Poster #46

Randomized, Double-Blind, Placebo-Controlled Confirmatory Phase 3 Trial of Bedtime Sublingual Cyclobenzaprine (TNX-102 SL) in Fibromyalgia

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INTRODUCTION

- Fibromyalgia (FM) is a chronic pain disorder estimated to affect 6 to 12 million U.S. adults, predominantly women
  - FM is characterized by chronic widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction
  - More recently, FM has been understood as the prototypic 'nociplastic syndrome'[1]
- Nociplastic pain, a third category of pain distinct from nociceptive pain and neuropathic pain, is characterized by pain arising from altered nociception despite no pathology in peripheral nociceptors or the somatosensory system
  - Nociplastic pain is driven by dysregulation in the processing of pain signals within the central nervous system (CNS) and may involve changes in neurotransmitter levels, central sensitization, and maladaptive neuroplasticity, all of which can amplify pain perception and contribute to the persistent, diffuse pain that typifies FM
- Approximately 50 years ago, Dr. Harvey Moldofsky recognized the role of nonrestorative sleep in the pathogenesis and persistence of FM[2,3]
  - Individuals with FM typically suffer from disruptions in the deep restorative stages of sleep, and poor sleep quality is highly associated with the exacerbation and perpetuation of nociplastic pain
- Understanding nociplastic syndrome is critical for developing effective treatment strategies in not only FM but also several other chronic overlapping pain conditions (COPCs) including myalgic encephalomyelitis/chronic fatigue syndrome
  - Traditional analgesics like NSAIDs or opioids in nociplastic syndrome often prove ineffective if not deleterious, and there is common dissatisfaction with currently marketed products in patients with FM
- Tonmya™ (TNX-102 SL) is an innovative sublingual tablet formulation of cyclobenzaprine HCl (CBP), distinct from oral CBP in providing rapid sublingual transmucosal absorption, greater bioavailability, and reduced production of a long half-life active metabolite, norcyclobenzaprine, due to bypassing of first-pass hepatic metabolism
- Among its activities, CBP potently binds and antagonizes the 5-HT_{2A}-serotonergic, α_1-adrenergic, M_1-muscarinic acetylcholine, and H_1-histaminergic receptors, each of which impacts aspects of sleep architecture
- TNX-102 SL is hypothesized to work by targeting nonrestorative sleep, a core characteristic of FM
- This study assessed the efficacy and safety of bedtime TNX-102 SL in FM and suggests a role of disturbed sleep in the persistence and exacerbation of FM[4]

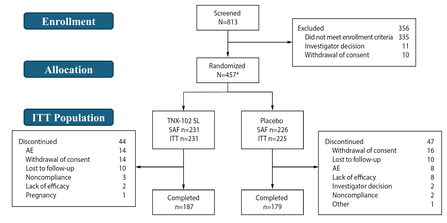
METHODS

- Across 33 U.S. sites, the RESILIENT study randomized FM patients 1:1 to receive TNX-102 SL 2.8 mg for 2 weeks followed by 5.6 mg for 12 weeks or matching placebo for 14 weeks
- The primary endpoint was change from baseline to Week 14 in weekly average of daily diary pain numeric rating scale (NRS) scores analyzed by mixed-model repeated-measures (MMRM) analysis, with multiple imputation (MI) for missing data
- Key secondary endpoints included Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire - Revised (FIQR) Symptoms and Function domains, PROMIS Sleep Disturbance and Fatigue instruments, and daily sleep quality NRS scores evaluated at Week 14
- Continuous key secondary endpoints were analyzed in the same manner as primary, MMRM with MI, with multiplicity adjustment and type 1 error control by prespecified sequential test procedure
- PGIC responder analysis was by Pearson chi-squared testing
  - Individual FIQR item scores (**Table 3**), analyzed by MMRM, and the Changes in Sexual Functioning Questionnaire short form (CSFQ-14) analyses, by ANCOVA, were not corrected for multiple comparisons
- Outside the primary and 6 key secondary endpoints at Week 14, all p-values are descriptive (i.e., no correction for multiplicity)
- Safety was assessed by adverse events, vital signs/weight, physical exams, clinical lab tests, C-SSRS, and Beck Depression Inventory II (BDI-II)

RESULTS

- As per **Figure 1**, 813 FM patients were assessed for eligibility. A total of 457 were randomized, of whom 231 received TNX-102 SL and 226 received placebo; 456 were in the intent-to-treat (ITT) population
- Study completion: 81.0% of TNX-102 SL group, 79.2% of placebo group
  - See **Figure 1** for discontinuation reasons
- Demographics and baseline characteristics were comparable (**Table 1**)

Figure 1: CONSORT Diagram



*One placebo subject who was randomized in error (did not meet safety criteria) is included in safety population (SAF) but not in ITT population. AE, adverse event; ITT, intent-to-treat, SAF, safety population.

