Tonmya® (Cyclobenzaprine HCl Sublingual Tablets; CBP SL): Efficacy and Safety Analyses of CBP SL 2.8 mg and 5.6 mg in Adults with Fibromyalgia

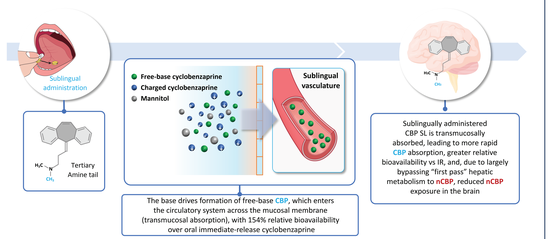
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BACKGROUND

- Fibromyalgia (FM) is a chronic nociplastic pain disorder that affects ~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]
- The role of nonrestorative sleep in the pathogenesis and persistence of FM has been recognized for over 50 years[4]
- Previously approved therapies for FM (duloxetine, pregabalin, and milnacipran) have been limited by unsatisfactory clinical efficacy and frequent side effects, which may lead to suboptimal adherence[5]
- Immediate-release (IR), orally administered cyclobenzaprine (CBP) 10-40 mg/d has been investigated in FM
  - Meta-analysis showed that effects of oral IR CBP on pain were short-lived and that side effects were prominent[6]
- Low-dose oral IR CBP has shown promise in the treatment of FM[7]
  - The slow absorption and poor bioavailability of oral IR CBP, however, suggest that new formulation technology mitigating these effects may increase its clinical utility
- Tonmya® (cyclobenzaprine hydrochloride sublingual tablets; CBP SL), a sublingual tablet formulation of low-dose CBP, is the first US FDA-approved treatment for FM in over 15 years[8]
  - CBP SL was designed for long-term daily bedtime use; with sublingual administration, CBP SL is rapidly absorbed and largely bypasses first-pass metabolism in the liver[9] (**Figure 1**)
  - CBP antagonizes 5-HT_{2A}-serotonergic, α_1-adrenergic, M_1-muscarinic, and H_1-histaminergic receptors,[9] potentially influencing sleep architecture and alleviating core fibromyalgia symptoms[10]
  - The clinical development of CBP SL in FM included clinical efficacy and safety studies conducted at doses of 2.8 mg/d and 5.6 mg/d

Figure 1. CBP SL Bypasses First-Pass Metabolism



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

- Here, the differential efficacy and safety of CBP SL 2.8 mg/d and 5.6 mg/d in FM are analyzed

METHODS

Study Design

- BESTFIT (NCT01903265) and AFFIRM (NCT02436096) were 12-week, randomized, multi-center, double-blind, placebo-controlled studies evaluating CBP SL 2.8 mg vs placebo in patients with FM
- RELIEF (NCT04172831) and RESILIENT (NCT05273749) were 14-week, randomized, multi-center, double-blind, placebo-controlled studies evaluating CBP SL 5.6 mg vs placebo in patients with FM (2.8 mg/d for 2 weeks, followed by 5.6 mg/d through Week 14 or placebo for 14 weeks)

Study Participants

- Each study enrolled adults ≥18 years with FM who met the 2010/2011 Fibromyalgia Diagnostic Criteria (American College of Rheumatology Preliminary Diagnostic Criteria) and/or the 2016 revisions thereof

Statistical Analyses

- To compare the effect of active treatment (CBP SL 2.8 mg/d or CBP SL 5.6 mg/d) to placebo in a real-world scenario, we analyzed the least-squares (LS) mean and standard error (SE) of the change from baseline to end of study in the weekly average of daily numeric rating scale (NRS) pain scores (11-point scale, scores 0-10) using a mixed-model repeated-measures analysis with multiple imputation for missing values. Each study was analyzed separately.
  - The LS means for the active treatment from each analysis are displayed graphically
  - To align with the CBP SL 5.6 mg pivotal trial analyses, the analytical methods for BESTFIT and AFFIRM were performed post hoc
- Standard safety assessments were conducted to identify any adverse events (AEs), laboratory abnormalities, abnormal physical examination findings, and abnormal vital sign findings in each study

