Tonmya® (TNX-102 SL; Cyclobenzaprine HCl Sublingual Tablets [CBP SL]) Improves Sleep Disturbance and Reduces Fatigue in Adults with Fibromyalgia

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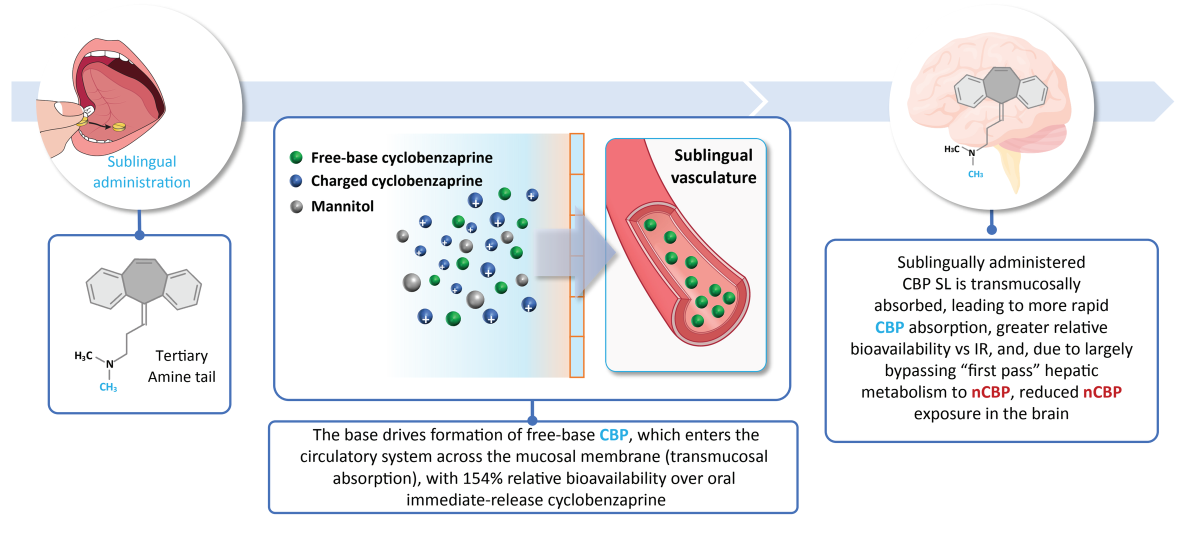
INTRODUCTION

- Fibromyalgia is a chronic 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 from 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) CBP, 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.

