

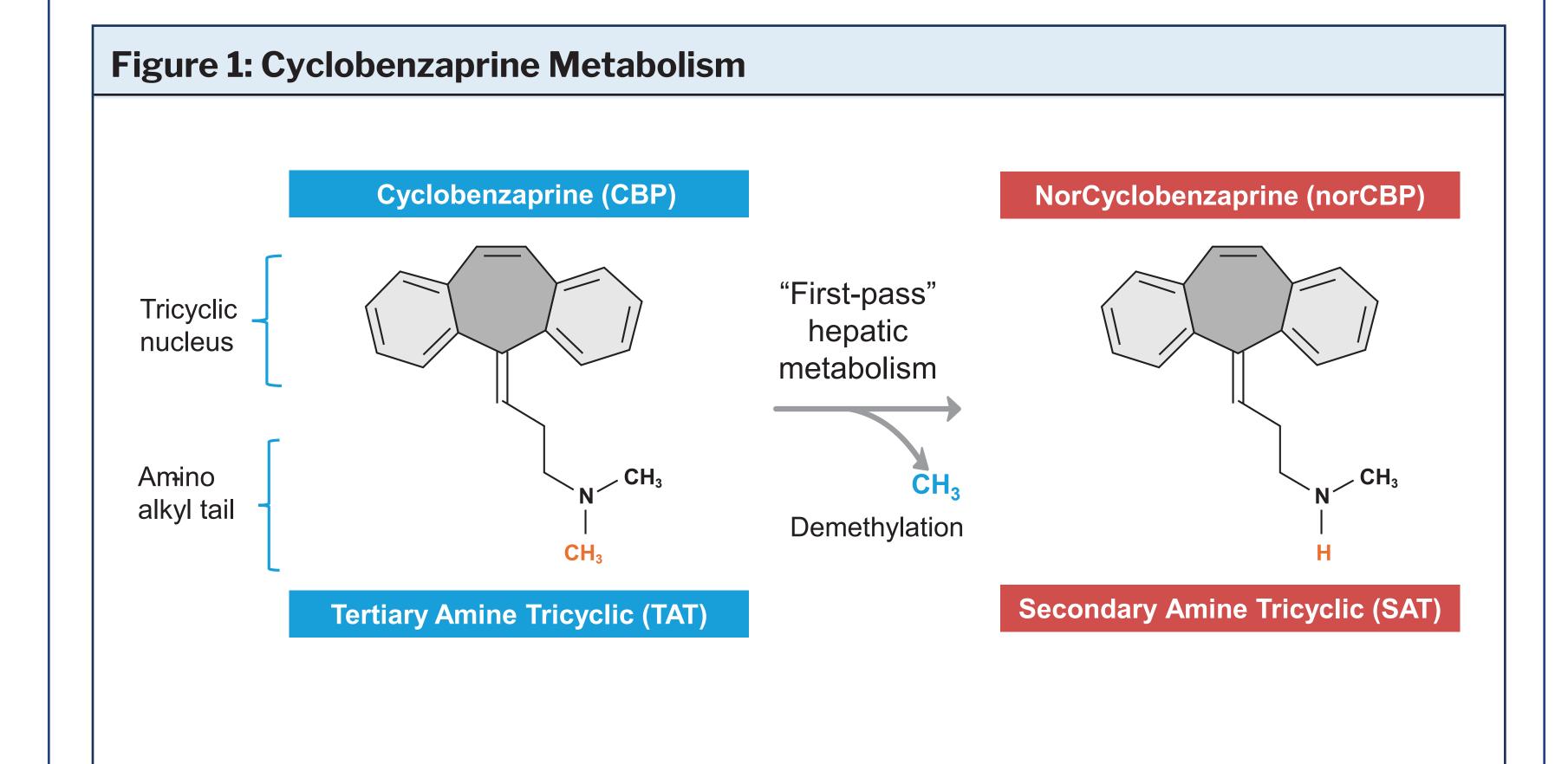
Sublingual Cyclobenzaprine (TNX-102 SL) for Fibromyalgia: Efficacy and Safety in Two Randomized, Placebo-Controlled Trials

