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TNX-102 SL (Sublingual Cyclobenzaprine) for the Treatment of Fibromyalgia in the RELIEF Study

Positive Results of a Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Efficacy and Safety Trial

Gregory Sullivan MD

Tonix Pharmaceutical Inc

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Disclosures

- Presenting author Gregory Sullivan MD is an officer of Tonix Pharmaceuticals Inc (Tonix)
- Dr. Sullivan holds stock and stock options in Tonix
- Tonix owns composition of matter and use patents for the investigational product in the RELIEF trial and its use for the fibromyalgia indication
- TNX-102 SL (sublingual cyclobenzaprine) is an investigational new drug that is not approved for any indication

Evidence-Based Medicine (EBM) or Key References

- Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. J Rheumatol. 2011 Dec;38(12):2653-63. doi: 10.3899/jrheum.110194. Epub 2011 Sep 1. PMID: 21885490.

- Choy EH. The role of sleep in pain and fibromyalgia. Nat Rev Rheumatol. 2015 Sep;11(9):513-20. doi: 10.1038/nrrheum.2015.56. Epub 2015 Apr 28. PMID: 25907704.

- Sullivan GM, Gendreau RM, Gendreau J, Peters P, Peters A, Engels J, Daugherty BL, Vaughn B, Weathers FW, Lederman S. Randomized clinical trial of bedtime sublingual cyclobenzaprine (TNX-102 SL) in military-related PTSD and the role of sleep quality in treatment response. Psychiatry Res. 2021 Jul;301:113974. doi: 10.1016/j.psychres.2021.113974. Epub 2021 Apr 30. PMID: 33979763.

Trial TNX-CY-F304 ('RELIEF' Study)

- General Study Design: Phase 3, Randomized, Multicenter (39), Parallel Group, Double-Blind, Placebo-Controlled 14 Week Study
- Objectives: To evaluate efficacy and safety of bedtime TNX-102 SL in fibromyalgia (FM)
- Investigational Product (IP): TNX-102 SL (sublingual cyclobenzaprine) is a tricyclic drug that potently binds and antagonizes: hydroxytryptamine-2A, α1-adrenergic, H1-histaminergic, and M1-muscarinic acetylcholine receptors
- Study Visits: Screening, Baseline, and four treatment (Weeks 2, 6, 10 & 14/ET) visits
- IP Dosage: first 2 weeks on 1 tablet (TNX-102 SL 2.8 mg); at Week 2 visit the dose is increased to 2 tablets providing 5.6 mg of TNX-102 SL at bedtime for 12 weeks
- Patient Population: diagnosis of primary FM as defined by 2016 Revision to the 2010/2011 FM diagnostic criteria (ACR Preliminary Diagnostic Criteria)
- Exclusionary Medications: duloxetine, milnacipran, pregabalin, gabapentin, tramadol, tapentadol, muscle relaxants, tricyclic antidepressants, MAOIs, trazodone, narcotics/opioids, naltrexone, benzodiazepines, anticonvulsants (exception for migraine), sodium oxybate, ketamine, CGRP/CGRP-R meds, and all other cyclobenzaprine

Demographics

Variable	Placebo N=255	TNX-102 SL N=248	Total N=503
Age, years (mean, SD)	49.3 (10.2)	50.0 (9.4)	49.6 (9.8)
Sex, female	247 (96.9%)	232 (93.5%)	479 (95.2%)
Ethnicity, Hispanic/Latino	42 (16.5%)	43 (17.3%)	85 (16.9%)
Race			
White or Caucasian	216 (84.7%)	222 (89.5%)	438 (87.1%)
Black or African American	20 (7.8%)	19 (7.7%)	39 (7.8%)
All Other	19 (7.5%)	7 (2.8%)	26 (5.9%)
BMI (kg/m^2)	31.6 (6.3)	32.4 (6.6)	32.0 (6.4)
Education, some college or greater	212 (83.1%)	205 (82.7%)	417 (82.9%)
Employed, currently	158 (62.0%)	182 (73.4%)	340 (67.6%)
Unable to work due to fibromyalgia	15 (5.9%)	16 (6.5%)	31 (6.2%)
Duration of fibromyalgia, years	9.0 (8.1)	9.2 (8.4)	9.1 (8.2)

Primary Efficacy Endpoint Analysis

Endpoint: change from baseline to Week 14 endpoint in diary NRS weekly average of daily self-reported average pain severity

Visit Statistic	Placebo (N = 255) Value	Placebo (N = 255) Change from Baseline	TNX-102 SL (N = 248) Value	TNX-102 SL (N = 248) Change from Baseline
Baseline				
Mean (SD)	**6.0 (1.08)**		**6.1 (1.06)**	
Week 14				
LS mean (SE) [1]	4.6 (0.12)	**-1.5 (0.12)**	4.2 (0.12)	**-1.9 (0.12)**
95% CI [1]	(4.3, 4.8)	(-1.7, -1.3)	(3.9, 4.4)	(-2.1, -1.7)
Difference in LS mean (SE)				**-0.4 (0.16)**
95% CI for difference in LS mean				(-0.7, -0.1)
p-value for difference				**0.010**

* p <0.0452, adjusted p-value necessary for significance due to alpha-spend from an interim analysis; for Week 14 results, Cui, Hung, & Wang methodology used to combine p-values for interim and post-interim subjects

[1] Least squares means, differences, and CIs were based on an MMRM with fixed, categorical effects of treatment, center, study week, and treatment-by-study week interaction, as well as the fixed covariates of baseline value and baseline value-by-study week interaction. Missing values for Week 14 were imputed with multiple imputation, accounting for the reasons for study discontinuation (if due to adverse events or lack of efficacy, considered missing not-at-random. Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed model repeated measures; SD = standard deviation; SE = standard error