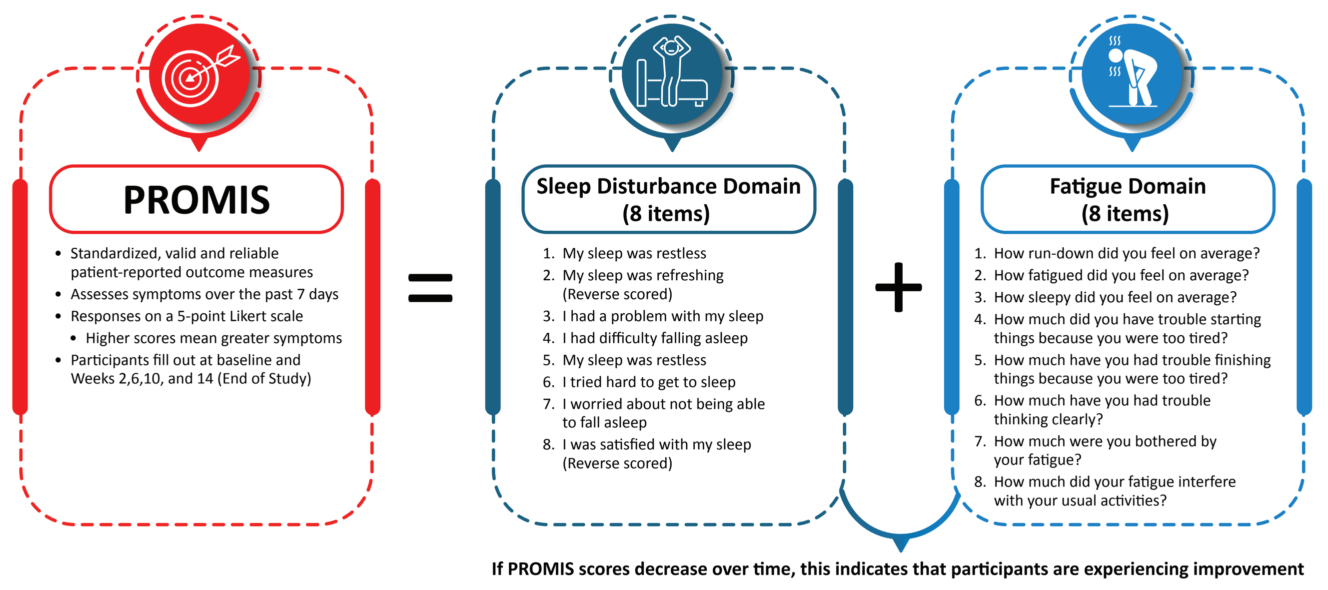
OBJECTIVE

- To evaluate the effect of CBP SL compared with placebo on core fibromyalgia symptoms of sleep disturbance and fatigue, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS), in 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[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
    - Change from baseline in the FIQR Function domain score
    - **Change from baseline in the PROMIS Sleep Disturbance 8a score (Figure 2)**
    - **Change from baseline in the PROMIS Fatigue 8a score (Figure 2)**
    - Change from baseline in the weekly average of the daily diary assessment of sleep quality

Figure 2. PROMIS Sleep Disturbance and Fatigue Domains



PROMIS, Patient-Reported Outcomes Measurement Information System.

- 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**)

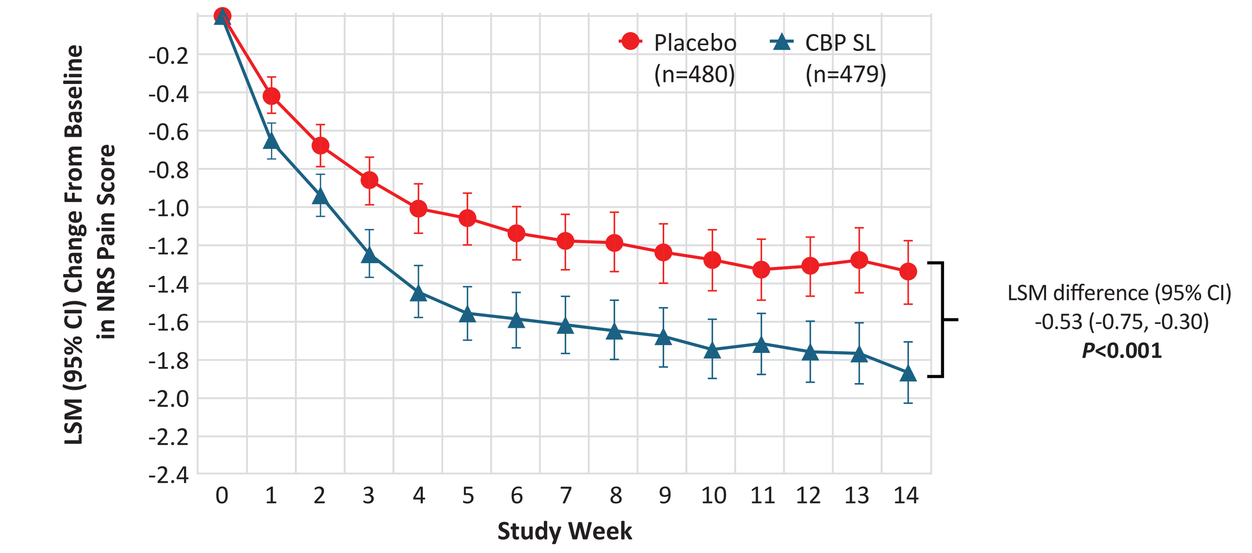
Table 1. Baseline Patient Demographics and Characteristics from RELIEF and RESILIENT Trials

