0.64)	-6.5 (0.61)	-2.9 (0.82) (P<0.001)	-8.4 (0.57)	-4.2 (0.56)	-4.2 (0.79) (P<0.001)
PROMIS Fatigue, LSM (SE)[d]	-8.0 (0.58)	-6.2 (0.59)	-1.8 (0.76) (P=0.018)	-7.2 (0.55)	-4.2 (0.56)	-3.0 (0.77) (P<0.001)
Diary sleep quality ratings, LSM (SE)[d]	-2.0 (0.12)	-1.5 (0.12)	-0.6 (0.17) (P<0.001)	-1.8 (0.12)	-1.2 (0.12)	-0.6 (0.17) (P<0.001)

[a]PGIC response defined as "much" or "very much" improved.
[b]P-value and odds ratio obtained from a logistic regression run on each visit individually with a main effect for treatment.
[c]P-values were obtained from a Pearson chi-squared test, with the difference in proportions 95% confidence intervals obtained from the difference in proportions Z-test.
[d]Least-squares means, differences, and CIs were based on an MMRM with fixed, categorical effects of treatment, center, study week, and treatment-by-study week interaction, as well as the fixed covariates of baseline value and baseline value-by-study week interaction. An unstructured covariance matrix was used.
CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; LSM, least-squares mean; MMRM, mixed model for repeated measures; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

- CBP SL was generally well tolerated, with an AE profile consistent with previous studies; no new safety signals were observed (**Table 3**)
- The most common treatment-emergent adverse events (TEAEs) were local oral administration site reactions, including numbness, tingling, and negative or bitter aftertaste, consistent with the known profile of sublingual treatments
  - These local events were typically mild, transient, and self-limited and uncommonly led to treatment discontinuation

Table 3. TEAEs Reported by ≥3% of Patients

	RELIEF		RESILIENT	
	CBP SL (n=248)	Placebo (n=255)	CBP SL (n=231)	Placebo (n=226)
All TEAEs	148 (59.7)	118 (46.3)	136 (58.9)	83 (36.7)
Oral hypoesthesia	43 (17.3)	1 (0.4)	55 (23.8)	1 (0.4)
Product taste abnormal	11 (4.4)	1 (0.4)	27 (11.7)	2 (0.9)
Tongue discomfort	7 (2.8)	1 (0.4)	16 (6.9)	0
Paresthesia oral	14 (5.6)	1 (0.4)	16 (6.9)	2 (0.9)
COVID-19	5 (2.0)	1 (0.4)	10 (4.3)	7 (3.1)
Glossodynia	9 (3.6)	2 (0.8)	1 (0.4)	5 (2.2)
Sedation	9 (3.6)	1 (0.4)	0	3 (1.3)
Fatigue	9 (3.6)	4 (1.6)	6 (2.6)	5 (2.2)
Dry mouth	8 (3.2)	7 (2.7)	4 (1.7)	3 (1.3)
Headache	3 (1.2)	6 (2.4)	7 (3.0)	4 (1.8)
Somnolence	5 (2.0)	2 (0.8)	7 (3.0)	3 (1.3)

CBP SL, cyclobenzaprine HCl sublingual tablets; TEAEs, treatment-emergent adverse events.

CONCLUSION

- The RELIEF and RESILIENT trials demonstrated that CBP SL treatment significantly improves a broad spectrum of core fibromyalgia symptoms, including widespread pain and nonrestorative sleep
- Importantly, CBP SL significantly improved patient-reported fibromyalgia symptoms and physical functioning vs placebo, as measured by the FIQR Symptoms and Function domains at Week 14
- CBP SL treatment was associated with a low systemic AE burden
  - While prominent, local oral AEs were generally transient, resolved without treatment, and uncommonly led to treatment discontinuation
- These results provide a better understanding of the multifaceted symptoms of fibromyalgia—including pain, sleep disturbance, and fatigue—and their impact on function
- The findings also highlight CBP SL as a potential treatment option to help address patient needs

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Disclosures

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