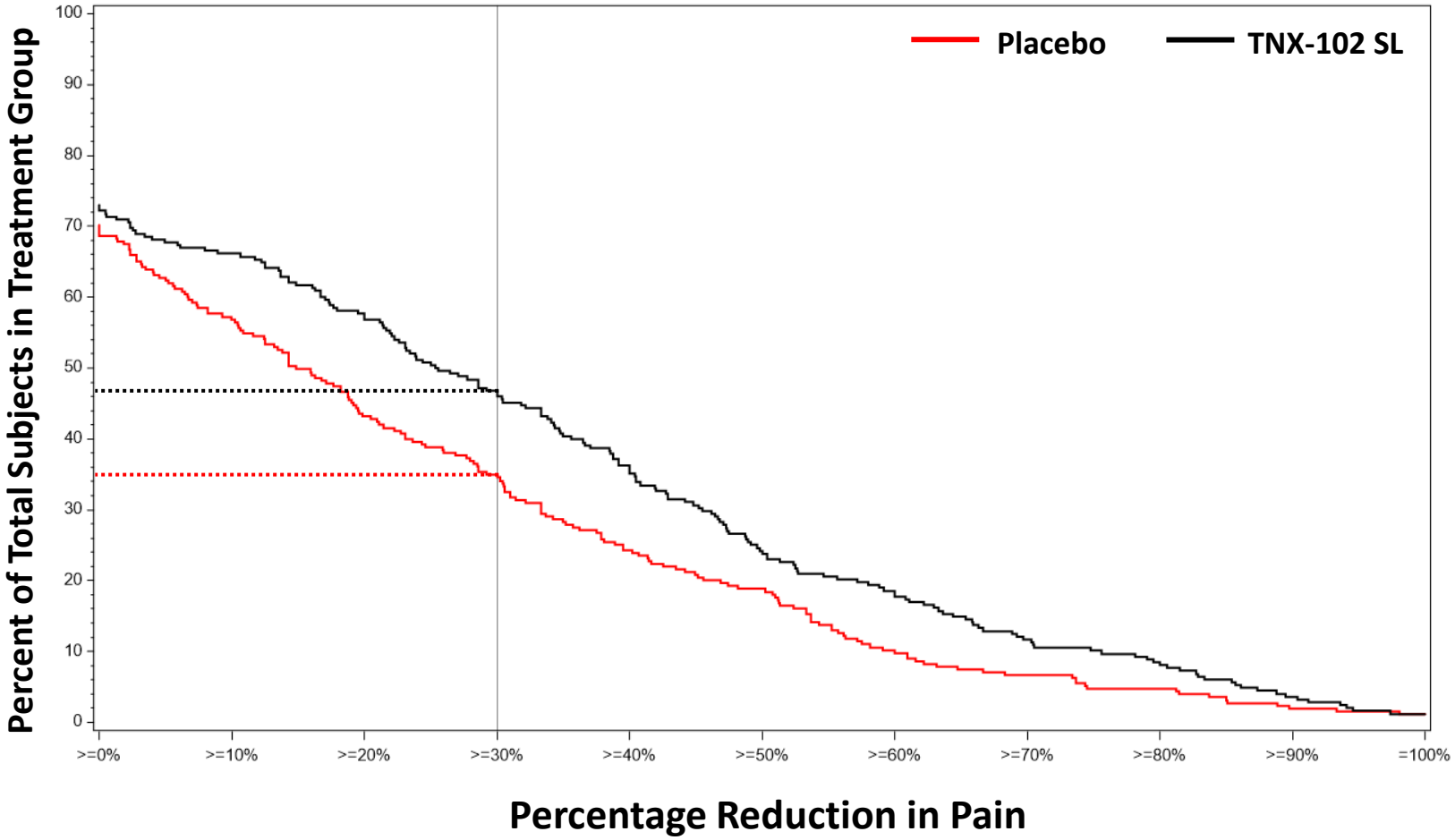
Responder Rates

Continuous Responder Graph shows a selected percent pain reduction rate (x-axis) for responder status versus percent of responders in each treatment group (y-axis)