	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)
PROMIS Sleep Disturbance score, mean (SD)	59.72 (6.835)	58.75 (6.216)
PROMIS Fatigue score, mean (SD)	63.68 (6.650)	63.05 (5.948)

Data shown for the pooled intent-to-treat (ITT) population.
CBP SL, cyclobenzaprine HCl sublingual tablets; FM, fibromyalgia; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System; 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

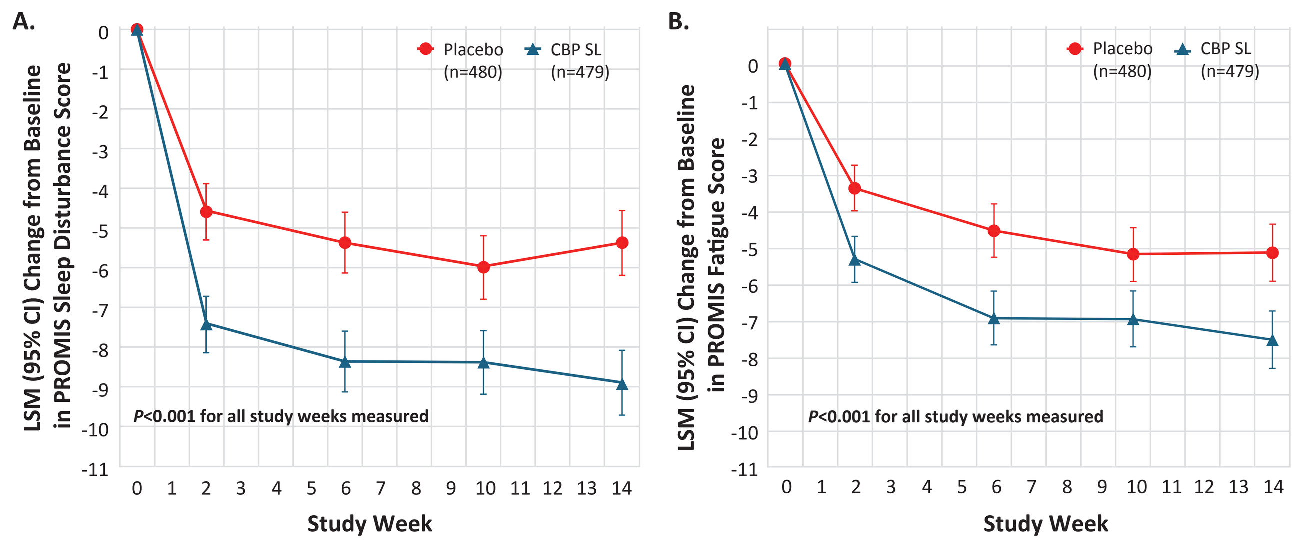
Figure 3: Mean Change from Baseline in Weekly Averages of Daily NRS Pain Scores



Data shown for the pooled RELIEF and RESILIENT 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

