Cyclobenzaprine HCl Sublingual Tablets for the Treatment of Fibromyalgia: Number Needed to Treat and Number Needed to Harm

P-02

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INTRODUCTION

- Fibromyalgia (FM) is a chronic nociplastic pain disorder affecting 2–4% of US adults and is characterized by widespread pain, poor sleep, fatigue, and functional impairment[1-5]
- Cyclobenzaprine HCl sublingual tablets (CBP SL) are the first FDA-approved treatment for adults with FM in over 15 years[6-8]
- Number needed to treat (NNT) and number needed to harm (NNH) estimate benefit and risk and allow cross-trial comparisons when head-to-head data are unavailable[9,10]

OBJECTIVE

- To assess the benefit–risk profile of CBP SL in adults with FM using NNT, NNH, and likelihood to be helped or harmed (LHH)

METHODS

Study design and population

- Pooled post hoc analysis of two 14-week, randomized, placebo-controlled phase 3 trials in adults with FM (RELIEF [NCT04172831][6]; RESILIENT [NCT05273749])[7]

Benefit-risk analyses

- NNT (rounded up) and NNH (rounded down) were calculated as the inverse of the absolute risk reduction (ARR)
- NNT was calculated based on ≥30% pain reduction at Week 14 (clinically meaningful threshold)
  - Similar to other studies[11-14], NNH was calculated for discontinuation due to adverse events (AEs); additional values are also presented for other AEs
- LHH (≥30% pain reduction/discontinuation due to AE) assessed the balance between clinical benefit and harm

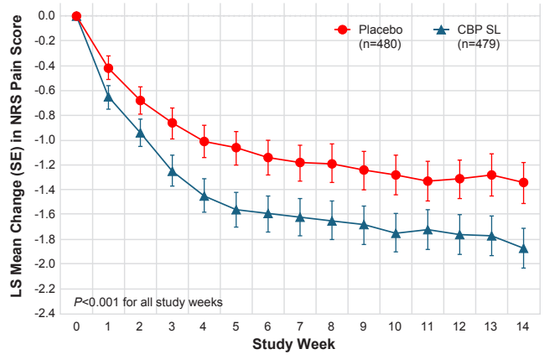
RESULTS

- A total of 959 participants were included in the pooled analysis; 783 (81.6%) completed the studies
- Baseline demographics were similar between groups (mean age, 49.4 years, 95.3% female)

Efficacy

- CBP SL treatment significantly improved the primary pain endpoint and all key secondary endpoints (**Figure 1** and **Table 1**) vs placebo

Figure 1. Mean Change from Baseline in Weekly Averages of Daily NRS Pain Scores[a]



[a]Based on post-hoc pooled analysis of 959 study participants using mixed model repeated measures with multiple imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction. P-values uncorrected for multiplicity.
ITT, intention-to-treat; LS, least-squares; NRS, numeric rating scale; SE, standard error.

Table 1. Primary and Key Secondary Endpoints at Week 14[a]

	Placebo (n=481)	CBP SL (n=479)	Treatment Difference vs Placebo	*P* value
Primary Endpoint				
Pain score (0-10), LSM (SE)	-1.34 (0.082)	-1.87 (0.083)	-0.53 (0.113)	<0.001
Secondary Endpoints				
PGIC responders[b], n (%)	118 (24.6)	174 (36.3)	+11.8 (6.1,17.6)[c]	<0.001
FIQR symptoms, LSM (SE)	-11.25 (0.847)	-17.13 (0.846)	-5.87 (1.154)	<0.001
FIQR function, LSM (SE)	-8.05 (0.875)	-12.83 (0.875)	-4.78 (1.204)	<0.001
PROMIS sleep disturbance, LSM (SE)	-5.37 (0.413)	-8.92 (0.426)	-3.55 (0.567)	<0.001
PROMIS fatigue, LSM (SE)	-5.16 (0.393)	-7.53 (0.400)	-2.37 (0.531)	<0.001
Diary sleep quality ratings, LSM (SE)	-1.33 (0.086)	-1.90 (0.087)	-0.57 (0.119)	<0.001