<u>For a ≥30% Pain Reduction Responder Analysis:</u>

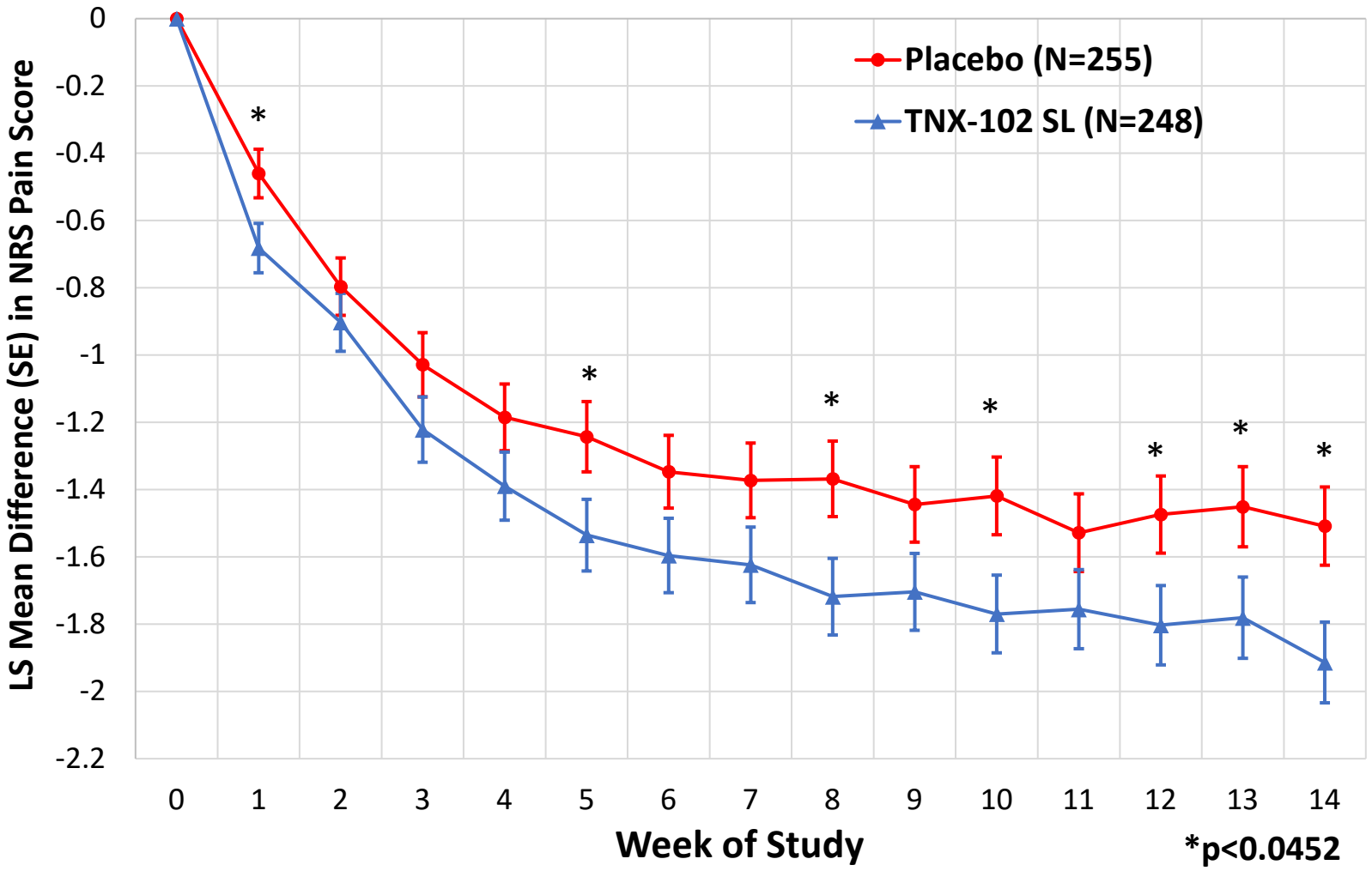
- Choose ≥30% on x-axis
- On y-axis find
  - TNX-102 SL at 46.8%
  - Placebo at 34.9%
  - Logistic Regression Odds Ratio (95% CI) of **1.67 (1.16, 2.40), p=0.006**

Continuous Responder Graph
RELIEF STUDY



Pain Reduction by Daily Diary Across 14 Weeks of Study

- Note: in addition to statistically significant pain reduction at Week 14, TNX-102 SL separated from Placebo at Weeks 1, 5, 8, 10, 12, & 13; all p<0.0452



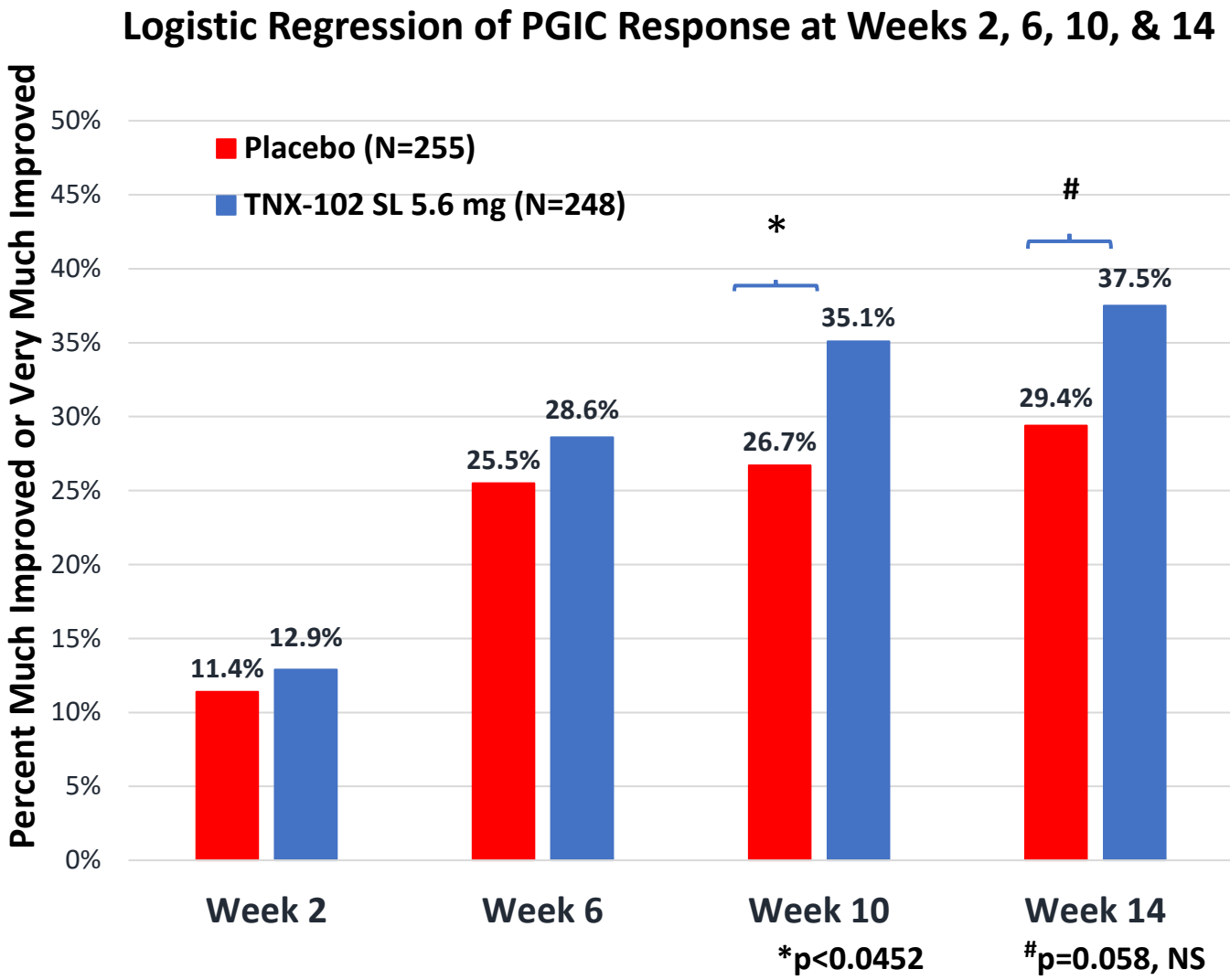
Key Secondary Efficacy Endpoint Analyses