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INTRODUCTION

- Fibromyalgia (FM) is a chronic pain disorder estimated to 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'
- Nociplastic pain, a third category of pain distinct from nociceptive pain and neuropathic pain, is characterized by pain arising from altered nociception despite a lack of 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 patients with FM
- Cyclobenzaprine HCl (CBP) is a tertiary amine tricyclic (TAT) metabolized in the liver via demethylation to norcyclobenzaprine (norCBP), an active secondary amine tricyclic 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, which may disrupt restorative sleep
- Like other TATs, 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 in treating FM demonstrated short-lived improvements in sleep without significant benefits to pain or fatigue⁴
- Tonmya[™] (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 norCBP 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 M_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

METHODS

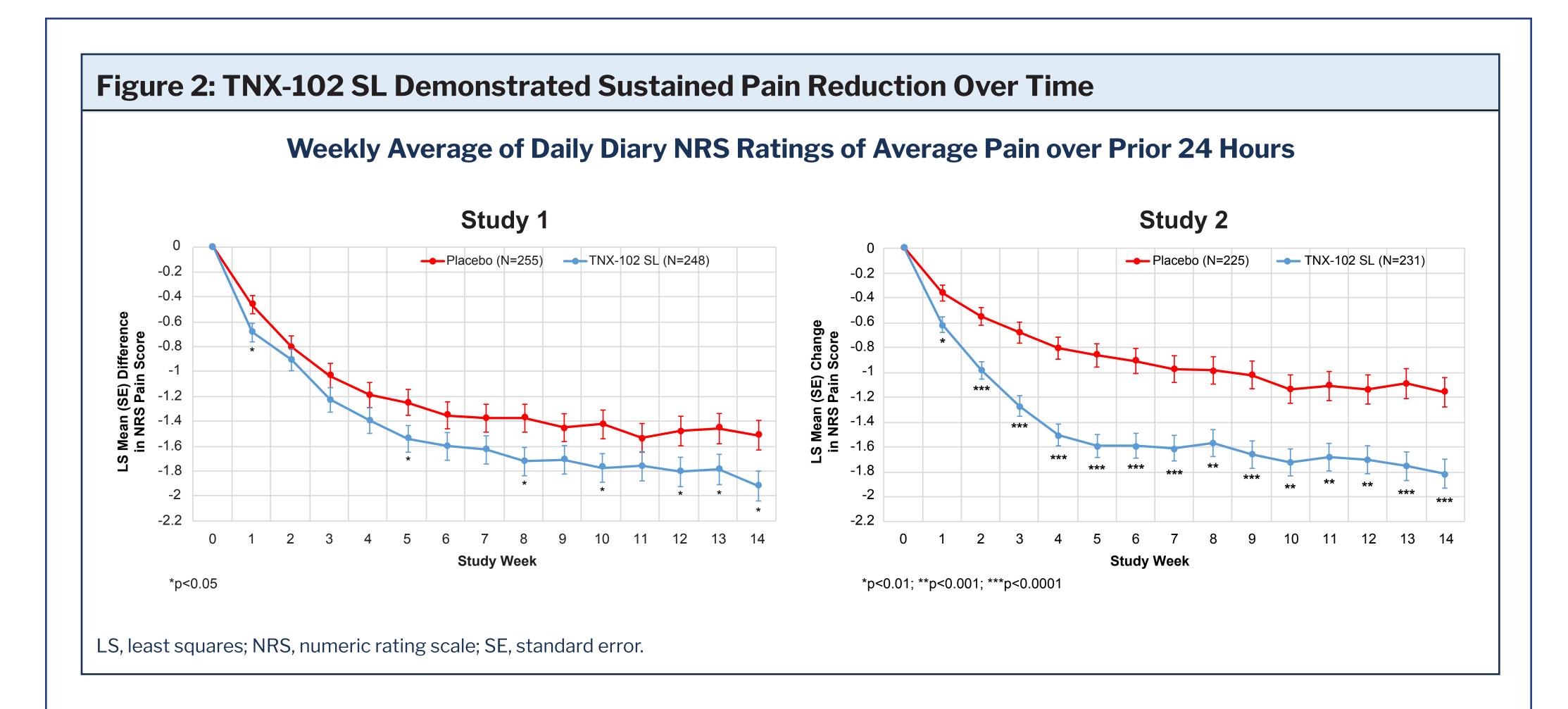
- Two pivotal 14-week, randomized, double-blind, placebo-controlled studies were conducted in subjects with FM: RELIEF⁵ (Study 1) and RESILIENT⁶ (Study 2)
- Both studies randomized subjects 1:1 to receive TNX-102 SL 2.8 mg for 2 weeks followed by 5.6 mg for 12 weeks or matching placebo for 14 weeks
- The primary endpoint was change from baseline to Week 14 in weekly average
 of daily self-reported average pain numeric rating scale (NRS) scores analyzed by
 mixed-model repeated-measures (MMRM) analysis, with multiple imputation (MI) for
 missing data
- To assess clinically meaningful improvements in pain, 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

