Tonmya® (TNX-102 SL; Cyclobenzaprine HCl Sublingual Tablets [CBP SL]) for the Treatment of Adults With Fibromyalgia: Number Needed to Treat, Numbers Needed to Harm and Likelihood to be Helped or Harmed: Results From a Pooled Analysis of Two Phase 3 Studies

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INTRODUCTION

- Fibromyalgia (FM) is a chronic nociplastic pain disorder affecting 2–3% of US adults and is characterized by widespread pain, poor sleep, fatigue, and functional impairment[1-3]
- Tonmya® (TNX-102 SL; cyclobenzaprine HCl sublingual tablets, CBP SL) is the first FDA-approved treatment for adults with FM in over 15 years[4-6]
- Number needed to treat (NNT) analyses estimate the number of patients needing to be treated with one intervention rather than another for one additional patient to achieve the desired outcome; the smaller the NNT values are, the better the efficacy
- Number needed to harm (NNH) analyses estimate how many patients would need to be exposed to one intervention instead of another for one extra patient to experience a specific adverse event (AE) attributable to that treatment; the larger the NNH values are, the better the tolerability
- The likelihood to be helped or harmed (LHH), calculated as NNH/NNT, provides a clinically intuitive risk-benefit summary that goes beyond reporting NNH or NNT values separately
- NNT and NNH estimate benefit and risk and allow cross-trial comparisons when head-to-head data are unavailable[7,8]

OBJECTIVE

- To assess the benefit–risk profile of CBP SL 5.6 mg/d in adults with FM using NNT, NNH, and 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][4]; RESILIENT [NCT05273749][5]), assessing the efficacy and safety of CBP SL 5.6 mg/d

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 from baseline at Week 14 (clinically meaningful threshold)
- Similar to other studies,[9-12] NNH was calculated for discontinuation due to 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 (**Table 1**); 783 (81.6%) completed the studies

Table 1. Baseline Patient Demographics and Characteristics[a] from Pooled RELIEF and RESILIENT Trials

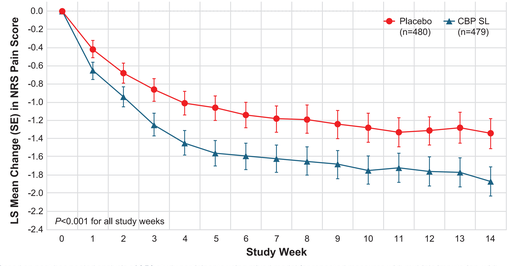
	Placebo (n=480)	CBP SL 5.6 mg/d (n=479)
Age, years, mean (SD)	49.4 (10.72)	49.7 (9.91)
Female, n (%)	458 (95.4)	456 (95.2)
Race, n (%)		
White	408 (85.0)	416 (86.8)
Black/African American	46 (9.6)	51 (10.6)
Asian	10 (2.1)	3 (0.6)
Employed currently, n (%)	308 (64.2)	329 (68.7)
Duration of FM disease, years, mean (SD)	9.4 (8.78)	8.9 (8.43)
Pain at baseline, NRS, mean (SD)	5.97 (1.080)	5.99 (1.060)

[a]Pooled ITT population.
CBP SL, cyclobenzaprine sublingual tablets; FM, fibromyalgia; ITT, intention-to-treat; NRS, numeric rating scale; SD, standard deviation.

Efficacy

- Treatment with CBP SL 5.6 mg/d treatment significantly improved the primary pain endpoint and all key secondary endpoints (**Figure 1** and **Table 2**) vs placebo
  - CBP SL provided a statistically significant reduction in pain scores (-1.87; 95% CI: -2.03, -1.71) vs placebo (-1.34; 95% CI: -1.51, -1.18), with an LS mean (95% CI) difference of -0.53 (-0.75, -0.30); *P*<0.001

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

- In the pooled efficacy population, a ≥30% pain reduction was observed in 46.3% of patients treated with CBP SL 5.6 mg/d vs 31.3% treated with placebo; *P*<0.001.
- The NNT (95% CI) for a ≥30% pain reduction with CBP SL was 7 (5-12)

RESULTS

Table 2. Primary and Key Secondary Endpoints at Week 14[a]

	Placebo (n=481)	CBP SL 5.6 mg/d (n=479)	Treatment Difference vs Placebo	*P* values[d]
Primary Endpoint				
Weekly average NRS 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). [d]*P* values reported are nominal.
CBP SL, cyclobenzaprine sublingual tablets; CI, confidence interval; FIQR, Fibromyalgia Impact Questionnaire – Revised; ITT, intention-to-treat; LSM, least-squares mean; NRS, numeric rating scale; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

Safety

- CBP SL 5.6 mg/d 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 5.6 mg/d and 201 (41.8%) participants taking placebo
- The most common TEAEs were in the oral cavity and were typically mild, transient, self-limited, and uncommonly led to treatment discontinuation (**Table 3**)

Table 3. Oral Cavity TEAEs with Incidence of ≥3% in Any Treatment Group

Oral Cavity Adverse Event	Placebo (n=481)[a]	CBP SL 5.6 mg/d (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 tablets; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.

- Somnolence and fatigue were the only systemic TEAEs that occurred ≥3% of the pooled patient population treated with CBP SL (**Table 4**)

RESULTS

- The NNH (95% CI) for discontinuation due to an AE was 26 (14-110); additional NNH values for select safety outcomes are detailed in **Table 4**

Table 4. ARR and NNH Values for Select Safety Outcomes

Outcome	Placebo (n=481)	CBP SL 5.6 mg/d (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

Outcome data for CBP SL and placebo are presented as n (%) of patients. 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. NNH = 1/ARR, calculated prior to rounding.
AE, adverse event; ARR, absolute risk reduction; CBP SL, cyclobenzaprine sublingual tablets; D/C, discontinuation; FM, fibromyalgia; ITT, intention-to-treat; NNH, number needed to harm.

- Based on the NNH (26) and NNT (7) values, LHH was 3.7, suggesting treatment provides a nearly four-fold greater likelihood of clinical benefit than treatment discontinuation

CONCLUSION

- In this pooled post hoc analysis of phase 3 data from the RELIEF and RESILIENT studies, CBP SL 5.6 mg/d 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: Employees of Tonix Pharmaceuticals, Inc. and own stock and/or stock options in Tonix Pharmaceuticals Holding Corp.

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