



TNX-102 SL (sublingual cyclobenzaprine) for Fibromyalgia

**MHSRS Presentation for Breakout Session:
“Assuaging Agony: Novel Pain Therapeutics”**

NASDAQ: TNXP



Cautionary Note on Forward-Looking Statements

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are “forward-looking statements” as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate” and “intend,” among others. These forward-looking statements are based on Tonix’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the “SEC”) on April 1, 2024, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

Disclosure

Title: Efficacy and Safety of Bedtime TNX-102 SL (Sublingual Cyclobenzaprine HCl) for the Management of Fibromyalgia: Results from the Confirmatory Phase 3 Randomized, Double-Blind, Placebo-Controlled RESILIENT Trial

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TNX-102 SL has not been approved for any indication.

Co-authors Seth Lederman, Mary Kelley, Jean Engels and Greg Sullivan are employees of Tonix Pharmaceuticals, Inc. and own stock and/or stock options in the company. Ben Vaughn is an employee of Rho, Inc.



About Fibromyalgia

Fibromyalgia is a **chronic pain disorder** resulting from amplified sensory and pain signaling within the CNS¹

Fibromyalgia is a **syndrome** comprised of the **symptoms**: chronic widespread pain, **nonrestorative sleep**, and fatigue



Multisite
pain



Non-Restorative Sleep

Fatigue



Fibromyalgia is considered a chronic overlapping pain condition (COPC)
- the **only COPC** with any **FDA-approved drugs**³

Fibromyalgia is the prototypic nociplastic syndrome

¹American Chronic Pain Association (www.theacpa.org, 2019)

³CFS/ME = chronic fatigue syndrome/myalgic encephalomyelitis

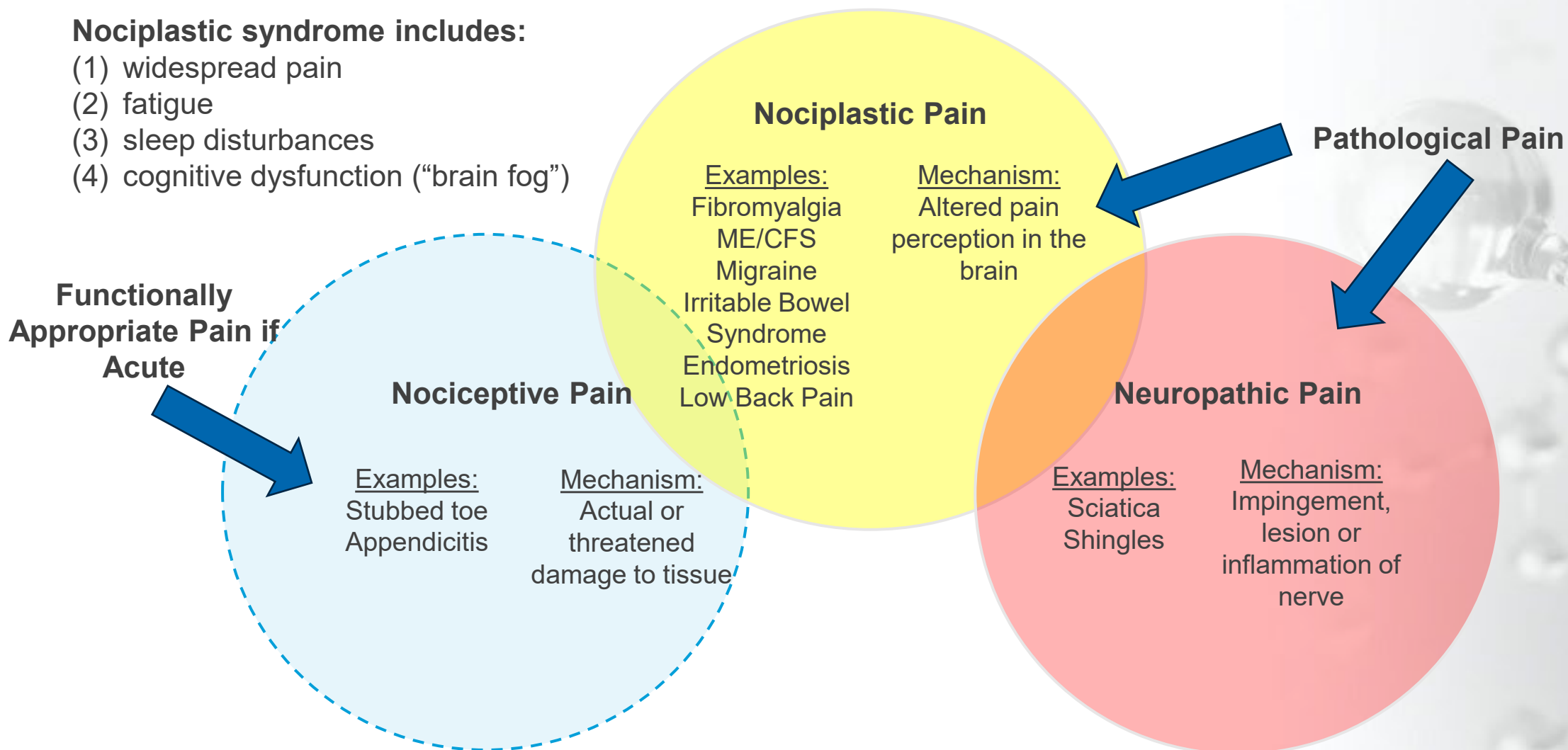
³The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)



The Third Primary Type of Pain: Nociplastic Pain¹⁻⁴

Nociplastic syndrome includes:

- (1) widespread pain
- (2) fatigue
- (3) sleep disturbances
- (4) cognitive dysfunction (“brain fog”)



¹Trouvin AP, et al. *Best Pract Res Clin Rheumatol*. 2019;33(3):101415.

²Fitzcharles MA, et al. *Lancet* 2021;397:2098-110

³Kaplan CM, et al. *Nat Rev Neurol*. 2024 20(6):347-363..