- Sequential test procedure to adjust for multiplicity applied to primary and key secondary endpoints; hierarchy of key secondaries:
  - **PGIC**, responder analysis, proportion with '2' or '1' at Week 14
  - **FIQR Symptoms** domain, change from baseline at Week 14
  - **FIQR Function** domain, change from baseline at Week 14
  - **PROMIS Sleep Disturbance** (8a), change from baseline at Week 14
  - **PROMIS Fatigue** (8a), change from baseline at Week 14
  - **Sleep Quality** by daily diary, change from baseline at Week 14

FIQR = Fibromyalgia Impact Questionnaire – Revised; PGIC = Patient Global Impression of Change ('2' = much improved; '1' = very much improved); PROMIS = Patient-Reported Outcomes Measurement Information System

Patient Global Impression of Change

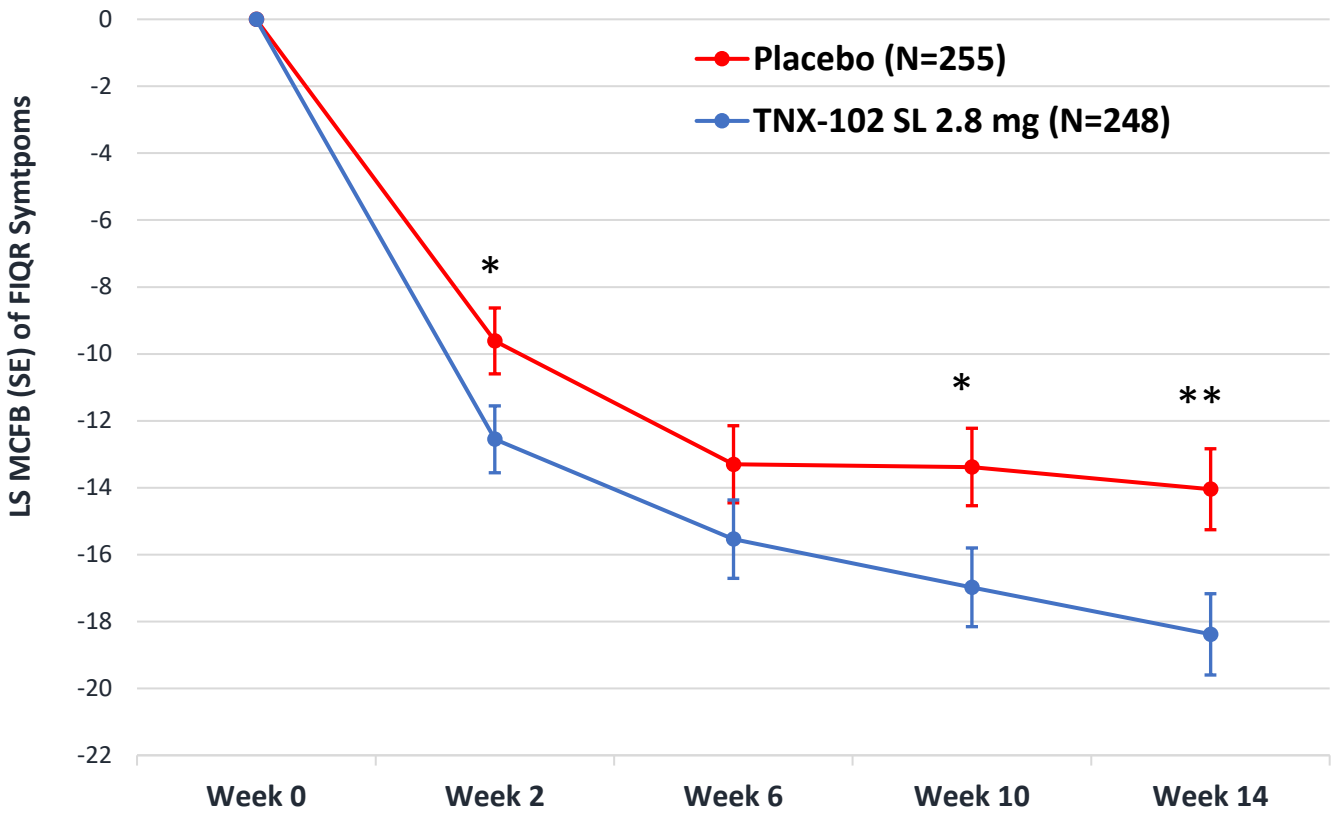
- At Week 14, greater proportion of responders to TNX-102 SL, at 37.5% versus Placebo, at 29.4%; however, did not achieve statistical significance
- Remaining secondary endpoints in hierarchy automatically considered non-significant regardless of the p-value
- Note: Week 10 separated at p<0.0452