RESULTS

Table 1. Baseline Patient Demographics and Characteristics of Active Treatment Groups in the BESTFIT, AFFIRM, RELIEF, and RESILENT Trials

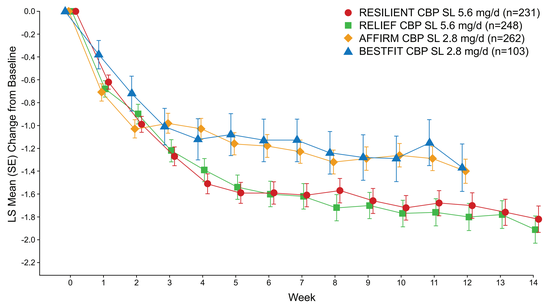
	BESTFIT	AFFIRM	RELIEF	RESILIENT
	CBP SL 2.8 mg/d (n=103)	CBP SL 2.8 mg/d (n=262)	CBP SL 5.6 mg/d (n=248)[a]	CBP SL 5.6 mg/d (n=231)
Age, years, mean (SD)	50.7 (9.9)	47.9 (11.1)	50.0 (9.4)	49.3 (10.5)
Female, n (%)	96 (93.2)	252 (96.2)	232 (93.5)	224 (97.0)
Race, n (%)				
White	91 (88.3)	242 (92.4)	222 (89.5)	194 (84.0)
Black/African American	11 (10.7)	11 (4.2)	19 (7.7)	32 (13.9)
Asian	0	1 (0.4)	2 (0.8)	1 (0.4)
American Indian/Alaska Native	0	2 (0.8)	1 (0.4)	2 (0.9)
Native Hawaiian/Pacific Islander	0	2 (0.8)	0	0
Multiple	1 (1.0)	1 (0.4)	3 (1.2)	2 (0.9)
Other	0	3 (1.1)	0	0
Ethnicity, n (%)				
Not Hispanic/Latino	95 (92.2)	231 (88.2)	205 (82.7)	195 (84.4)
BMI, kg/m², mean (SD)	30.05 (5.75)	30.91 (5.91)	32.43 (6.58)	31.14 (6.34)
Duration of FM, years, mean (SD)	--	9.5 (7.9)	9.2 (8.4)	8.6 (8.4)
NRS pain score, mean (SD)	6.5 (1.2)	6.3 (1.1)	6.1 (1.1)	5.9 (1.1)

[a]For RELIEF, race data was missing for 1 patient.
BMI, body mass index; CBP SL, cyclobenzaprine sublingual tablets; FM, fibromyalgia; n, number of patients; NRS, numeric rating scale; SD, standard deviation.

RESULTS

- The active treatment groups of the BESTFIT and AFFIRM studies included 103 and 262 patients, respectively, who were administered CBP SL 2.8 mg/d
  - In total, 89 (86.4%) and 203 (77.5%) patients in the active treatment groups completed BESTFIT and AFFIRM, respectively
  - Treatment with CBP SL 2.8 mg/d did not provide a statistically significant improvement vs placebo on the primary efficacy endpoint in either BESTFIT (mean change from baseline in the weekly average daily diary pain score) or AFFIRM (≥30% improvement in the weekly average of the daily self-reported average NRS pain severity score) at Week 12
- The active treatment groups of the RELIEF and RESILIENT studies included 248 and 231 patients, respectively, who were administered CBP SL 5.6 mg/d
  - In total, 204 (82.3%) and 187 (81.0%) patients in the active treatment groups completed RELIEF and RESILENT, respectively
  - Treatment with CBP SL 5.6 mg/d provided a significant reduction in the weekly average of daily diary pain scores vs placebo in both RELIEF (P=0.010) and RESILIENT (P<0.001) at Week 14
- During the first two weeks of treatment, when all 4 active treatment arms in these studies were administered CBP SL 2.8 mg/d, NRS pain score reduction was similar among all 4 groups (**Figure 2**)
  - Thereafter, when CBP SL was titrated up to 5.6 mg/d in the RELIEF and RESILIENT studies, NRS pain scores continued at the initial, steeper downward slope for an additional 1-2 weeks, whereas NRS pain scores leveled off in the CBP SL 2.8 mg/d arms
  - This divergence resulted in an ~0.5 NRS pain score difference between doses at endpoint, favoring CBP SL 5.6 mg/d
- TEAE frequencies for CBP SL 2.8 mg/d and 5.6 mg/d are detailed in **Table 2**

Figure 2. Least-Squares Change from Baseline in NRS Pain Scores with Active Treatment: CBP SL 5.6 mg/d vs CBP SL 2.8 mg/d



CBP SL, cyclobenzaprine sublingual tablets; LS, least-squares; NRS, numeric rating scale; SE, standard error.