Table 1: Demographics and Baseline Characteristics in Safety Population

	TNX-102 SL (N=231)	Placebo (N=226)	Total (N=457)
Females, n (%)	224 (97.0%)	212 (93.8%)	436 (95.4%)
Age, years, mean (SD)	49.3 (10.45)	49.5 (11.32)	49.4 (10.88)
Race, n (%)			
White/Caucasian	194 (84.0%)	192 (85.0%)	386 (84.5%)
Black/African American	32 (13.9%)	27 (11.9%)	59 (12.9%)
Asian	1 (0.4%)	5 (2.2%)	6 (1.3%)
Ethnicity, n (%)			
Hispanic or Latino	36 (15.6%)	35 (15.5%)	71 (15.5%)
BMI, kg/m², mean (SD)	31.1 (6.34)	31.1 (6.32)	31.1 (6.33)
Employed currently, n (%)	147 (63.6%)	150 (66.4%)	297 (65.0%)
Unable to work due to FM symptoms, n (%)	13 (5.6%)	12 (5.3%)	25 (5.5%)
Education, some college or beyond, n (%)	187 (81.0%)	193 (85.4%)	380 (83.2%)
Duration of FM disease in years, mean (SD)	8.6 (8.44)	9.9 (9.52)	9.2 (9.00)
Pain at baseline, NRS, mean (SD)*	5.9 (1.05)	5.9 (1.08)	5.9 (1.06)

*Pain reported for ITT population. BMI, basal metabolic rate; SD, standard deviation.

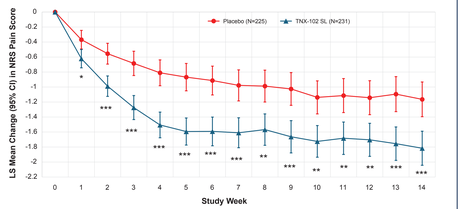
- As seen in **Table 2**, TNX-102 SL demonstrated highly statistically significant improvement in the primary endpoint of mean weekly pain scores over placebo at Week 14 (p=0.00005), also displayed by study week in **Figure 2** (p-values descriptive for Weeks 1-13)
- Furthermore, all six key secondary endpoints were statistically significant (all p-values ≤0.001)
  - Effect size for primary endpoint was 0.38, and all five continuous key secondaries were in the range of 0.30 – 0.50
- All items, including affective and cognitive items on FIQR in **Table 3**, show similar improvement by MMRM
  - PGIC responder analysis by study visit is presented in **Figure 3** (p-values descriptive for Weeks 2, 8 & 10)
- Correlation between sleep and pain improvement from baseline to Week 14 was similar in drug and placebo groups as displayed in **Figure 4**

Table 2: Summary of Results of the Primary and 6 Key Secondary* Endpoints at Week 14

	TNX-102 SL LS Mean (SE)	PBO LS Mean (SE)	LS Mean (SE) Difference	*P*-value	Effect Size^
Primary Endpoint					
Daily Diary Pain ratings	-1.82 (0.116)	-1.16 (0.118)	-0.65 (0.161)	0.00005	0.38
Key Secondary Endpoints					
PGIC, responders#	35.1%	19.1%	16.0% (7.9%, 24.0%)	0.00013	#
FIQR – Symptoms domain	-16.02 (1.166)	-8.36 (1.173)	-7.67 (1.619)	0.000002	0.44
FIQR – Function domain	-12.22 (1.190)	-6.81 (1.207)	-5.41 (1.661)	0.001	0.30
PROMIS Sleep Disturbance	-8.44 (0.575)	-4.20 (0.564)	-4.24 (0.789)	0.0000001	0.50
PROMIS Fatigue	-7.18 (0.550)	-4.16 (0.559)	-3.01 (0.768)	0.00009	0.37
Diary Sleep Quality ratings	-1.77 (0.119)	-1.20 (0.121)	-0.57 (0.168)	0.0007	0.32