FIQR Symptoms Domain

- On Fibromyalgia Impact Questionnaire – Revised Symptoms Domain at Week 14 TNX-102 SL separated from placebo by -4.3 (1.6) units, p=0.007
- Note: Week 2 p=0.020 and Week 10 p=0.019

FIQR Symptoms Domain MCFB at Weeks 2,6,10, & 14



*p<0.0452; **p<0.01

Fibromyalgia Impact Questionnaire – Revised: Symptoms & Impact Items

- **Broad range** of FM symptoms and both global impact items demonstrated TNX-102 SL separated from placebo at $p<0.0452$
- Only level of anxiety and balance problems were $p>0.0452$
- **Syndromal coverage** of core FM symptoms:
  - widespread pain
  - fatigue/low energy
  - sleep disturbance
  - mood disturbance
  - memory problems
  - sensory sensitivity

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Week 14 FIQR Please rate your…(last 7 days)	TNX-102 SL LS MCFB (SE)	Placebo LS MCFB (SE)	Difference in LS Means (SE)	p-value
Level of Pain	-2.3 (0.15)	-1.9 (0.15)	-0.5 (0.20)	0.014*
Level of Energy	-2.1 (0.16)	-1.3 (0.16)	-0.7 (0.22)	<0.001***
Level of Stiffness	-2.4 (0.17)	-1.8 (0.17)	-0.6 (0.23)	0.009**
Quality of Sleep	-3.1 (0.20)	-2.1 (0.20)	-0.9 (0.26)	<0.001***
Level of Depression	-1.1 (0.14)	-0.4 (0.13)	-0.7 (0.18)	<0.001***
Level of Memory Problems	-1.6 (0.16)	-1.0 (0.16)	-0.6 (0.21)	0.004**
Level of Anxiety	-1.2 (0.16)	-0.9 (0.16)	-0.4 (0.22)	0.084
Level of Tenderness to Touch	-2.4 (0.19)	-1.8 (0.19)	-0.6 (0.25)	0.017*
Level of Balance Problems	-1.4 (0.15)	-1.1 (0.15)	-0.3 (0.19)	0.149
Level of (Sensory) Sensitivity^	-2.4 (0.18)	-1.8 (0.18)	-0.5 (0.23)	0.021*
FM over the last 7 days…				
Prevented Accomplishing Goals	-2.6 (0.18)	-1.9 (0.18)	-0.7 (0.24)	0.003**
Completely Overwhelmed Me	-2.1 (0.18)	-1.5 (0.18)	-0.7 (0.24)	0.005**

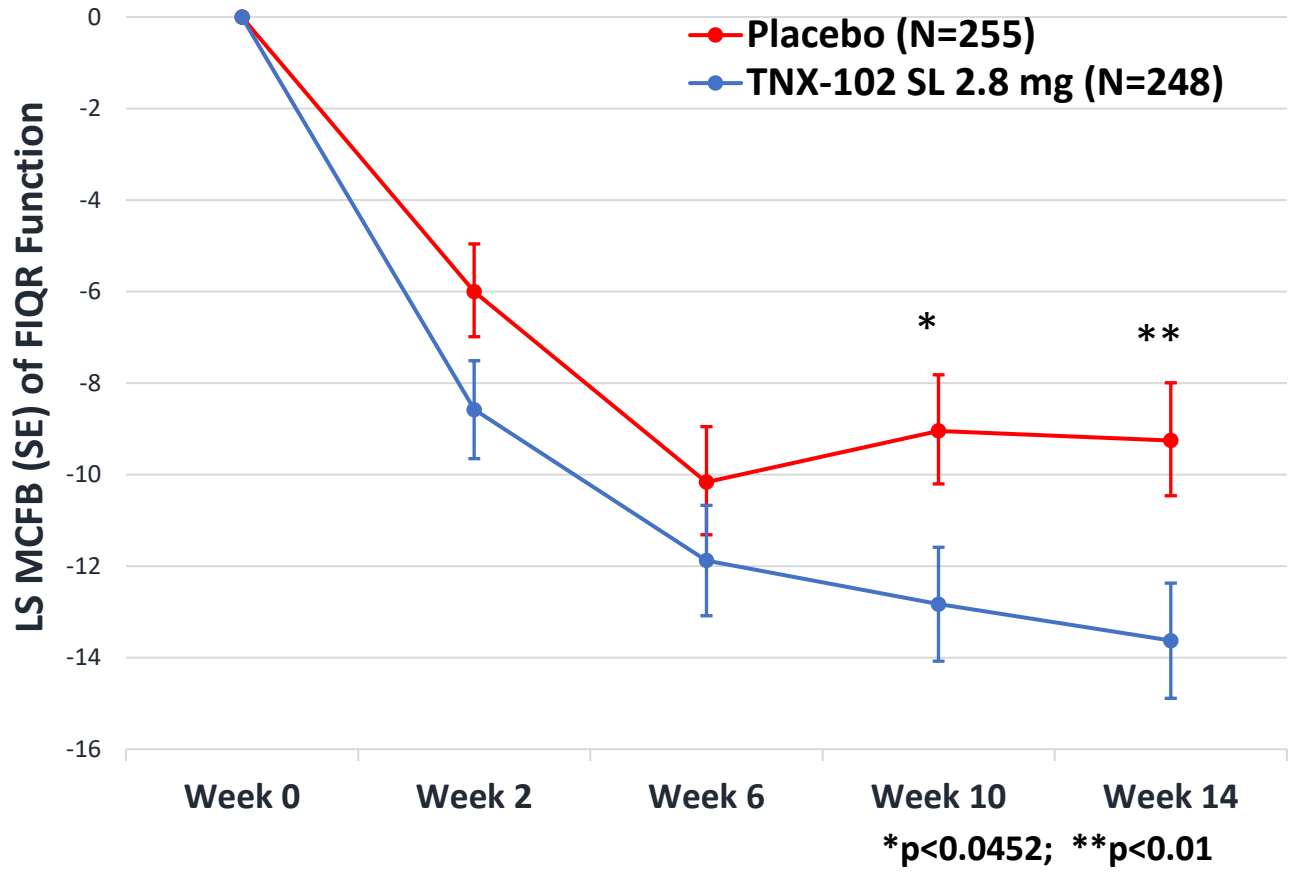
^to loud noises, bright lights, odors, and cold *p<0.0452; **p<0.01; ***p<0.001