⁴Clauw DJ. *Ann Rheum Dis*. 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.



Fibromyalgia is a Large, Underserved and Dissatisfied Population

- **~10 million U.S. adults are affected – predominantly women^{1,2}**
 - Debilitating and life altering condition
 - Significant economic impact
- **Patients are dissatisfied, despite three FDA approved drugs^{3,4}**
 - 85% of patients fail first-line therapy⁵: efficacy variability, tolerability issues especially when used long-term and lack of broad-spectrum activity
 - Typical for patients to rotate between drugs and be on multiple drugs at the same time; 79% of FM patients are on multiple therapies⁵
- **~2.7 million FM patients diagnosed and treated⁶**
 - >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year^{7,8}
- **No new Rx product since 2009**
- *The treatment objective is to **restore functionality and quality of life** by broadly improving symptoms while avoiding significant side effects*

¹American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)

²Vincent A, et al. *Arthritis Care Res (Hoboken)*. 2013 65(5):786-92. doi: 10.1002; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population

³Robinson RL, et al. *Pain Med*. 2012 13(10):1366-76. doi: 10.1111; 85% received drug treatment

⁴The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)

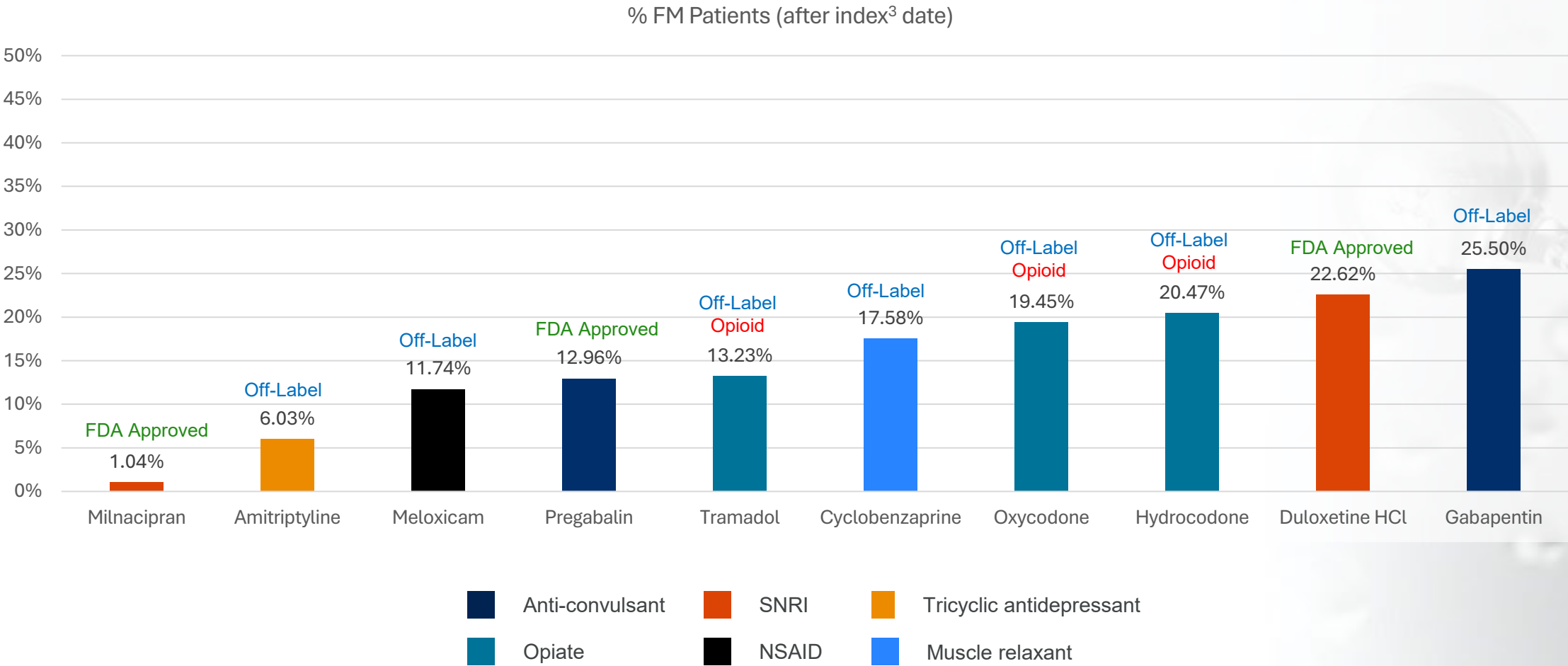
⁵EVERSANA primary physician research, May 2024; commissioned by Tonix

⁶EVERSANA analysis of claims database, May 2024; commissioned by Tonix

⁷Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.

⁸Market research by Frost & Sullivan, commissioned by Tonix, 2011

Many Fibromyalgia Patients are Prescribed Off-Label Drugs; ~53% FM Patients Prescribed Opioids Off-Label^{1,2}