*In order of statistical serial gate-keeping hierarchy to control overall type 1 error.
^Effect size calculated as: effect size = (difference in LS means/standard error) x square root ($1/N_{placebo} + 1/N_{active}$).
#PGIC was a responder analysis; difference in proportions [95% CI], with no calculation of effect size.
FIQR, Fibromyalgia Impact Questionnaire - Revised; LS, least-squares; PGIC, Patient Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

Figure 2: Mean Change from Baseline in Weekly Averages of Daily NRS Pain Scores



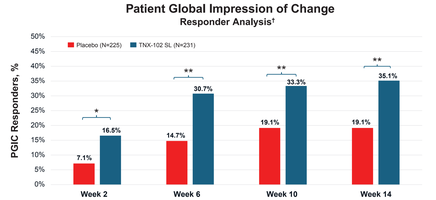
*p<0.01; **p<0.001; ***p<0.0001.

Table 3: Change from Baseline in FIQR Items* at Week 14

	TNX-102 SL LS Mean (SE)	PBO LS Mean (SE)	LS Mean (SE) Difference	P-value^
FIQR SYMPTOMS DOMAIN: Please rate your... (past 7 days)				
Level of pain	−2.2 (0.15)	−1.2 (0.15)	−1.0 (0.21)	<0.001
Level of energy	−1.6 (0.16)	−0.9 (0.17)	−0.8 (0.23)	<0.001
Level of stiffness	−2.0 (0.17)	−1.2 (0.17)	−0.8 (0.24)	<0.001
Quality of sleep	−2.9 (0.19)	−1.5 (0.19)	−1.4 (0.26)	<0.001
Level of depression	−0.9 (0.15)	−0.2 (0.15)	−0.8 (0.21)	<0.001
Level of memory problems	−1.3 (0.16)	−0.6 (0.17)	−0.8 (0.23)	0.001
Level of anxiety	−1.2 (0.17)	−0.4 (0.17)	−0.8 (0.24)	0.001
Level of tenderness to touch	−2.1 (0.18)	−1.3 (0.18)	−0.8 (0.25)	0.001
Level of balance problems	−1.1 (0.15)	−0.6 (0.15)	−0.5 (0.21)	0.015
Level of sensory sensitivity†	−1.8 (0.18)	−1.3 (0.18)	−0.6 (0.24)	0.020
FIQR IMPACT DOMAIN: Over the last 7 days, fibromyalgia...				
Prevented accomplishing goals	−2.4 (0.18)	−1.6 (0.18)	−0.8 (0.25)	0.001
Completely overwhelmed me	−2.1 (0.18)	−1.4 (0.18)	−0.7 (0.25)	0.005

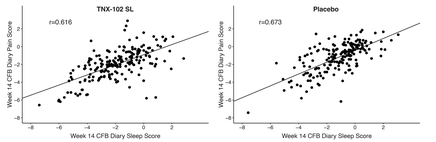
*Reported as LS mean (SE) change from baseline; †Too loud noises, bright lights, odors, and cold; ^All p-values in table are descriptive.
FIQR, Fibromyalgia Impact Questionnaire - Revised; LS, least-squares; SE, standard error.

Figure 3: Patient Global Impression of Change Responder Analysis†



*p<0.01; **p<0.001. †Response on the PGIC was defined as a score of 2, 'much improved', or 1, 'very much improved'; all other scores and all discontinuations were treated as non-responders.

Figure 4: Correlation Between Changes from Baseline in Diary Pain and in Sleep Quality



CFB, change from baseline.

