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Treatment with Tonmya™ (TNX-102 SL; CBP SL) Produces Clinically Meaningful Improvements in Patient-Centered Outcomes in Fibromyalgia

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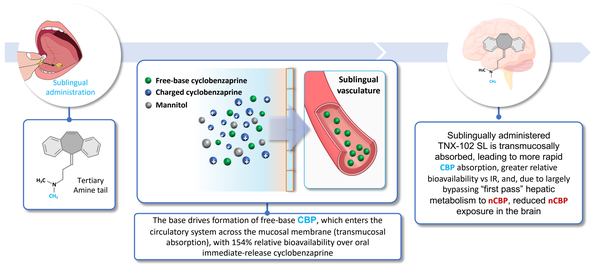
INTRODUCTION

- Fibromyalgia (FM) is a chronic pain disorder that affects ~2 to 4% of US adults, occurs predominantly in women, and is characterized by widespread pain, nonrestorative sleep, fatigue, cognitive dysfunction, and functional impairment[1-3]
- FM is the prototypic nociplastic pain syndrome, with pain arising from abnormal processing in the central nervous system (CNS), not from tissue or nerve injury, resulting in amplified and widespread pain[4,5]
- Disruptions to deep restorative sleep are common in FM, and poor sleep quality is strongly associated with greater nociplastic pain[6]
- Tonmya™ (TNX-102 SL; cyclobenzaprine hydrochloride sublingual tablets [CBP SL]) is FDA-approved for adults with FM, based in part on the Phase 3 RESILIENT trial results[7-9]
  - 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 oral IR CBP, which may minimize next-day sedation and support restorative sleep[10] (**Figure 1**)
  - Although ≥30% pain reduction with treatment is recognized as clinically meaningful in FM, considering pain outcomes in isolation may not thoroughly capture the broader treatment benefits of CBP SL[11]

Figure 1. TNX-102 SL Largely Bypasses First-Pass Hepatic Metabolism



CBP, cyclobenzaprine; IR, immediate release; nCBP, norcyclobenzaprine.

OBJECTIVE

- To assess pain reduction and other patient-reported outcomes to further establish the clinical meaningfulness of CBP SL efficacy

METHODS

- The RESILIENT Phase 3 trial (NCT05273749) assessed the efficacy and safety of CBP SL vs placebo in adults with FM (2016 American College of Rheumatology [ACR] diagnostic criteria) over 14 weeks
- In RESILIENT, the primary efficacy endpoint was the change from baseline in the weekly average of daily self-reported NRS pain scores (0-10) at Week 14 for CBP SL vs placebo
- Key added 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 and Function domain scores
  - Change from baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue 8a and PROMIS sleep disturbance 8a
  - Change from baseline in the weekly average of the daily diary assessment of sleep quality
- Primary and continuous key secondary endpoints over multiple time points were analyzed using mixed model for repeated measures with multiple imputation for missing data
- The proportion of participants with ≥30% reduction in the primary pain endpoint scores from baseline to Week 14 was also evaluated
- In a post hoc analysis, the proportion of participants achieving a composite response criterion (≥30% pain reduction and a PGIC response of "very much" or "much" improved) and proportion of participants achieving ≥50% improvement in FIQR total scores were assessed
- Binary endpoints were analyzed with the Pearson chi-squared test; missing data were treated as non-response
- Safety assessments included reporting of adverse events (AEs)

RESULTS

- A total of 457 adults with FM 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
- Baseline characteristics and demographics were well-balanced between CBP SL (n=231) and placebo (n=225) groups (**Table 1**)

Table 1. Baseline Characteristics and Demographics of the RESILIENT Trial

	CBP SL (n=231)	Placebo (n=225[a])
Age, years, mean (SD)	49.3 (10.5)	49.5 (11.4)
Female, n (%)	224 (97.0)	212 (93.8)
Diary pain score, 0-10 NRS, mean (SD)	5.9 (1.1)	5.9 (1.1)
Duration of FM, years, mean (SD)	8.6 (8.4)	9.9 (9.5)
BMI, kg/m^2 mean (SD)	31.1 (6.3)	31.1 (6.3)
FIQR Symptoms domain score, mean (SD)	53.1 (14.9)	54.1 (14.6)
FIQR Function domain score, mean (SD)	38.5 (19.9)	37.9 (19.1)
PROMIS Sleep Disturbance 8a score, mean (SD)	59.2 (6.0)	59.4 (7.2)
PROMIS Fatigue 8a score, mean (SD)	63.7 (5.9)	63.9 (7.1)
Diary sleep score, mean (SD)	5.8 (1.3)	5.7 (1.3)

[a]Does not include 1 patient who was inadvertently randomized and received placebo.
BMI, body mass index; FIQR, Fibromyalgia Impact Questionnaire Revised; FM, fibromyalgia; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

- The primary and all key secondary endpoints were statistically significantly in favor of CBP SL over placebo, (**Table 2**)

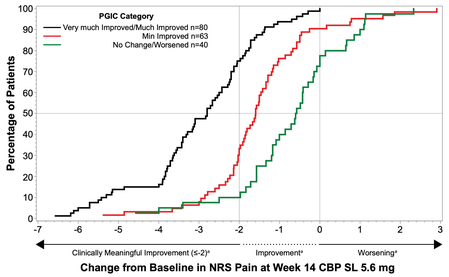
Table 2. Efficacy Summary[a]: Primary and 6 Key Secondary[b] Endpoints at Week 14

