Targeting Non-Restorative Sleep in Fibromyalgia with Bedtime TNX-102 SL (Sublingual Cyclobenzaprine HCl) Significantly Improves Pain in RESILIENT, a Confirmatory Phase 3 Randomized Clinical Trial

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TNX-102 SL (Tonmya™) is an investigational drug and has not been approved for any indication
*Tonmya is conditionally accepted by the US FDA as the tradename for TNX-102 SL

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INTRODUCTION

Fibromyalgia (FM) is a chronic pain disorder that is understood to result from amplified sensory and pain signaling within the central nervous system. FM afflicts an estimated 6 to 12 million adults in the U.S., the majority of whom are women. Symptoms of FM include chronic widespread pain, nonrestorative sleep, and fatigue. Physicians and patients report common dissatisfaction with currently marketed products. TNX-102 SL (Tonmya™)* is an innovative sublingual tablet formulation of cyclobenzaprine HCl (CBP) which is distinct from oral immediate-release CBP in providing rapid sublingual transmucosal absorption, greater bioavailability, and reduced production of a long half-life active metabolite, norcyclobenzaprine, due to bypass of first-pass hepatic metabolism. CBP potently binds and antagonizes 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 believed to work in FM by targeting improvement in sleep quality.

METHODS

Across 33 U.S. sites, RESILIENT enrolled 457 FM patients; the intent-to-treat (ITT) population received TNX-102 SL 2.8 mg for 2 weeks, followed by 5.6 mg for 12 weeks (N=231) or matching placebo (N=225). The primary endpoint was change from baseline at Week 14 in the weekly averages of daily diary pain numeric rating scale (NRS) scores using mixed model repeated measures (MMRM) with multiple imputation (MI). Secondary key endpoints included Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire - Revised (FIQR) Symptoms and Function domains, PROMIS Sleep Disturbance and Fatigue. Other endpoints included the Beck Depression Inventory-II (BDE-II). Safety was assessed by adverse events, vital signs/weight, physical exams, and Changes in Sexual Functioning Questionnaire short form (CSFQ-14). Continuous key secondary endpoints were analyzed in same manner as primary, MMRM with MI. See **Table 2** for responder analysis (PGIC).

RESULTS

Figure 1: CONSORT Diagram

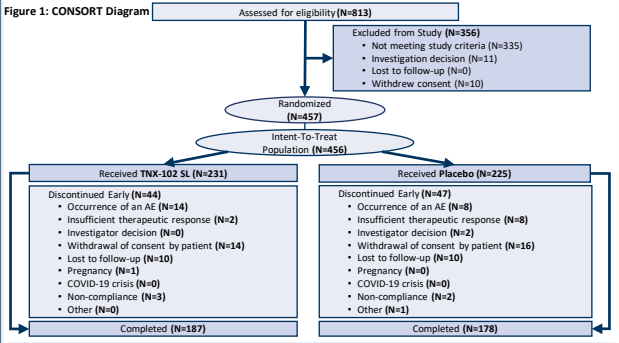


Table 1: Demographics and Baseline Characteristics in Safety Population

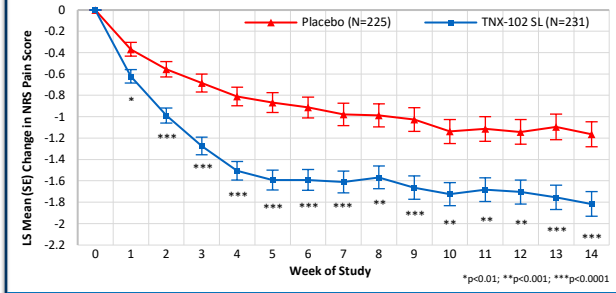
	TNX-102 SL (N=231)	Placebo (N=226)	Total (N=457)
Females, n (%)	224 (97.0%)	212 (93.8%)	436 (95.4%)
Age in years, mean (SD)	49.3 (10.45)	49.5 (11.32)	49.4 (10.88)
Race, n (%)			
White/Caucasian	194 (84.0%)	192 (85.0%)	386 (84.5%)
Black/African American	32 (13.9%)	27 (11.9%)	59 (12.9%)
Asian	1 (0.4%)	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)	

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

	P-value	Effect Size (ES)
Primary Endpoint		
Daily Diary Pain ratings	$p = 0.00005$	ES = 0.38
Key Secondary Endpoints		
Patient Global Impression of Change (PGIC), responders	$p = 0.00013$	#
Fibromyalgia Impact Questionnaire – Symptoms domain	$p = 0.000002$	ES = 0.44
Fibromyalgia Impact Questionnaire – Function domain	$p = 0.001$	ES = 0.30
PROMIS Sleep Disturbance instrument	$p = 0.0000001$	ES = 0.50
PROMIS Fatigue instrument	$p = 0.00009$	ES = 0.37
Diary Sleep Quality ratings	$p = 0.0007$	ES = 0.32