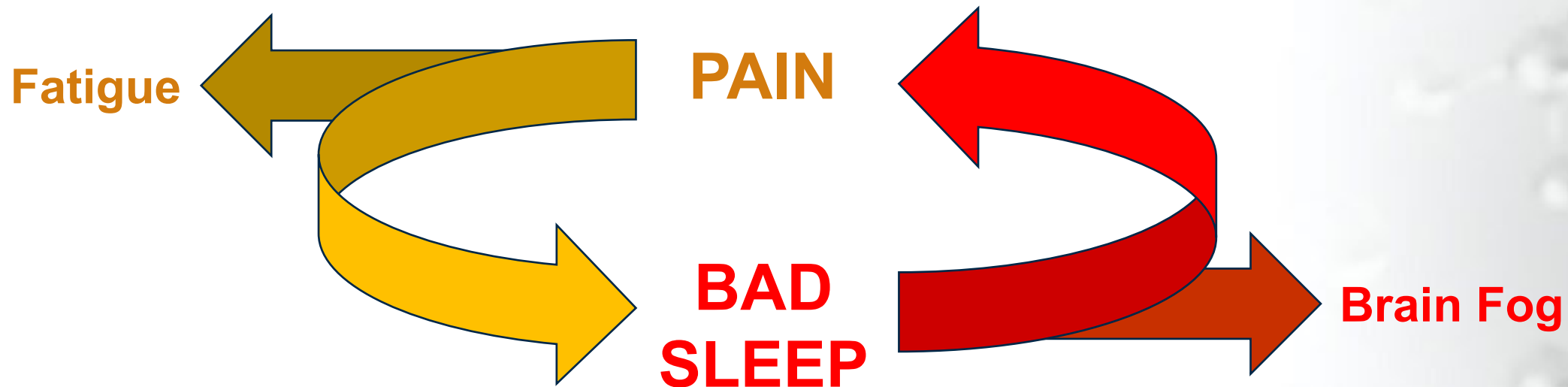


¹ 2022-2023
² EVERSANA analysis of claims database, May 2024; commissioned by Tonix
³ Index date refers to date when ICD10 code was entered into database



Poor Sleep and Pain have Bi-directional Reinforcing Effects¹

- Poor sleep and pain form a vicious cycle in driving fibromyalgia decompensation
 - Can't sleep → worse pain / In pain → can't sleep
 - Poor sleep and pain contribute to persistence, chronicity and severity
 - Syndrome includes symptoms of fatigue and brain fog
- Treating sleep disturbance in fibromyalgia has the potential to break the vicious cycle
 - Potential to remove an obstacle to recovery
 - Using the right medicine is important – some sedative/hypnotics don't work^{1,2}



¹Moldofsky H, et al. *J Rheumatol*. 1996;23:529–533.

²Grönwald M, et al. *Clin Rheumatol*. 1993;12(2):186–191



Fibromyalgia: Unrefreshing Sleep and Cyclobenzaprine Treatment

- **Non-restorative sleep^{1,2}**
 - Harvey Moldofsky – recognition of unrefreshing/non-restorative sleep:
 - Symptom
 - Potential causative or potentiating factor
- **Cyclobenzaprine^{3,9}**
 - Potentially the earliest drug studied in fibromyalgia as an oral swallowed agent
 - Studies showed equivocal effects and tolerability issues at “muscle spasm” doses
- **Bedtime, low-dose cyclobenzaprine targeting non-restorative sleep¹⁰⁻¹¹**
 - Recognition of unrefreshing sleep as a target of therapy
 - Primitive oral, swallowed formulation – “flat” pharmacokinetics
- **Bedtime, sublingual transmucosal cyclobenzaprine targeting non-restorative sleep¹²**
 - Dynamic pharmacokinetic profile, rapid absorption, decrease in major metabolite
 - Two studies (Phase 2 and Phase 3) at 2.8 mg; three Phase 3 studies at 5.6 mg.

¹Moldofsky H et al. *Psychosom Med*. 1975. 37:341-51.

²Moldofsky H and Scarisbrick P. *Psychosom Med*. 1976. 38:35-44.

³Bennett RM, et al. *Arthritis Rheum* 1988. 31:1535-42.

⁴Quimby LG, et al. *J Rheumatol Suppl*, 1989 Nov;19:140-3.

⁵Reynolds WJ, et al. *J Rheumatol*. 1991.18:452-4.

⁶Santandrea S, et al. *J Int Med Res*. 1993.21:74-80.

⁷Cantini F, et al. *Minerva Med*. 1994. 85:97-100.

⁸Carette S, et al. *Arthritis Rheum*. 1994. 37:32-40.

⁹Tofferi JK, et al. *Arthritis Rheum*. 2004. 51:9-13.1

¹⁰Iglehart IW. 2003; US Patent 6,541,523.

¹¹Moldofsky et al. *J Rheumatol*. 2011. 38:2653-2663

¹²Lederman S et al. *Arthritis Care Res*. 2023. 75:2359-2368.



Tonmya™ (TNX-102 SL, Cyclobenzaprine HCl Sublingual Tablets)¹

- **Non-opioid analgesic designed for long-term daily bedtime use in fibromyalgia patients**
 - Targets non-restorative sleep
 - Potent binding and antagonist activities at the serotonin-5-HT_{2A}, α ₁-adrenergic, histaminergic-H₁, and muscarinic-M₁ receptors
 - No recognized risk for abuse
- **Improves sleep quality, does not increase sleep quantity:**
 - Not a traditional hypnotic or sedative
- **Proprietary, sublingual transmucosal formulation of cyclobenzaprine designed to optimize delivery and absorption**
 - Protectic® formulation based on eutectic composition of matter
 - Rapid absorption
 - Decrease in major metabolite by bypassing first-pass hepatic metabolism

¹Tonmya™ is conditionally accepted by the U.S. Food and Drug Administration (FDA) as the tradename for TNX-102 SL for the management of fibromyalgia. *Tonmya has not been approved for any indication.



Fibromyalgia Program Status

Tonmya™
(TNX-102 SL)
Cyclobenzaprine Protectic®
Sublingual Tablets

Fibromyalgia

**Statistically Significant 2nd Phase 3 Topline Results
Reported 4Q'23**

- **First pivotal Phase 3 study (*RELIEF*) reported – December 2020¹**
- **Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021**
- **Confirmatory pivotal Phase 3 study (*RESILIENT*) reported – December 2023**
- **Pre-NDA meetings with FDA completed with alignment on requirements for filing and potential approval**
- **Granted FDA Fast Track Designation – July 2024**

Next Steps:

- **NDA filing expected 2H'24**
- **FDA decision on NDA approval expected 2025**

¹Lederman S, et al. *Arthritis Care Res (Hoboken)*. 2023 Nov;75(11):2359-2368. doi: 10.1002.