RESULTS

Table 2. Treatment-Emergent Adverse Events Occurring in ≥3% of Patients Taking CBP SL 2.8 mg/d or 5.6 mg/d

	BESTFIT	AFFIRM	RELIEF	RESILIENT
	CBP SL 2.8 mg/d (n=103)	CBP SL 2.8 mg/d (n=262)	CBP SL 5.6 mg/d (n=248)	CBP SL 5.6 mg/d (n=231)
All TEAEs, n (%)	82 (79.6)	192 (73.3)	148 (59.7)	136 (58.9)
Oral hypoesthesia	45 (43.7)	105 (40.1)	43 (17.3)	55 (23.8)
Product taste abnormal	8 (7.8)	16 (6.1)	11 (4.4)	27 (11.7)
Tongue or oral discomfort	--	8 (3.1)	7 (2.8)	16 (6.9)
Paresthesia oral	3 (2.9)	20 (7.6)	14 (5.6)	16 (6.9)
COVID-19	--	--	5 (2.0)	10 (4.3)
Glossodynia	2 (1.9)	24 (9.2)	9 (3.6)	1 (0.4)
Sedation	2 (1.9)	2 (0.8)	9 (3.6)	0
Fatigue	2 (1.9)	15 (5.7)	9 (3.6)	6 (2.6)
Dry mouth	4 (3.9)	3 (1.1)	8 (3.2)	4 (1.7)
Headache	2 (1.9)	9 (3.4)	3 (1.2)	7 (3.0)
Somnolence	2 (1.9)	8 (3.1)	5 (2.0)	7 (3.0)
Nausea	5 (4.9)	5 (1.9)	1 (0.4)	3 (1.3)
Constipation	4 (3.9)	1 (0.4)	1 (0.4)	3 (1.3)
Vomiting	4 (3.9)	1 (0.4)	1 (0.4)	1 (0.4)
Sinusitis	4 (3.9)	7 (2.7)	2 (0.8)	1 (0.4)
Urinary tract infection	4 (3.9)	2 (0.8)	2 (0.8)	3 (1.3)
Back pain	5 (4.9)	1 (0.4)	1 (0.4)	0

CBP SL, cyclobenzaprine sublingual tablets; n, number of patients; TEAE, treatment-emergent adverse event.

CONCLUSION

- These results indicate that while pain improved with CBP SL at both 2.8 mg/d and 5.6 mg/d, titrating to the full 5.6 mg/d dose provided greater overall pain relief, emphasizing the importance of following the product label titration instructions[8]
  - A limitation of this analysis is that the doses were not directly compared across studies
- CBP SL 5.6 mg was generally well tolerated, with tolerability similar to that observed at the 2.8 mg/d dose
- CBP SL 5.6 mg/d represents the first new on-label non-opioid analgesic treatment option for adults with FM in over 15 years

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DISCLOSURES

YCL: Advisory Board for Tonix Pharmaceuticals, Inc., and owned stock in CVS Health (sold 8/2025).
SN: Consultant/Speaker for Tonix Pharmaceuticals, Inc., consultant for Semnur Pharma, principal investigator for EmVenio Research
EG: Employee of Tonix Medicines, Inc., and owns stock and/or stock options in Tonix Pharmaceuticals Holding Corp.
BV: Employee of Latigo Biotherapeutics and owns stock options in Latigo Biotherapeutics.
JH, GMS: Employees of Tonix Pharmaceuticals, Inc., and own stock and/or stock options in Tonix Pharmaceuticals Holding Corp.

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