Tonmya® (Cyclobenzaprine HCl Sublingual Tablets) Reduces Overall Impact of Fibromyalgia on Physical Symptoms and Functional Capacity

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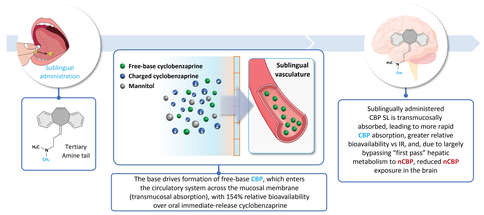
INTRODUCTION

- 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 U.S 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 tablet in a eutectic formulation that is administered sublingually for transmucosal absorption into the circulatory system[7] (**Figure 1**)
  - 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 minimize next-day sedation and support restorative sleep[7]

Figure 1. CBP SL Bypasses First-Pass Metabolism



CBP, cyclobenzaprine; CBP SL, cyclobenzaprine HCl sublingual tablets; IR, immediate-release; nCBP, norcyclobenzaprine.

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 a pooled dataset 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 for 12 weeks) or placebo
- 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 Fibromyalgia Impact Questionnaire – Revised (FIQR) Symptoms domain score (Figure 2)**
    - **Change from baseline in the FIQR Function domain score (Figure 2)**
    - Change from baseline in the 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 2. Fibromyalgia Impact Questionnaire – Revised Function and Symptom Domains

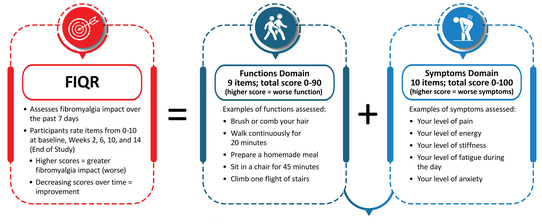


Figure contains examples of some of the items from the full measure.
FIQR, Fibromyalgia Impact Questionnaire – Revised.

- The two studies used the same pre-specified statistical hierarchy for controlling 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 and RESILIENT were pooled for this analysis; 81.6% (n=783) completed the two trials
- Baseline characteristics and demographics were well-balanced between CBP SL (n=479) and placebo (n=480) in the pooled study groups (**Table 1**)

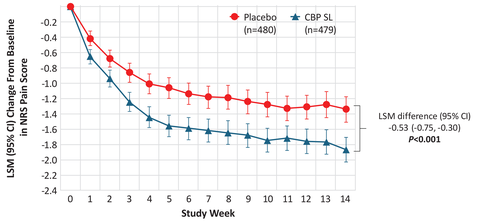
Table 1. Baseline Patient Demographics and Characteristics from RELIEF and RESILIENT Trials

	Placebo (n=480)	CBP SL (n=479)
Age, years, mean (SD)	49.4 (10.72)	49.7 (9.91)
Female, n (%)	458 (95.4)	456 (95.2)
Race, n (%)		
White	408 (85.0)	416 (86.8)
Black/African American	46 (9.6)	51 (10.6)
Asian	10 (2.1)	3 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	77 (16.0)	79 (16.5)
Weight, kg, mean (SD)	84.5 (18.07)	86.0 (18.54)
Duration of FM disease, years, mean (SD)	9.4 (8.78)	8.9 (8.43)
NRS pain rating at baseline, mean (SD)	5.97 (1.080)	5.99 (1.060)
FIQR Symptoms score, mean (SD)	54.16 (14.492)	52.71 (14.496)
FIQR Function score, mean (SD)	37.49 (19.551)	37.01 (20.244)

Data shown for the pooled intent-to-treat (ITT) population.
CBP SL, cyclobenzaprine HCl sublingual tablets; FIQR, Fibromyalgia Impact Questionnaire – Revised; FM, fibromyalgia; ITT, intention-to-treat; NRS, numeric rating scale; SD, standard deviation.

- CBP SL treatment provided statistically significant improvements ($P<0.001$) over placebo on the primary endpoint, change from baseline in the weekly average of daily self-reported NRS pain scores at Week 14; results are displayed by study week in **Figure 3**
  - At Week 14, the least-squares mean difference (95% confidence interval [CI]) between CBP SL and placebo was -0.53 (-0.75, -0.30; $P<0.001$), favoring CBP SL

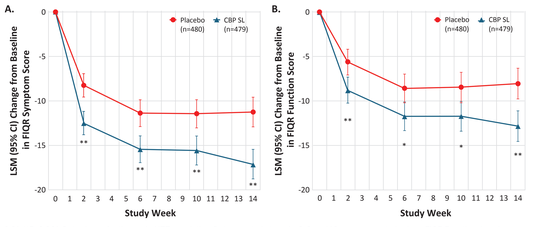
Figure 3: Mean Change from Baseline in Weekly Averages of Daily NRS Pain Scores



Data shown for the pooled ITT population. Pain rated on a 0-10 NRS.
CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; ITT, intention-to-treat; LSM, least-squares mean; NRS, numeric rating scale.