Tonmya™ (TNX-102 SL): Phase 3 *RESILIENT* Study Design



General study characteristics:

- Randomized, double-blind, multicenter, placebo-controlled study in fibromyalgia
- 33 U.S. sites enrolled 457 participants with fibromyalgia as defined by 2016 Revisions to the 2010/2011 FM Diagnostic Criteria¹

Primary Endpoint:

- Change from baseline to Week 14 (TNX-102 SL vs. placebo) in weekly averages of daily diary average pain severity score

TNX-102 SL once-daily at bedtime
5.6 mg (2 x 2.8 mg tablets)*

Placebo once-daily at bedtime

14 weeks

*Two-week run-in at 2.8 mg dose at bedtime
followed by 12 weeks at 5.6 mg dose

ClinicalTrials.gov Identifier: **NCT05273749**

Study Title: A Phase 3 Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily in Patients With Fibromyalgia (RESILIENT)

Trial ID: TNY-CY-F307 ('RESILIENT')

¹Wolfe F, et al. *Semin Arthritis Rheum*. 2016 46(3):319-329. doi: 10.1016



RESILIENT Summary of Primary and Key Secondary Endpoints

Endpoint	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

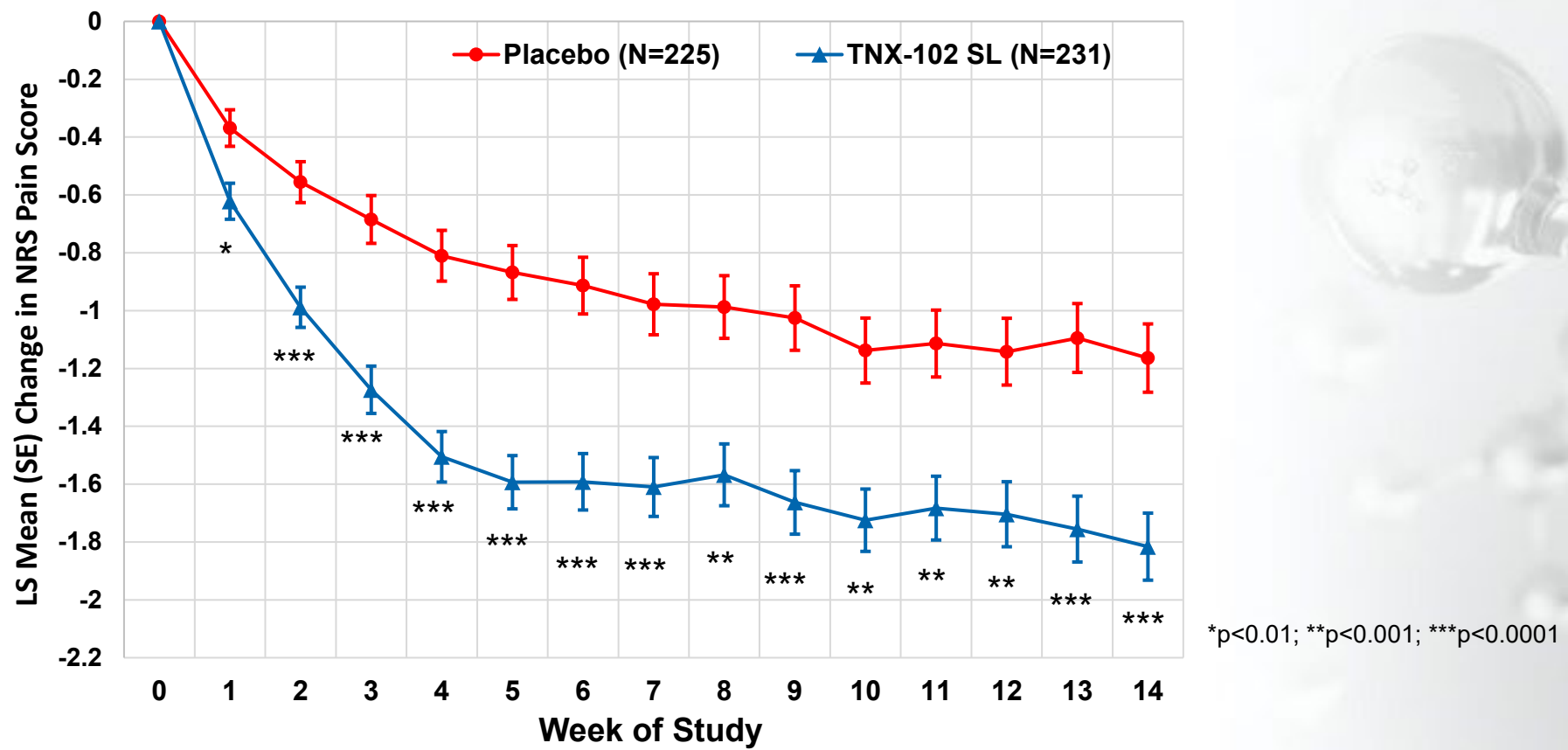
*In order of statistical serial gate-keeping hierarchy (or, “waterfall”) to control overall Type 1 error