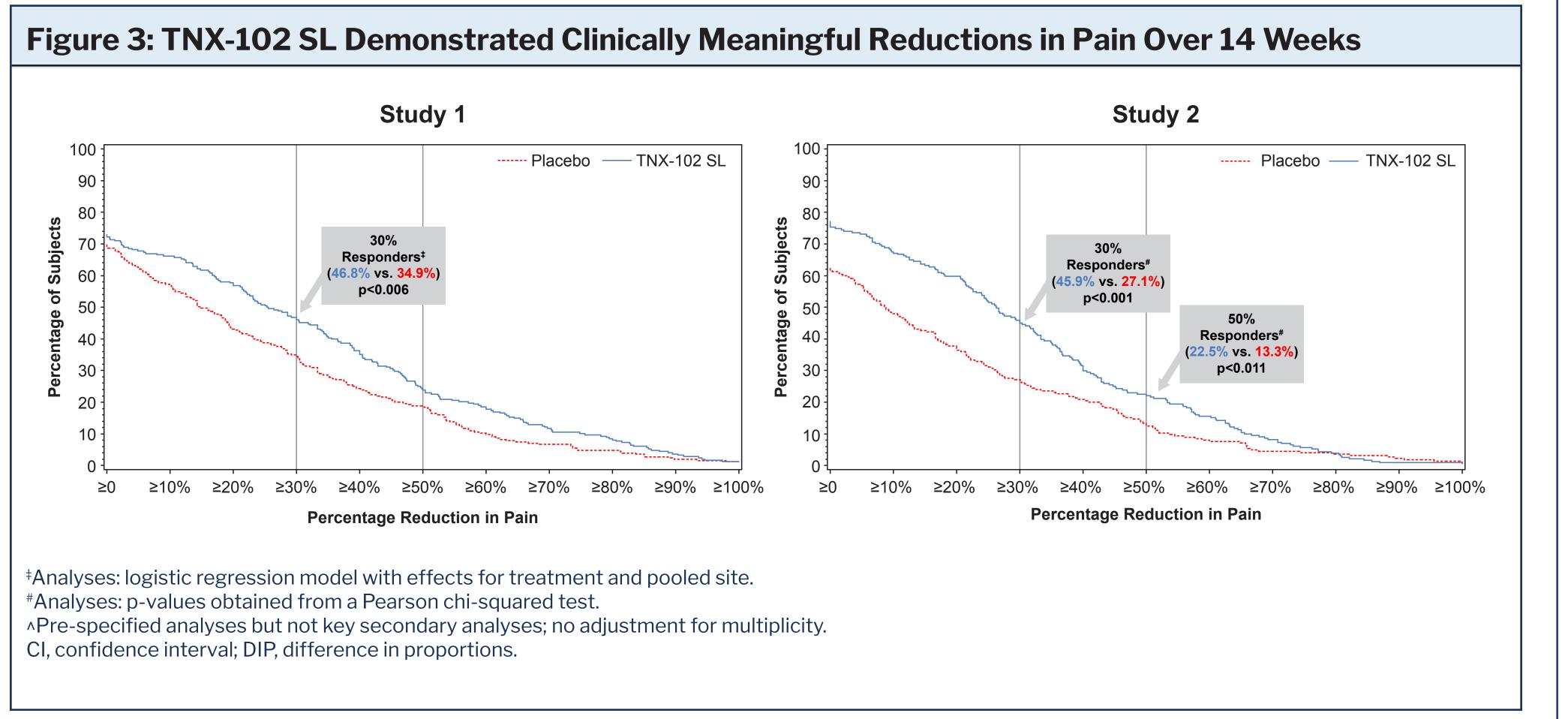
RESULTS

Table 1: Mean Change from Baseline in Weekly Average of Daily 24-Hour Recall Pain Intensity Scores - MMRM with MI 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 |

CFB, change from baseline; LSM, least-squares mean; SD, standard deviation; SE, standard error.