SAFETY

- Treatment-emergent adverse events (TEAEs) at ≥3% rate are displayed in **Table 4**
- There were no safety signals by vital signs, weight, clinical labs, or physical exams or on C-SSRS or BDI-II
- TEAE-related discontinuations occurred in 6.1% and 3.6% of subjects in the TNX-102 SL and placebo groups, respectively
- TEAEs rated mild or moderate were 99.1% of AEs on TNX-102 SL and 97.2% on placebo

No Clinically Meaningful Differences Between Groups in Blood Pressure (BP) or Weight CFB

- Change from baseline (CFB) in Week 14 mean systolic BP (standard deviation (SD)): TNX-102 SL = 0.7 (12.38) mmHg; Placebo = 0.5 (10.42) mmHg
- CFB in Week 14 mean diastolic BP (SD): TNX-102 SL = 1.1 (8.60) mmHg; Placebo = 0.2 (8.22) mmHg
- CFB in Week 14 mean weight (SD): TNX-102 SL = 0.02 (2.940) kg; Placebo = 0.20 (2.932) kg

Changes in Sexual Functioning Questionnaire short form (Exploratory Efficacy/ Tolerability)*

- In females, CSFQ-14 total score improved (indicating better sexual functioning) to a greater extent in the TNX-102 SL group compared with the placebo group, p=0.010
- Orgasm/Completion (p=0.007) and Desire/Frequency (p=0.010) were also improved over placebo

*p-values provided for CSFQ-14 total and subscales are descriptive.

Table 4: TEAEs Occurring in ≥3% of Participants in Either Treatment Group

System Organ Class Preferred Term	TNX-102 SL (N=231)	Placebo (N=226)	Total (N=457)
Systemic Adverse Events, n (%)			
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%)
Oral Cavity Adverse Events, n (%)			
Hypoaesthesia oral	55 (23.8%)	1 (0.4%)	56 (12.3%)
Product taste abnormal	27 (11.7%)	2 (0.9%)	29 (6.3%)
Paraesthesia oral	16 (6.9%)	2 (0.9%)	18 (3.9%)
Tongue discomfort	16 (6.9%)	0 (0.0%)	16 (3.5%)

DISCUSSION

- FM is the prototypic nociplastic syndrome and COPC with CNS symptoms of widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction
- By pharmacologically targeting nonrestorative sleep, treatment with bedtime TNX-102 SL reduced the pain primary endpoint and resulted in broad symptom improvement shown by:

Efficacy

- Statistically significant improvement on primary endpoint (daily pain) and on all six key secondary endpoints, indicating broad FM symptom improvement
- Improvement in sleep quality – or target engagement – was shown by TNX-102 SL-mediated improvements over placebo on the PROMIS Sleep Disturbance instrument and Sleep Quality diary
- Improvement in Week 14 pain score was correlated with improvement in Week 14 sleep score in both treatment groups, suggesting TNX-102 SL treatment increases the number of responders over placebo/spontaneous remission (**Figure 4**)
- Improvements on exploratory endpoints:
  - (1) mood and cognitive dysfunction and
  - (2) female sexual functioning nominally improved over course of treatment, including the orgasm/completion domain (note: too few males in study to meaningfully compare groups on male version of CSFQ-14)

Safety

- Systemic TEAEs were low, with only headache, somnolence, and COVID-19 at a rate ≥3%
- Most common TEAEs were oral administration site reactions, tongue/mouth numbness or tingling and bitter aftertaste, which were typically transient, self-limited, not severe, and rarely led to discontinuation

Tolerability

- Completion rate: 81.0% of the TNX-102 SL group and 79.2% of the placebo group
- Generally well tolerated: no clinically meaningful weight or blood pressure change, low rate of somnolence TEAE, and nominally improved cognitive symptoms (memory item of FIQR)

OVERALL CONCLUSIONS

- TNX-102 SL reduced the pain primary endpoint in FM and appears to lead to syndromal improvement
- Results of TNX-102 SL therapy in RESILIENT support the hypothesis that targeting nonrestorative sleep in FM has the potential for syndromal improvement, and it is generally well tolerated
- Together, these findings are consistent with the concept that disturbed sleep in FM is an obstacle to recovery and pharmacological targeting of nonrestorative sleep may facilitate recovery

References

1. Clauw DJ. *Ann Rheum Dis*. 2024;83:1421-1427. 2. Moldofsky H, et al. *PsychosomMed*. 1975;37:341-51. 3. Moldofsky H and Scarisbrick P. *PsychosomMed*. 1976;38:35-44. 4. Lederman S, et al. *Pain Med*. 2025:pnaf089.

Disclosures

SL, MK, JE, GMS: Employee of and stock ownership in Tonix Pharmaceuticals, Inc.

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