**Statistical significance met

RESILIENT Primary Outcome Measure

Reduction in Widespread Pain

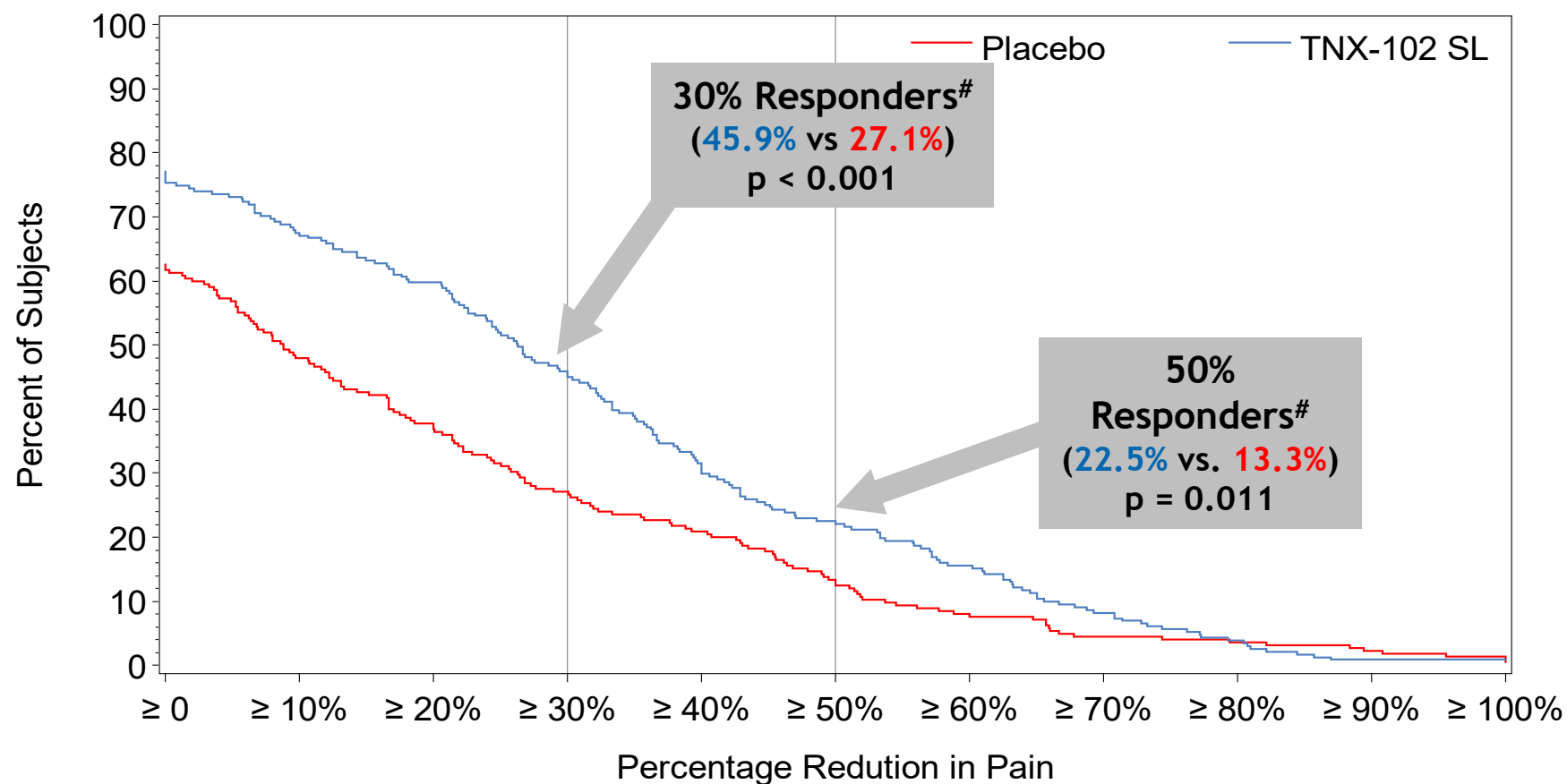
Weekly Average of Daily Diary NRS Ratings of Average Pain Over Prior 24 Hours



Week 14 LS mean (SE) change from baseline for TNX-102 SL -1.82 (0.12) and for placebo -1.16 (0.12); LSMD from placebo -0.65 (0.16); **p=0.00005**[#]

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction. Abbreviations: LS, least squares; LSMD, least squares mean difference; NRS, numerical rating scale; SE, standard error

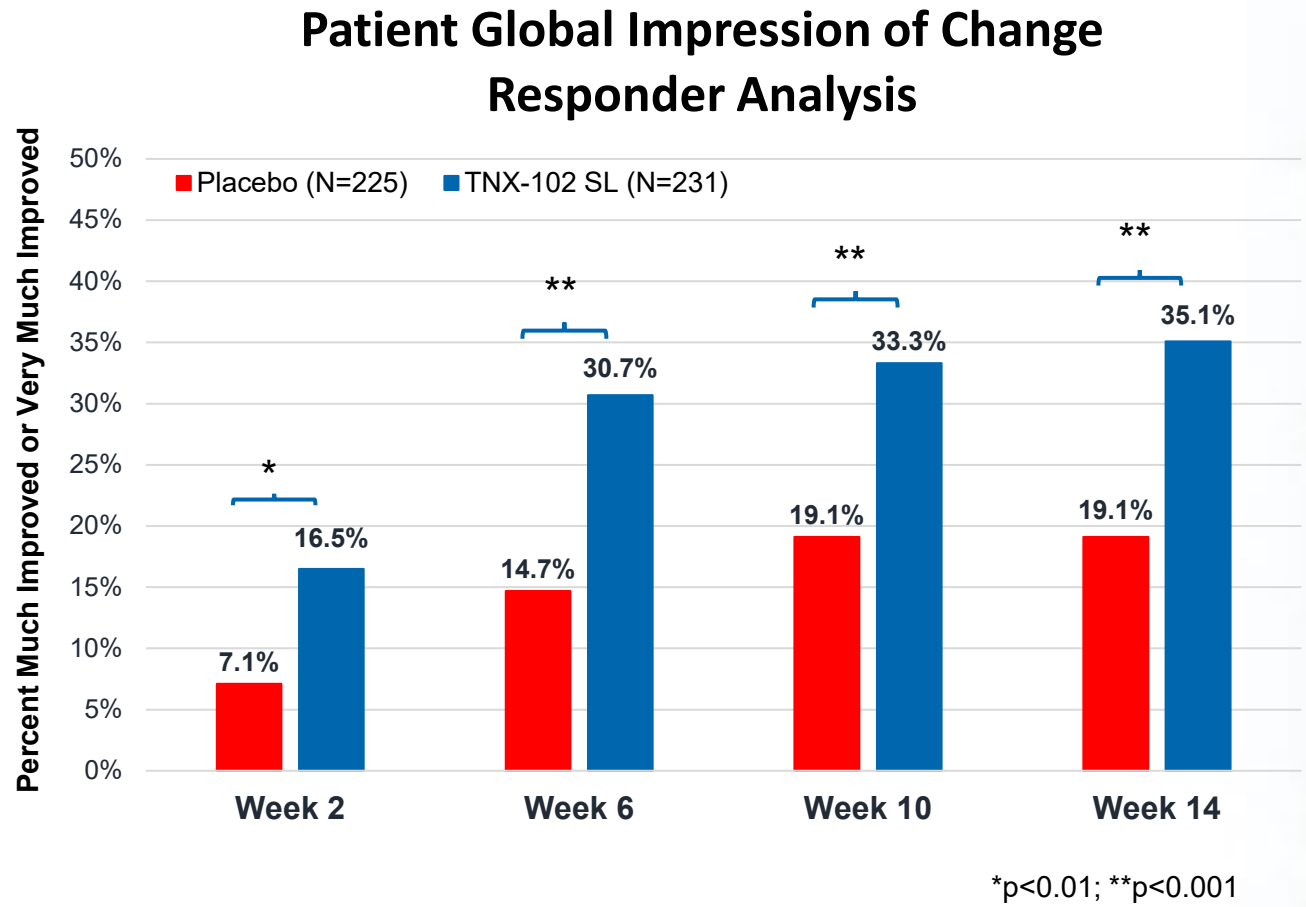
RESILIENT Continuous Pain Responder Graph