Abbreviations: FIQR = Fibromyalgia Impact Questionnaire – Revised; FM = fibromyalgia; LS = least squares; MCFB = mean change from baseline; p = probability; SE = standard error

FIQR Function Domain

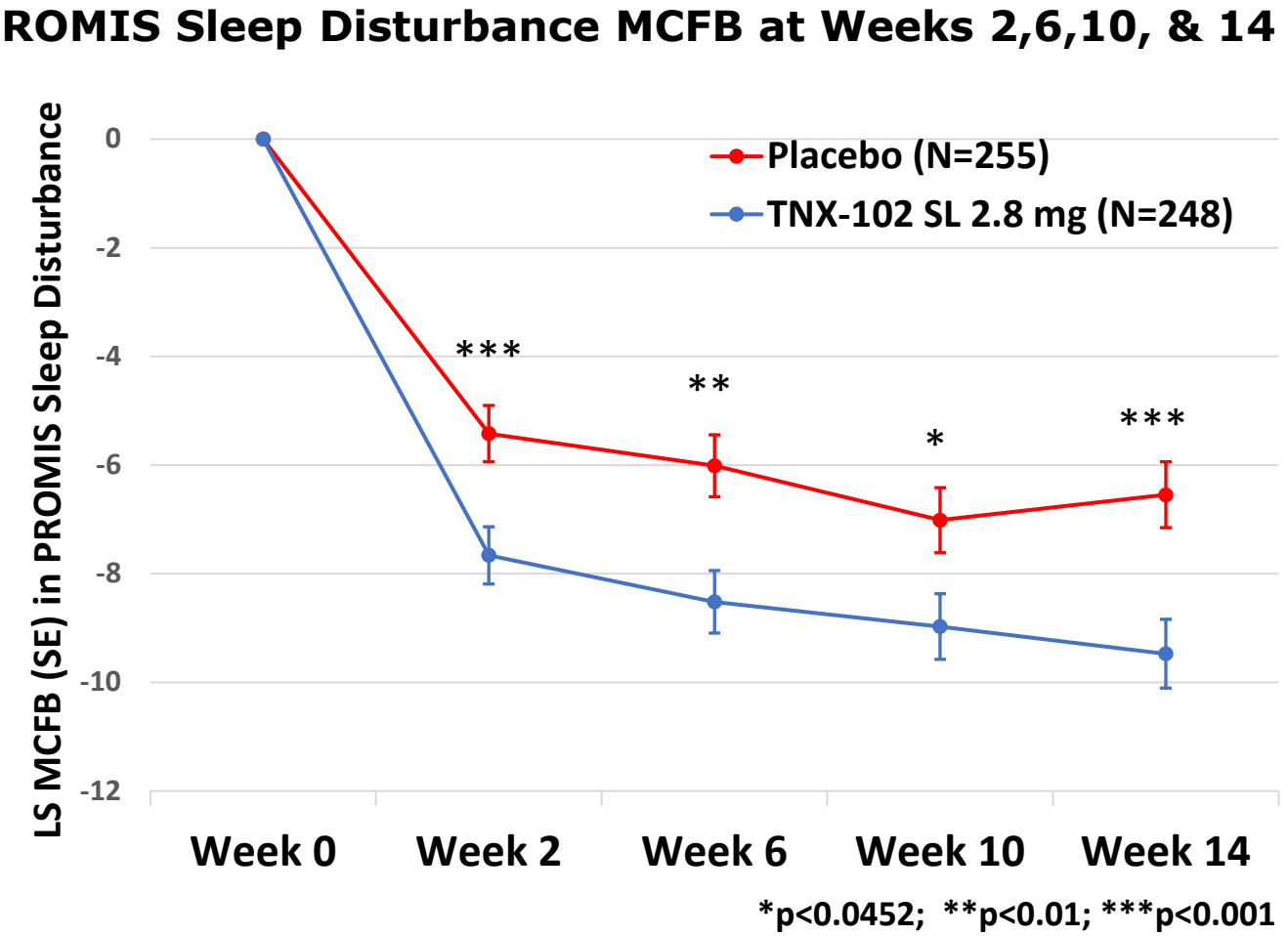
- On Fibromyalgia Impact Questionnaire – Revised Function Domain at Week 14 TNX-102 SL separated from Placebo by -4.4 (1.7) units, p=0.009
- Note: Week 10 p=0.016
- Slope remains downward after Week 6 for active but not for Placebo