	CBP SL (n=231)	Placebo (n=225)	LS Mean (SE) Difference	P-value
Primary Endpoint				
Daily diary pain ratings, LS Mean (SE)	-1.82 (0.116)	-1.16 (0.118)	-0.65 (0.161)	<0.001
Key Secondary Endpoints				
PGIC responders, %	35.1	19.1	16.0[c] (7.9, 24.0)	<0.001
FIQR–Symptoms domain score, LS Mean CFB (SE)	-16.02 (1.166)	-8.36 (1.173)	-7.67 (1.619)	<0.001
FIQR–Function domain score, LS Mean CFB (SE)	-12.22 (1.190)	-6.81 (1.207)	-5.41 (1.661)	0.001
PROMIS Sleep Disturbance score, LS Mean CFB (SE)	-8.44 (0.575)	-4.20 (0.564)	-4.24 (0.789)	<0.001
PROMIS Fatigue score, LS Mean CFB (SE)	-7.18 (0.550)	-4.16 (0.559)	-3.01 (0.768)	<0.001
Diary Sleep Quality ratings, LS Mean CFB (SE)	-1.77 (0.119)	-1.20 (0.121)	-0.57 (0.168)	<0.001

[a]Data derived from intention-to-treat (ITT) population. [b]In order of statistical serial gate-keeping hierarchy to control overall type 1 error. [c]Difference in proportions [95% CI]. CFB, change from baseline; FIQR, Fibromyalgia Impact Questionnaire - Revised; LS, least-squares; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

- At Week 14, 45.9% of CBP SL-treated participants and 27.1% of placebo-treated participants achieved ≥30% reduction in pain intensity (p<0.001, uncorrected) from baseline
- PGIC responders taking CBP SL experienced a median pain score reduction of 2.8 points, and those reporting minimal improvement had a median pain score reduction of 1.6 points (**Figure 2**)
  - 75% of PGIC responders treated with CBP SL achieved a reduction in pain score of ≥2 points (**Figure 2**)
- Participants reporting no change or worsening had a median increase in pain score of 0.67 points (**Figure 2**)

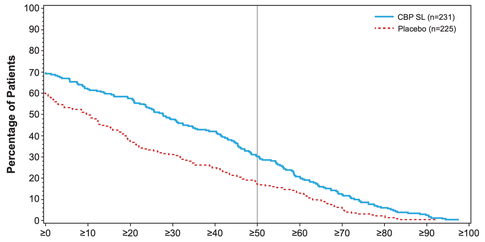
Figure 2. Cumulative NRS Pain Change from Baseline Scores by PGIC Categories for CBP SL at Week 14



[a]Negative values indicate improvement in NRS pain scores, with reductions of ≥2 points representing clinically meaningful improvement; positive values indicate worsening. Figure does not include participants with missing data at Week 14.
NRS, Numeric Rating Scale; PGIC, Patient Global Impression of Change.

- More participants treated with CBP SL vs placebo experienced ≥50% reduction in FIQR total score (30.3% vs 17.3%, respectively; p=0.001, uncorrected) (**Figure 3**)
- Similarly, CBP SL treatment was associated with a higher percentage of participants meeting the composite response criteria vs placebo (28.6% vs 15.1%, respectively; p<0.001, uncorrected)

Figure 3. Continuous Responder Graph of Percentage Change from Baseline Scores at Week 14 on the FIQR



FIQR, Fibromyalgia Impact Questionnaire – Revised.

- CBP SL was generally well tolerated, consistent with previous studies
  - 6.1% of participants discontinued CBP SL due to AEs
- The most commonly reported treatment-emergent adverse events (TEAEs) for CBP SL were mild, transient, and self-limited local oral administration site reactions that uncommonly led to study discontinuation (**Table 3**)

Table 3. TEAEs Reported by ≥2% of Patients in Either Treatment Group

	CBP SL (n=231)	Placebo (n=226)	Total (N=457)
Systemic Adverse Events			
COVID-19	10 (4.3)	7 (3.1)	17 (3.7)
Somnolence	7 (3.0)	3 (1.3)	10 (2.2)
Headache	7 (3.0)	4 (1.8)	11 (2.4)
Fatigue	6 (2.6)	5 (2.2)	11 (2.4)
Upper respiratory tract infection	6 (2.6)	1 (0.4)	7 (1.5)
Oral Cavity Adverse Events			
Hypoesthesia oral	55 (23.8)	1 (0.4)	56 (12.3)
Product taste abnormal	27 (11.7)	2 (0.9)	29 (6.3)
Paresthesia oral	16 (6.9)	2 (0.9)	18 (3.9)
Tongue discomfort	16 (6.9)	0	16 (3.5)
Oral mucosal erythema	6 (2.6)	2 (0.9)	8 (1.8)
Glossodynia	5 (2.2)	1 (0.4)	6 (1.3)
Tongue disorder	5 (2.2)	0	5 (1.1)

TEAEs, treatment-emergent adverse events.

CONCLUSIONS

- CBP SL treatment provided clinically meaningful improvements in pain (≥30%), FIQR total score (≥50%), and the composite endpoint of ≥30% pain reduction and PGIC response
- CBP SL treatment significantly improved sleep disturbance, fatigue and FIQR symptoms and function domain scores vs placebo
- CBP SL shows a low systemic adverse-event (AE) burden, with prominent but generally self-limited local oral AEs; in contrast, oral IR cyclobenzaprine is limited by classic tricyclic systemic AEs such as somnolence and anticholinergic effects at commonly prescribed doses
- Although study designs and methodologies differ, AE-related discontinuation rates observed with CBP SL were lower than those observed in registrational studies supporting previous US FDA-approved therapies (6.1% vs 14.7-32.6%) in FM, supporting CBP SL as a well-tolerated, patient-centered therapy for adults with FM[9,12-15]
- This analysis highlights the patient-centered and clinically meaningful effects of CBP SL across multiple symptom domains in adults with FM

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DISCLOSURES

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