#Analyses: Pearson's Chi Squared test for equality of proportions
Abbreviations: CI, confidence interval; DIP, difference in proportions
^pre-specified analyses but not key secondary analyses

RESILIENT Patient Global Impression of Change

Key Secondary Outcome Measure

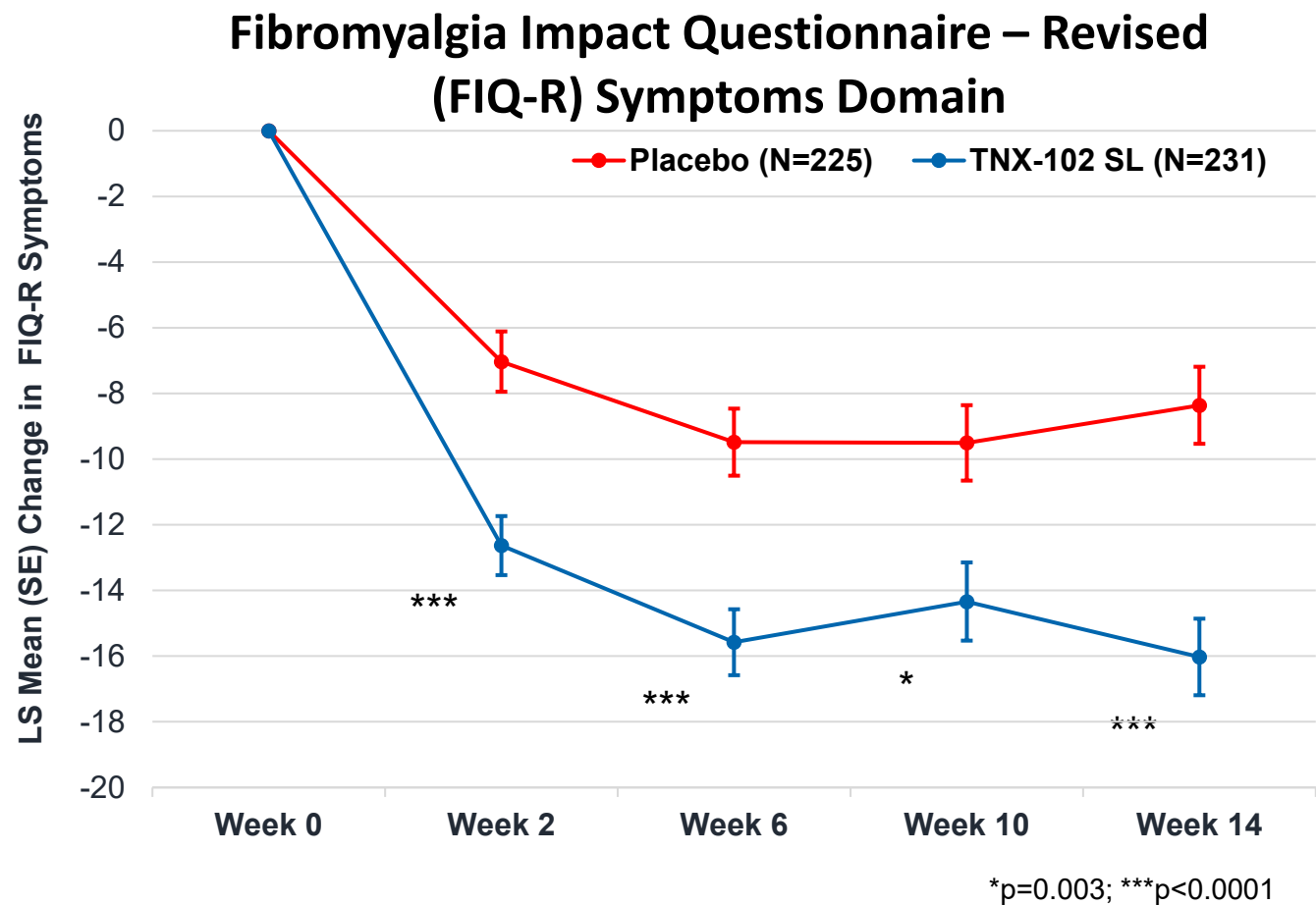


Week 14 TNX-102 SL responders 35.1%, and placebo responders 19.1%; difference in proportions (95% CI) 16% (7.9%, 24.0%); **p=0.00013[#]**

[#]Based on a Pearson Chi-Squared with differences in proportions 95% CIs from difference in proportions Z-test
Responders defined as subject that reply 'very much improved' or 'much improved' at Week 14; all others are non-responders
CI, confidence interval