FIQR Function Domain MCFB at Weeks 2,6,10, & 14



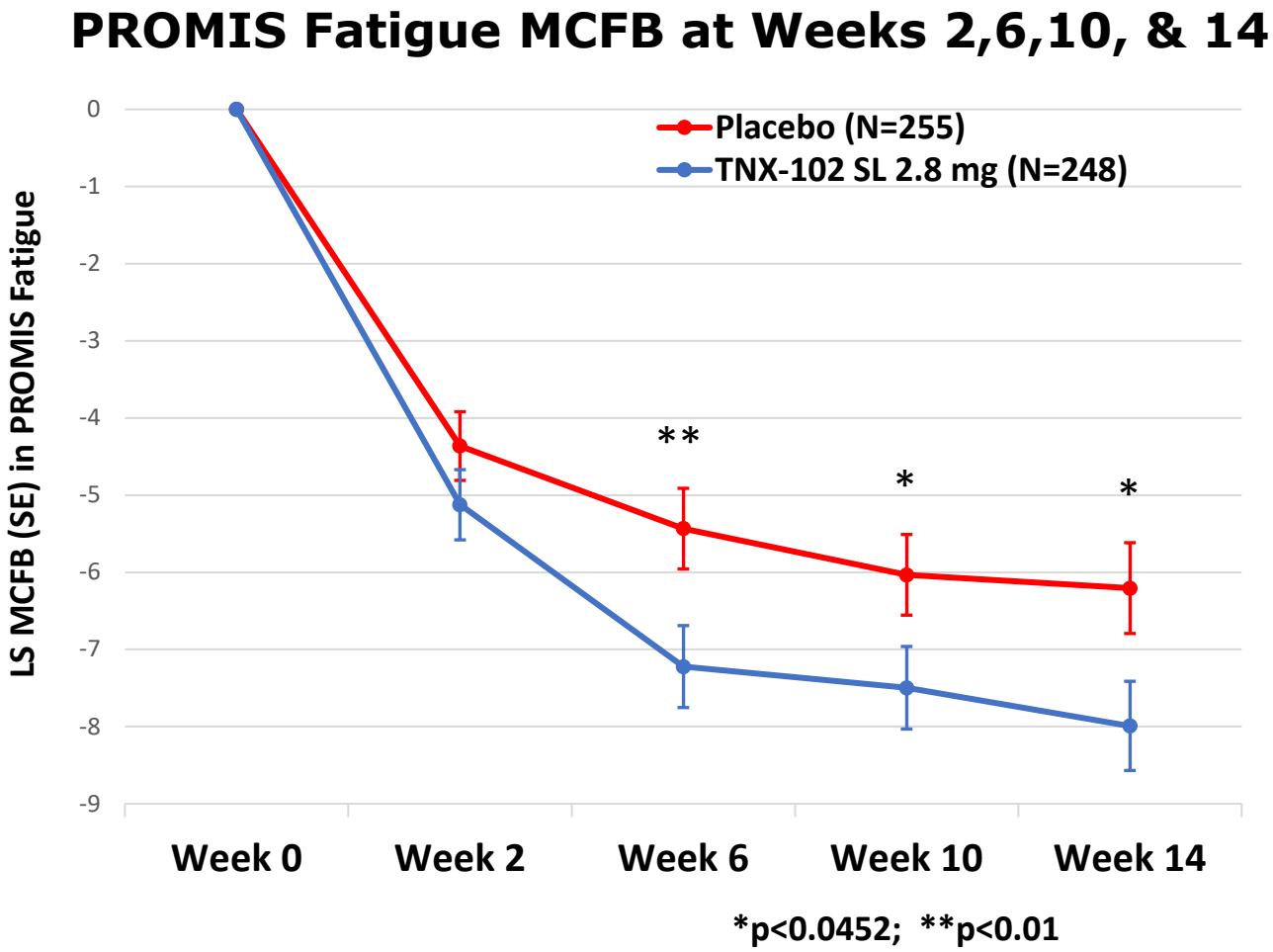
PROMIS Sleep Disturbance Instrument

- On PROMIS Sleep Disturbance instrument T-scores at Week 14 TNX-102 SL separated from placebo by -2.9 (0.82) units, p<0.001
- Note: Week 2 p<0.001, Week 6 p=0.001, Week 10 p=0.014