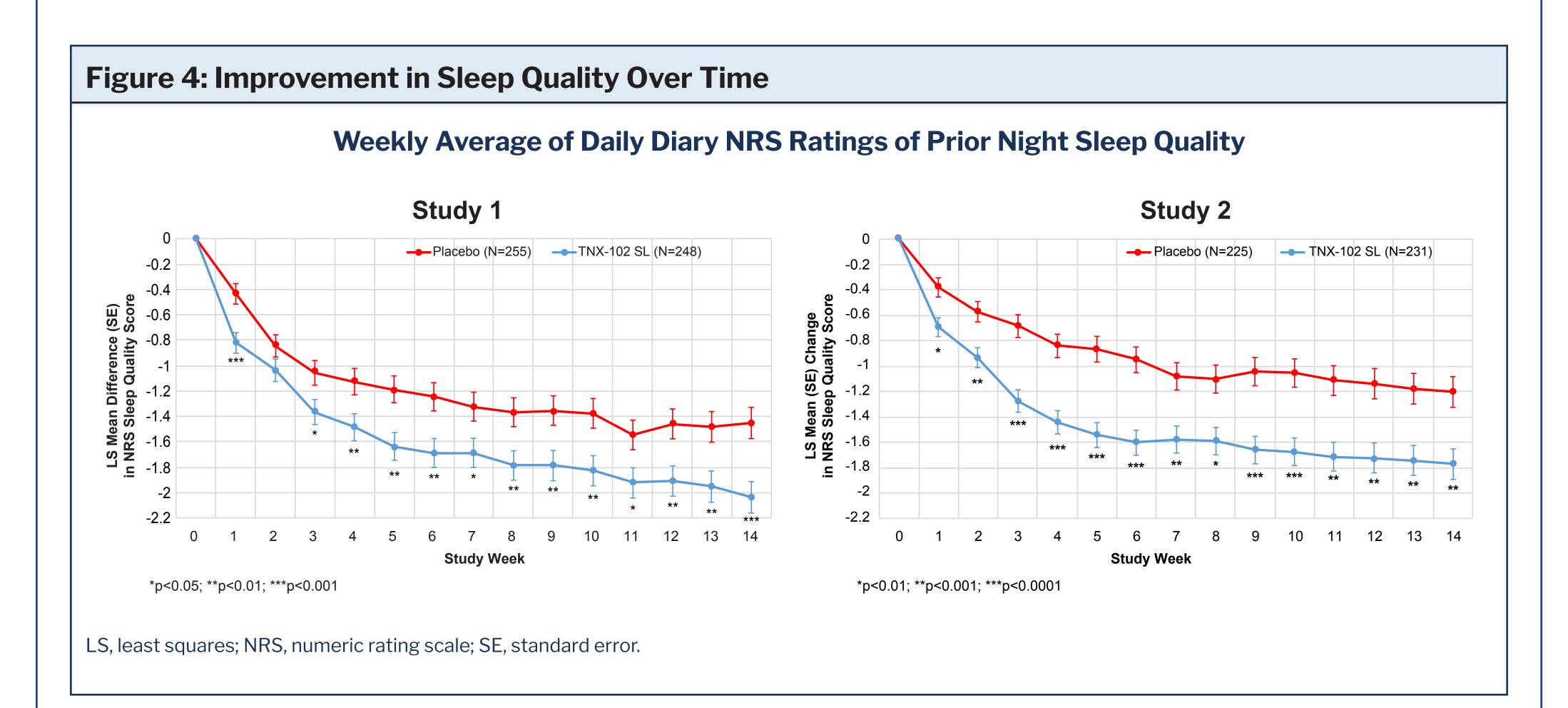


Table 2: Treatment-Emergent Adverse Events (TEAEs) Occurring at a Rate ≥3% in Either Treatment Group (Studies 1 and 2)

| | Placebo N=481 | TNX-102 SL N=479 | | |
|-----------------------------------|------------------|---------------------|--|--|
| Oral Cavity Adverse Events, n (%) | | | | |
| 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, n (%) | | | | |
| Fatigue | 9 (1.9%) | 15 (3.1%) | | |

CONCLUSIONS

- FM is the prototypic nociplastic syndrome and chronic overlapping pain condition 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 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, which were typically transient, self-limited, not 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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Disclosures

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

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