RESILIENT FIQ-R Symptoms Domain

Key Secondary Outcome Measure



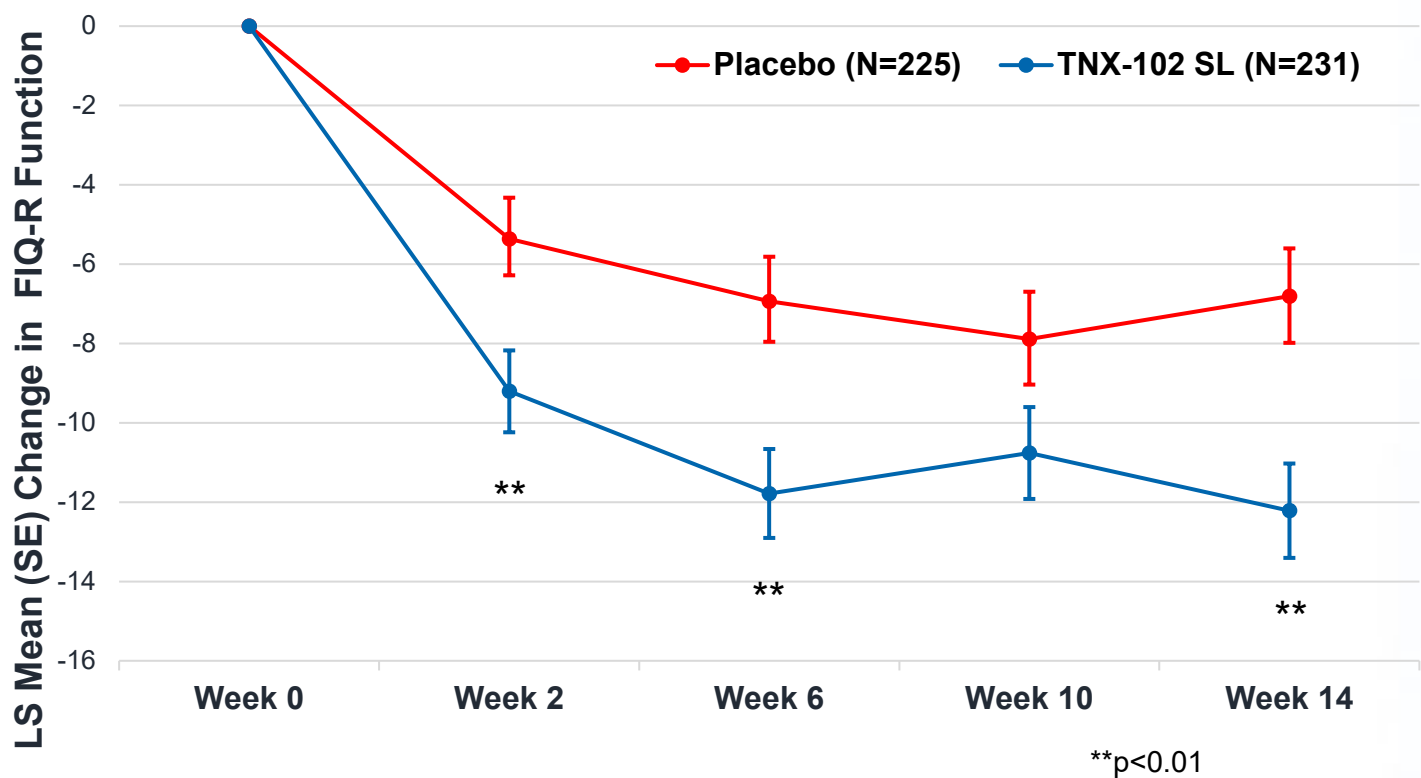
Week 14 LS mean (SE) change from baseline for TNX-102 SL -16.0 (1.17) and for placebo -8.4 (1.17); LSMD from placebo -7.7 (1.62); **p=0.000002**[#]