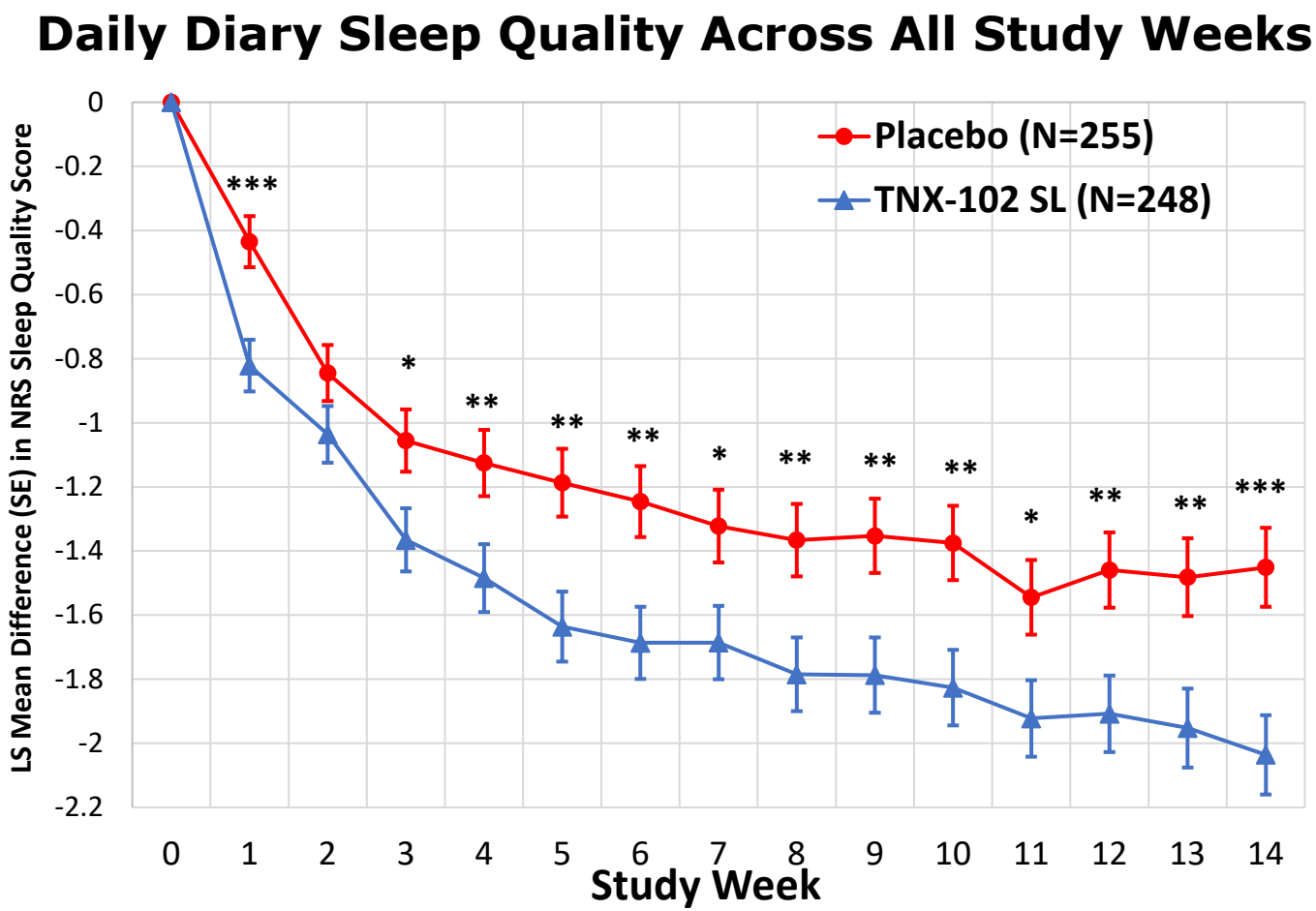
PROMIS Fatigue Instrument

- On PROMIS Fatigue instrument T-scores at Week 14 TNX-102 SL separated from placebo by -1.8 (0.76) units, p=0.018
- Note: Week 6 p=0.008, Week 10 p=0.032



Sleep Quality by Daily Diary

- Sleep Quality by weekly averages of daily diary NRS scores at Week 14 separated for TNX-102 SL from placebo by -0.6 (0.17) units, p<0.001
- All weeks except Week 2 were p<0.0452



*p<0.0452; **p<0.01; ***p<0.001

Safety

Exposure

Mean (SD) treatment duration (days): TNX-102 SL 88.9 (26.2); Placebo 88.7 (24.9)
Mean (SD) study days drug taken: TNX-102 SL 77.1 (25.2); Placebo 75.9 (23.6)

Treatment-Emergent Adverse Events (TEAEs) Rated as Severe

TNX-102 SL 4.4% of all TEAEs in group; Placebo 3.5% of all TEAEs in group

Incidence of Oral TEAEs

TNX-102 SL 40.7%; Placebo 9.0%

Discontinued Study Drug Due to TEAE

TNX-102 SL 8.9%; Placebo 3.9%

Serious Adverse Effects

TNX-102 SL 2 SAEs; Placebo 5 SAEs; none deemed related to study drug

Completion rates

TNX-102 SL 83.5%; Placebo 82.3%

Treatment Emergent Adverse Events (TEAEs)

All TEAEs at a rate of ≥ 3% in the TNX-102 SL group

	TNX-102 SL	Placebo	Total
Oral Cavity Adverse Events			
Hypoaesthesia oral	43 (17.3%)	1 (0.4%)	44 (8.7%)
Paraesthesia oral	14 (5.6%)	1 (0.4%)	15 (3.0%)
Dysgeusia	13 (5.2%)	1 (0.4%)	14 (2.8%)
Glossodynia	9 (3.6%)	2 (0.8%)	11 (2.2%)
Dry mouth	8 (3.2%)	7 (2.7%)	15 (3.0%)
Systemic Adverse Events			
Sedation	9 (3.6%)	1 (0.4%)	10 (2.0%)
Fatigue	9 (3.6%)	4 (1.6%)	13 (2.6%)

Conclusions

- TNX-102 SL reduced pain in fibromyalgia significantly more than Placebo (p=0.010) over 14 weeks of treatment
- 30% pain responder analysis demonstrated greater responders with TNX-102 SL at 46.8% than with Placebo at 34.9% (p=0.006)
- TNX-102 SL had broad syndromal effects across core fibromyalgia symptoms of widespread pain, fatigue, sleep disturbance, memory disturbance, mood disturbance, and sensory sensitivity
- Most common adverse event from active treatment is oral hypoaesthesia, a sensory administration site reaction that is typically transient, never rated as severe, and lead to only 1 discontinuation
- TNX-102 SL was very well tolerated, with the two highest rates of systemic adverse events, sedation and fatigue, both at 3.6%
- Only 16.5% of TNX-102 SL group discontinued early (17.7% on Placebo)

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[1]Tonix Pharmaceuticals, Inc., New York, NY,
[2]Gendreau Consulting LLC, Poway, CA
[3]Rho, Inc, Chapel Hill, NC

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