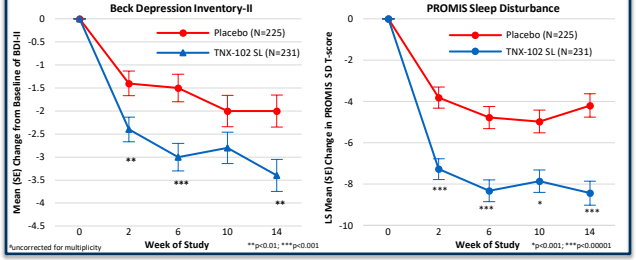
As seen in **Table 2**, TNX-102 SL demonstrated highly statistically significant improvement in primary endpoint of mean weekly pain scores over placebo at Week 14 ($p = 0.00005$). Furthermore, all six key secondary endpoints were statistically significant (all p-values ≤ 0.001). Cohen's *d* effect size for primary endpoint was 0.38 and all five continuous key secondaries in range of 0.30 – 0.50. #PGIC was a responder analysis; difference in proportions [95% CI] of 16.0% [7.9%, 24.0%]. *In order of statistical serial gate-keeping hierarchy to control overall Type 1 error.

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



Figures 3 & 4: CFB in Beck Depression Inventory-II and PROMIS Sleep Disturbance

Beck Depression	Placebo Mean (SE)	Placebo LS MCFB (SE)	TNX Mean (SE)	TNX LS MCFB (SE)	Difference in LS Means (SE)	95% CI for Difference	P-value	Effect Size
Baseline	10.0 (6.72)		9.6 (6.32)					
Week 14		-2.0 (0.35)		-3.4 (0.35)	-1.4 (0.49)	-2.3, -0.4	0.005#	0.27



SAFETY

Table 3: Treatment-Emergent Adverse Events at Rate of ≥ 3% in Either Treatment Group

System Organ Class Preferred Term	TNX-102 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%)
Oral Cavity Adverse Events			
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%)

*Safety population

Figure 5: Pain Reduction by Sensory AEs - Weekly Averages of Daily Diary NRS Scores

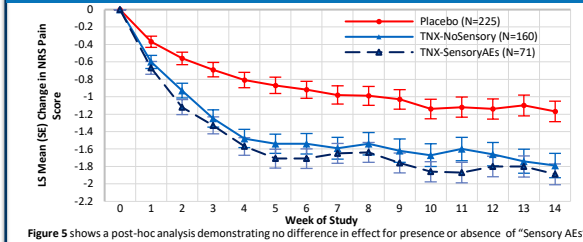


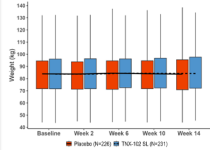
Figure 5 shows a post-hoc analysis demonstrating no difference in effect for presence or absence of "Sensory AEs", defined as oral numbness, oral tingling, and/or bitter aftertaste. TNX = TNX-102 SL

At Week 14	TNX-NoSensory v Placebo	TNX-SensoryAEs v Placebo	TNX-NoSensory v TNX-SensoryAEs
Difference in LS Mean (SE)	-0.62 (0.179)	-0.72 (0.239)	-0.10 (0.254)
P-value	p<0.001	p<0.003	p<0.701

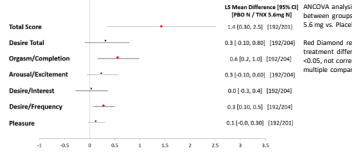
- Both TNX-102 SL subgroups show significantly greater pain reduction than placebo
- The two TNX-102 SL subgroups do not significantly differ from each other

Figures 6 & 7: Changes in Weight and Sexual Functioning Questionnaire

Changes in Weight from Baseline to Week 14



Changes in Sexual Functioning Questionnaire Change from Baseline to Week 14 in Females



DISCUSSION

- Treatment with bedtime TNX-102 SL significantly reduced daily pain and demonstrated broad FM symptom improvement, as demonstrated by statistically significant improvement on primary endpoint and all six key secondary endpoints
- Oral administration site reactions were transient, self-limited and did not account for the significant improvement on the primary endpoint (i.e., not unblinding)
- TNX-102 SL treatment was associated with improvement in depressive symptoms and female sexual function
- As seen in **Table 3 and Figures 6 & 7,** TNX-102 SL demonstrated a favorable safety and tolerability profile, avoiding common side effects associated with currently FDA-approved products such as increase in weight and decrease in sexual functioning
- Improvement in sleep quality mediated by TNX-102 SL appears to lead to syndromal improvement in FM