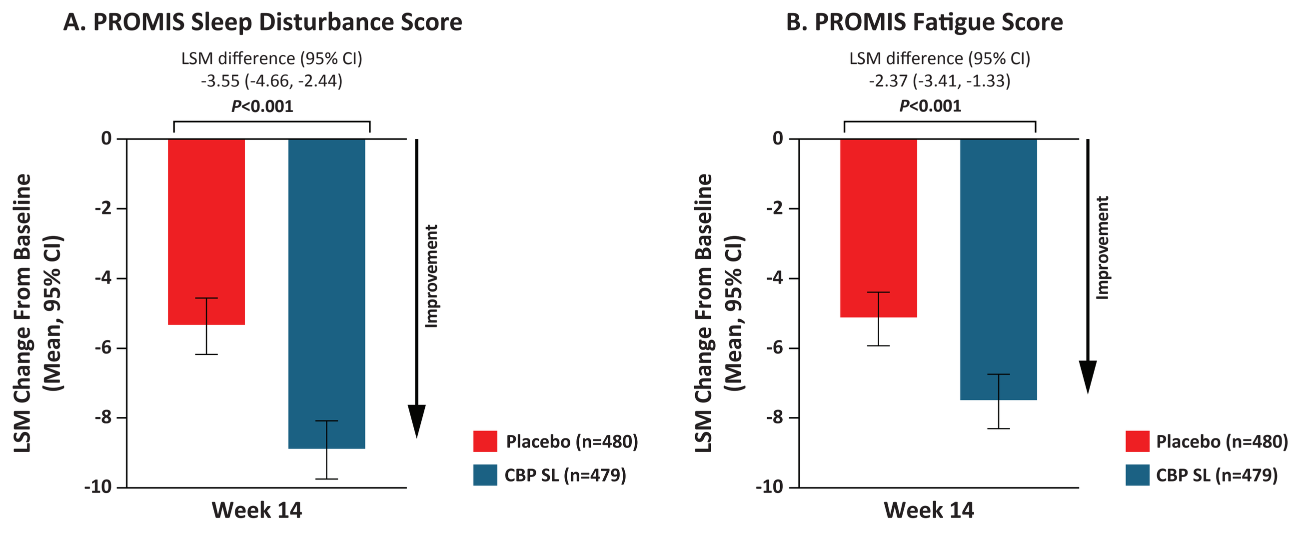
- CBP SL treatment provided significant improvements in PROMIS Sleep Disturbance and Fatigue scores compared to placebo at each assessment point (**Figure 4A** and **Figure 4B**) and from baseline to Week 14 (**Figure 5A** and **Figure 5B**)

Figure 4: Mean Change from Baseline in Weekly Averages of PROMIS Scores: (A) Sleep Disturbance and (B) Fatigue



Data shown for the pooled RELIEF and RESILIENT ITT population. Data reported at weeks 2, 6, and 10 are uncorrected values.
CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; ITT, intention-to-treat; LSM, least-squares mean; PROMIS, Patient-Reported Outcomes Measurement Information System.

Figure 5. Mean Change from Baseline to Week 14 in Pooled PROMIS (A) Sleep Disturbance and (B) Fatigue Scores



Data shown for the pooled RELIEF and RESILIENT ITT population.
CBP SL, cyclobenzaprine HCl sublingual tablets; CI, confidence interval; ITT, intention-to-treat; LSM, least-squares mean; PROMIS, Patient-Reported Outcomes Measurement Information System.

- **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
FIQR Symptoms domain, LSM (95% CI)	-11.25 (-12.91, -9.59)	-17.13 (-18.78, -15.47)	-5.87 (-8.14, -3.61)	<0.001
FIQR Function domain, LSM (95% CI)	-8.05 (-9.77, -6.33)	-12.83 (-14.55, -11.12)	-4.78 (-7.15, -2.42)	<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; FIQR, Fibromyalgia Impact Questionnaire – Revised; LSM, least-squares mean; PGIC, Patient Global Impression of Change.

- 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 provided statistically significant and clinically meaningful improvements vs placebo across primary and key secondary endpoints, positively impacting a broad spectrum of core fibromyalgia symptoms, including widespread pain, nonrestorative sleep, and global function
- Importantly, CBP SL also significantly reduced patient-reported sleep disturbance and fatigue, as measured by the PROMIS instrument, suggesting broad-spectrum symptom improvement
- CBP SL treatment was associated with a low systemic AE burden, with prominent but generally self-limited local oral AEs
- These results provide key insights to nurse practitioners, supporting a better understanding of the multifaceted symptoms of fibromyalgia, such as pain, sleep disturbance, and fatigue, and highlighting CBP SL as a potential treatment option to help address patient needs

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Disclosures

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