Sublingual Cyclobenzaprine (TNX-102 SL) for Fibromyalgia: Efficacy and Safety in Two Randomized, Placebo-Controlled Trials

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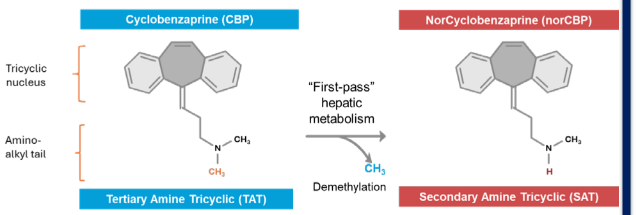
INTRODUCTION

Fibromyalgia (FM) is a chronic pain disorder estimated to afflict 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. 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 FM.

Cyclobenzaprine HCl (CBP) is a tertiary amine tricyclic (TAT) metabolized in the liver via demethylation to norcyclobenzaprine (norCBP), an active secondary amine tricyclic (SAT) metabolite (Figure 1). With daily oral administration, CBP exhibits a dynamic pharmacokinetic (PK) profile with a relatively short half-life. In contrast, norCBP has a significantly longer half-life, leading to its accumulation, a flattened PK profile, and steady-state concentrations that exceed those of CBP.

NorCBP not only interferes with the receptor binding of CBP but also acts as a potent inhibitor of the norepinephrine transporter (NET), which may disrupt restorative sleep. Like other TATs (e.g., tertiary amine tricyclic antidepressants), oral CBP in clinical studies was poorly tolerated (i.e., increased frequency of systemic adverse events), potentially due to reduced receptor binding caused by norCBP accumulation with daily dosing. Previous studies of oral CBP to treat FM demonstrated short lived improvements in sleep without significant benefits for pain or fatigue.[4]

Figure 1: Cyclobenzaprine Metabolism



TNX-102 SL is an innovative sublingual tablet formulation of CBP, distinct from oral CBP in providing rapid sublingual transmucosal absorption, greater bioavailability, and reduced production of a norCBP, due to bypassing of first-pass hepatic metabolism. Among its activities, CBP potently binds and antagonizes 5-HT2A-serotonergic, α_1-adrenergic, M1-muscarinic acetylcholine, and H-histaminergic receptors, each of which impacts aspects of sleep architecture. TNX-102 SL is hypothesized to work by targeting non-restorative sleep that is a characteristic of FM.

METHODS

Two pivotal 14-week, randomized, double-blind, placebo-controlled studies were conducted in subjects with FM, RELIEF[5] (Study 1) and RESILIENT (Study 2). Both studies randomized subjects 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 at Week 14 in weekly average of daily self-reported average pain numeric rating scale (NRS) scores analyzed by mixed model repeated measures (MMRM), with multiple imputation (MI) for missing data. To assess clinically meaningful improvements in pain, exploratory analyses included proportions of subjects with a ≥30% and ≥50% improvement from baseline to Weeks 14 in the weekly average of daily self-reported average pain severity scores. Safety was assessed by adverse events, vital signs/weight, physical exams, clinical lab tests, C-SSRS, and Beck Depression Inventory II (BDI-II).

TNX-102 SL is an investigational drug and has not been approved for any indication

RESULTS

Table 1: Mean Change from Baseline in Weekly Average of Daily 24-Hour Recall Pain Intensity Scores - MMRM with Multiple Imputation Analysis (ITT Population)

	Study 1 (RELIEF)		Study 2 (RESILIENT)	
	Placebo N=255	TNX-102 SL N=248	Placebo N=225	TNX-102 SL N=231
Baseline mean (SD)	6.0 (1.08)	6.1 (1.06)	5.9 (1.08)	5.9 (1.05)
CFB LSM (SE)	-1.5 (0.12)	-1.9 (0.12)	-1.2 (0.12)	-1.8 (0.12)
Difference in LSM (SE)		-0.4 (0.16)		-0.7 (0.16)
p-value for difference		0.01		<0.001

SD: Standard deviation; CFB: Change from baseline; LSM: Least squares mean; SE: Standard error

Figure 2: TNX-102 SL Demonstrates Sustained Pain Reduction Over Time

Weekly Average of Daily Diary NRS Ratings of Average Pain Over Prior 24 Hours

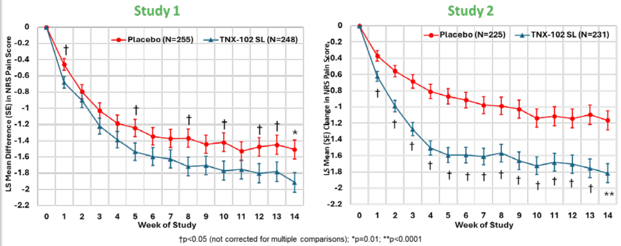


Figure 3: TNX-102 SL Demonstrates Clinically Meaningful Reductions in Pain Over 14 Weeks

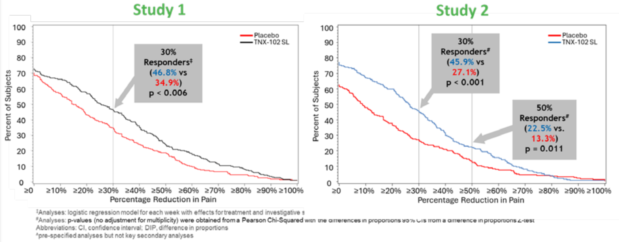


Figure 4: Improvement in Sleep Quality on Over Time

Weekly Average of Daily Diary NRS Ratings of Prior Night Sleep Quality

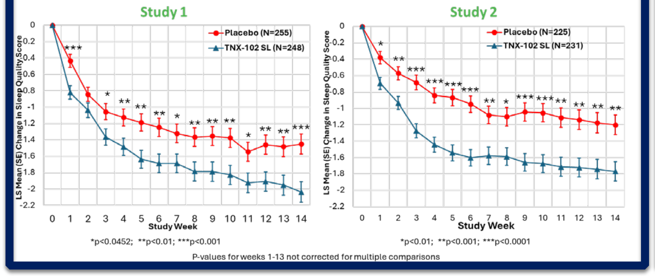


Table 2: Treatment-Emergent Adverse Events at a Rate ≥3% in Either Treatment Group (Studies 1 and 2)

	Placebo N=481	TNX-102 SL N=479
Oral Cavity Adverse Events		
Hypoaesthesia oral	2 (0.4%)	98 (20.5%)
Paraesthesia oral	3 (0.6%)	30 (6.3%)
Product Taste Abnormal	3 (0.6%)	38 (7.9%)
Tongue Discomfort	1 (0.2%)	23 (4.8%)
Systemic Adverse Events		
Fatigue	9 (1.9%)	15 (3.1%)

CONCLUSIONS

- 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 demonstrated clinically meaningful and substantial pain relief.
- TNX-102 SL was generally well tolerated – incidence of systemic treatment-emergent adverse events (TEAEs) was low, with only fatigue at a rate ≥3%.
- Most common TEAEs were oral administration site reactions, tongue/mouth numbness or tingling and bitter aftertaste, typically transient, self-limited, none severe, and rarely led to discontinuation.
- 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

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