[a]Data shown for the pooled ITT population. Treatment Difference vs Placebo column shows LS mean differences from baseline to Week 14 (CBP SL minus placebo) for continuous outcomes and absolute % difference for categorical endpoints (ie, 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. [c]Difference in proportions [95% CI].
CBP SL, cyclobenzaprine sublingual; CI, confidence interval; FIQR, Fibromyalgia Impact Questionnaire – Revised; LSM, least-squares mean; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

Table 2. TEAEs at Rate of ≥3% in Either Treatment Group

Oral Cavity Adverse Event	Placebo (n=481)[a]	CBP SL (n=479)
Hypoaesthesia oral, n (%)	2 (0.4)	98 (20.5)
Product taste abnormal, n (%)	3 (0.6)	38 (7.9)
Paraesthesia oral, n (%)	3 (0.6)	30 (6.3)
Tongue discomfort, n (%)	1 (0.2)	23 (4.8)

Data shown for the pooled safety population. [a]One placebo subject was randomized in error (did not meet safety criteria) and was included in safety population but not in ITT population.
CBP SL, cyclobenzaprine sublingual; TEAE, treatment-emergent adverse event.

Safety

- CBP SL was generally well tolerated; no new or unexpected safety signals were noted
- In the pooled cohort, ≥1 treatment-emergent adverse event (TEAE) occurred in 284 (59.3%) participants taking CBP SL and 201 (41.8%) participants taking placebo
- Most common TEAEs were in the oral cavity and were typically mild, transient, self-limited, and rarely led to treatment discontinuation (**Table 2**)
  - NNH values for select safety outcomes are detailed in **Table 3**

Benefit-risk analyses

- CBP SL demonstrated favorable NNT and NNH values
- The NNT (95% CI) for a ≥30% pain reduction with CBP SL was 7 (5-12)
- The NNH (95% CI) for discontinuation due to an AE was 26 (14-110)
- Based on these values, LHH was 3.7, suggesting treatment provides a nearly four-fold greater likelihood of clinical benefit than treatment discontinuation

RESULTS

Table 3. AE-Related NNH Values for CBP SL 5.6 mg and ARR

Outcome	Placebo (n=481)	CBP SL (n=479)	ARR	NNH
D/C due to AE	17 (3.5)	35 (7.3)	0.038	26
Severe AE	12 (2.5)	14 (2.9)	0.004	233
Severe oral AE	0 (0)	3 (0.6)	0.006	159
Somnolence[a]	11 (2.3)	22 (4.6)	0.023	43
Fatigue	9 (1.9)	15 (3.1)	0.013	79
Dry mouth[b]	10 (2.1)	14 (2.9)	0.008	118

Outcome data for CBP SL and Placebo are presented as n (%). Data were for pooled from RELIEF and RESILIENT studies, using the ITT population.
[a]Somnolence includes hypersomnia, lethargy, and sedation. [b]Dry mouth includes dry throat.
ARR = CBP SL event rate minus Placebo event rate. NNT and NNH = 1/ARR, calculated prior to rounding.
AE, adverse event; ARR, absolute risk reduction; CBP SL, cyclobenzaprine sublingual; D/C, discontinuation; FM, fibromyalgia; ITT, intention-to-treat; LHH, likelihood to be helped or harmed; N, total number of participants in analysis population; n, number of participants with outcome; NNH, number needed to harm; NNT, number needed to treat.

CONCLUSION

- In this pooled post hoc analysis of phase 3 data from the RELIEF and RESILIENT studies, CBP SL was associated with favorable NNT, NNH, and LHH values, suggesting treatment benefit is more likely than AE-related discontinuation

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DISCLOSURES

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

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