Tonmya® (TNX-102 SL; Cyclobenzaprine HCl Sublingual Tablets [CBP SL]) for the Treatment of Adults With Fibromyalgia: Number Needed to Treat, Number 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 2–4% of US adults and is characterized by widespread pain, poor sleep, fatigue, and functional impairment[1-5]
- Tonmya® (TNX-102 SL; cyclobenzaprine HCl sublingual tablets, CBP SL) is the first FDA-approved treatment for adults with FM in over 15 years[6-8]
- 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[9,10]

OBJECTIVE

- To assess the benefit–risk profile of CBP SL 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][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 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 (**Table 1**)

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

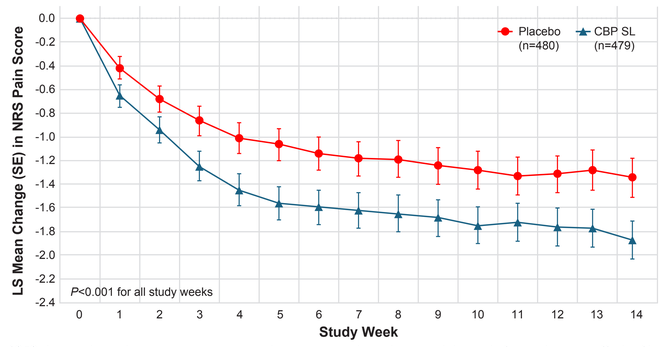
	Placebo (n=480)	CBP SL (n=479)
Age, years, mean (SD)	49.4 (10.72)	49.7 (9.91)
Female, n (%)	458 (95.4)	456 (95.2)
Race, n (%)		
White	408 (85.0)	416 (86.8)
Black/African American	46 (9.6)	51 (10.6)
Asian	10 (2.1)	3 (0.6)
Employed currently, n (%)	308 (64.2)	329 (68.7)
Duration of FM disease, years, mean (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.
FM, fibromyalgia; ITT, intention-to-treat; NRS, numeric rating scale; SD, standard deviation.

Efficacy

- CBP SL treatment significantly improved the primary pain endpoint and all key secondary endpoints (**Figure 1** and **Table 2**) vs placebo
  - CBP SL treatment (-1.87; 95% CI: -2.03, -1.71) provided a statistically significant reduction in pain scores 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 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; ITT, intention-to-treat; LS, least-squares; NRS, numeric rating scale; SE, standard error.

- The NNT (95% CI) for a ≥30% pain reduction with CBP SL was 7 (5-12)

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

	Placebo (n=481)	CBP SL (n=479)	Treatment Difference vs Placebo	*P* values[d]
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). [d]*P* values reported are nominal. CBP SL, cyclobenzaprine sublingual tablets; 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.

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 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 (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.

- 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 (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 (%) 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; LHH, likelihood to be helped or harmed; 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 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, SF: 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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