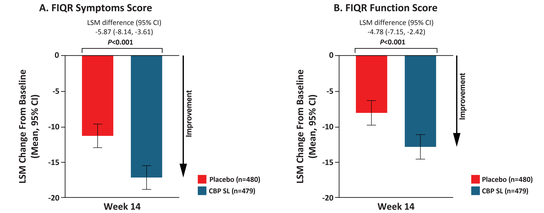
- CBP SL treatment yielded significant improvements vs placebo in both FIQR Symptoms and Function domains at each assessment point (**Figures 4A** and **4B**) and from baseline to Week 14 (**Figures 5A** and **5B**)

Figure 4: Mean Change from Baseline in Weekly Average FIQR Domain Scores: (A) Symptoms and (B) Function



*P≤0.01; **P≤0.001. Data shown for the pooled ITT population. Data reported at weeks 2, 6, and 10 are uncorrected values. FIQR Function domain score, FIQR Function subscale (9 items assessing difficulty with daily physical activities; higher scores indicate worse function); FIQR Symptoms domain score, FIQR Symptoms subscale (10 items assessing pain, fatigue, sleep, mood, and other fibromyalgia symptoms; higher scores indicate worse symptoms). CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; FIQR, Fibromyalgia Impact Questionnaire – Revised; ITT, intention-to-treat; LSM, least-squares mean.

Figure 5. Mean Change from Baseline to Week 14 in Pooled FIQR (A) Symptoms and (B) Function Scores



Data shown for the pooled ITT population. FIQR Function domain score, FIQR Function subscale (9 items assessing difficulty with daily physical activities; FIQR Symptoms domain score, FIQR Symptoms subscale (10 items assessing pain, fatigue, sleep, mood, and other fibromyalgia symptoms. CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; FIQR, Fibromyalgia Impact Questionnaire – Revised; ITT, intention-to-treat; LSM, least-squares mean.

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

Table 2. Pooled Efficacy Outcomes for CBP SL vs Placebo: Other Key Secondary Endpoints at Week 14

	Placebo (n=480)	CBP SL (n=479)	Treatment Difference vs Placebo[a]	*P* value
PGIC responders[b], n (%)	118 (24.6)	174 (36.3)	11.8 (6.1, 17.6)	<0.001
PROMIS Sleep Disturbance, LSM (95% CI)	-5.37 (-6.18, -4.56)	-8.92 (-9.75, -8.08)	-3.55 (-4.66, -2.44)	<0.001
PROMIS Fatigue, LSM (95% CI)	-5.16 (-5.93, -4.39)	-7.53 (-8.31, -6.75)	-2.37 (-3.41, -1.33)	<0.001
Diary sleep quality ratings, LSM (95% CI)	-1.33 (-1.50, -1.16)	-1.90 (-2.07, -1.73)	-0.57 (-0.80, -0.33)	<0.001

Data shown for the pooled ITT population. Negative LSM changes indicate improvement; larger negative values reflect greater improvement.
[a]Treatment Difference vs Placebo column shows LSM differences from baseline to Week 14 (CBP SL minus placebo) for continuous outcomes and absolute % difference for categorical endpoints (i.e., PGIC response).
[b]Responders reported a rating of "very much improved" or "much improved" on the PGIC. Participants with missing data were classified as non-responders.
CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; LSM, least-squares mean; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System.

- 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
- In this pooled analysis, fatigue was the only systemic adverse event with an incidence of ≥3%

Table 3. TEAEs Reported by ≥3% of Patients in Either Pooled Treatment Group

	Placebo n=481	CBP SL n=479
Oral cavity adverse events		
Hypoaesthesia oral	2 (0.4%)	98 (20.5%)
Product taste abnormal	3 (0.6%)	38 (7.9%)
Paresthesia oral	3 (0.6%)	30 (6.3%)
Tongue discomfort	1 (0.2%)	23 (4.8%)
Systemic adverse events		
Fatigue	9 (1.9%)	15 (3.1%)

Data shown for the pooled safety population.
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, with benefits emerging early that were maintained through 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 key insights to nurse practitioners, supporting a better understanding of the multi-faceted 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

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