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT FIQ-R Function Domain

Key Secondary Outcome Measure

Fibromyalgia Impact Questionnaire – Revised (FIQ-R)
Function Domain

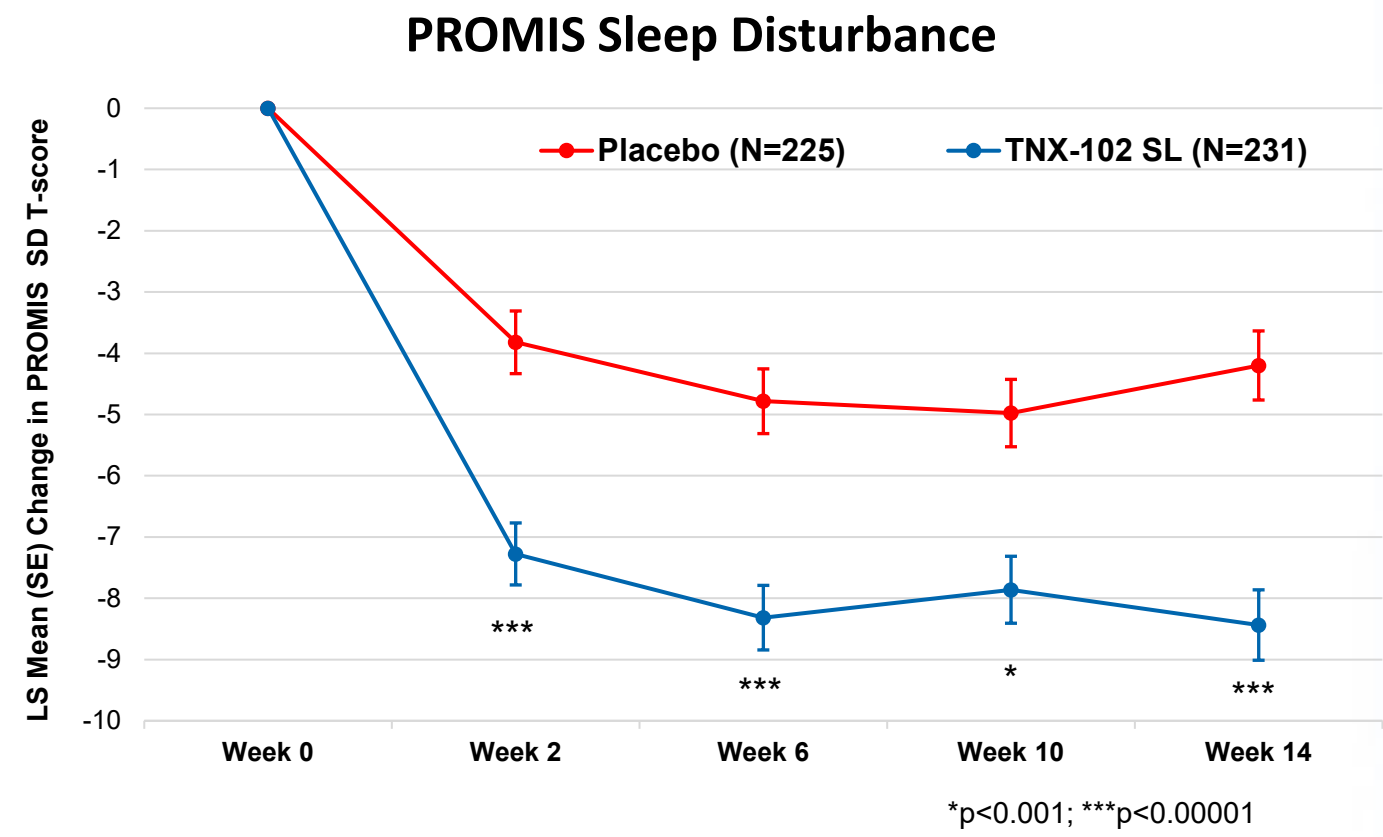


Week 14 LS mean (SE) change from baseline for TNX-102 SL -12.2 (1.19) and for placebo -6.8 (1.21); LSMD from placebo -5.4 (1.66); **p=0.001[#]**

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT PROMIS Sleep Disturbance Inventory

Key Secondary Outcome Measure

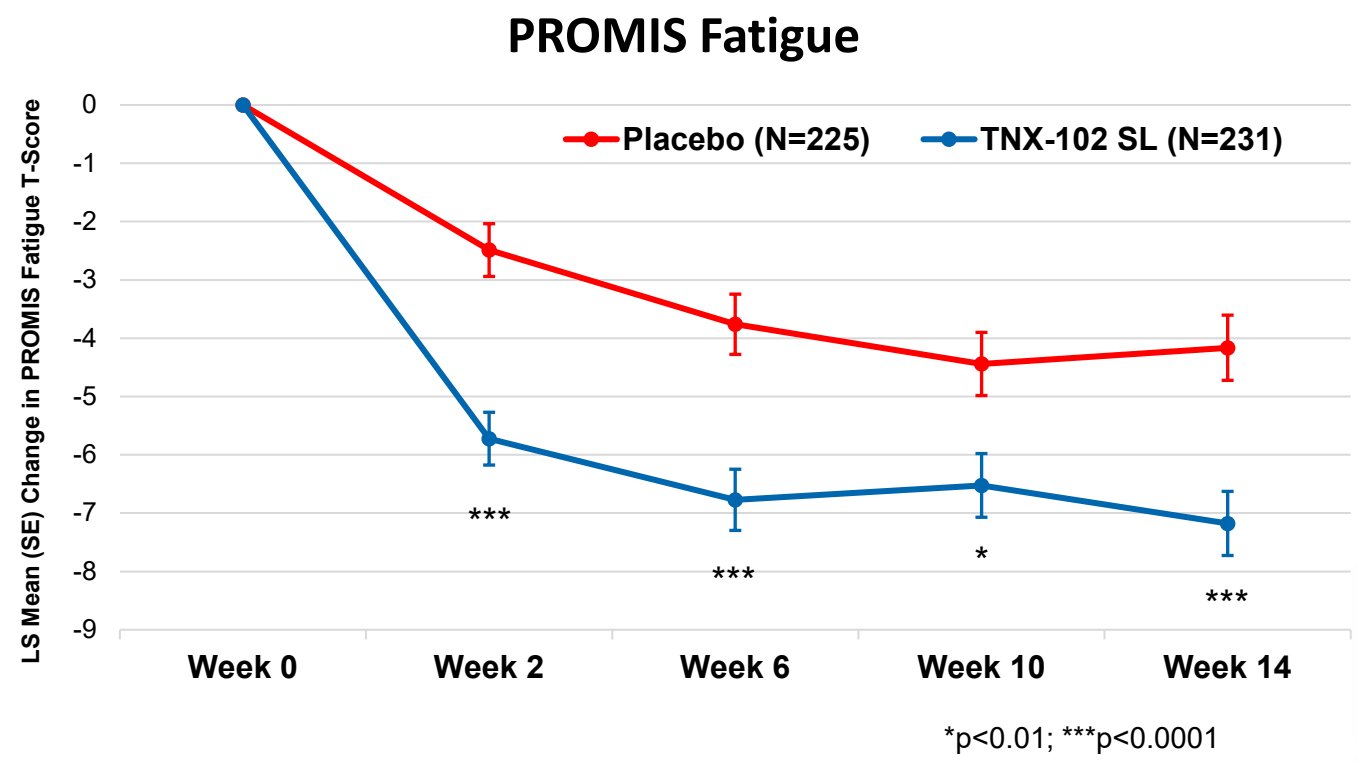


Week 14 LS mean (SE) change from baseline for TNX-102 SL -8.4 (0.57) and for placebo -4.2 (0.56); LSMD from placebo -4.2 (0.79); **p=0.0000001**[#]

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT PROMIS Fatigue Inventory

Key Secondary Outcome Measure



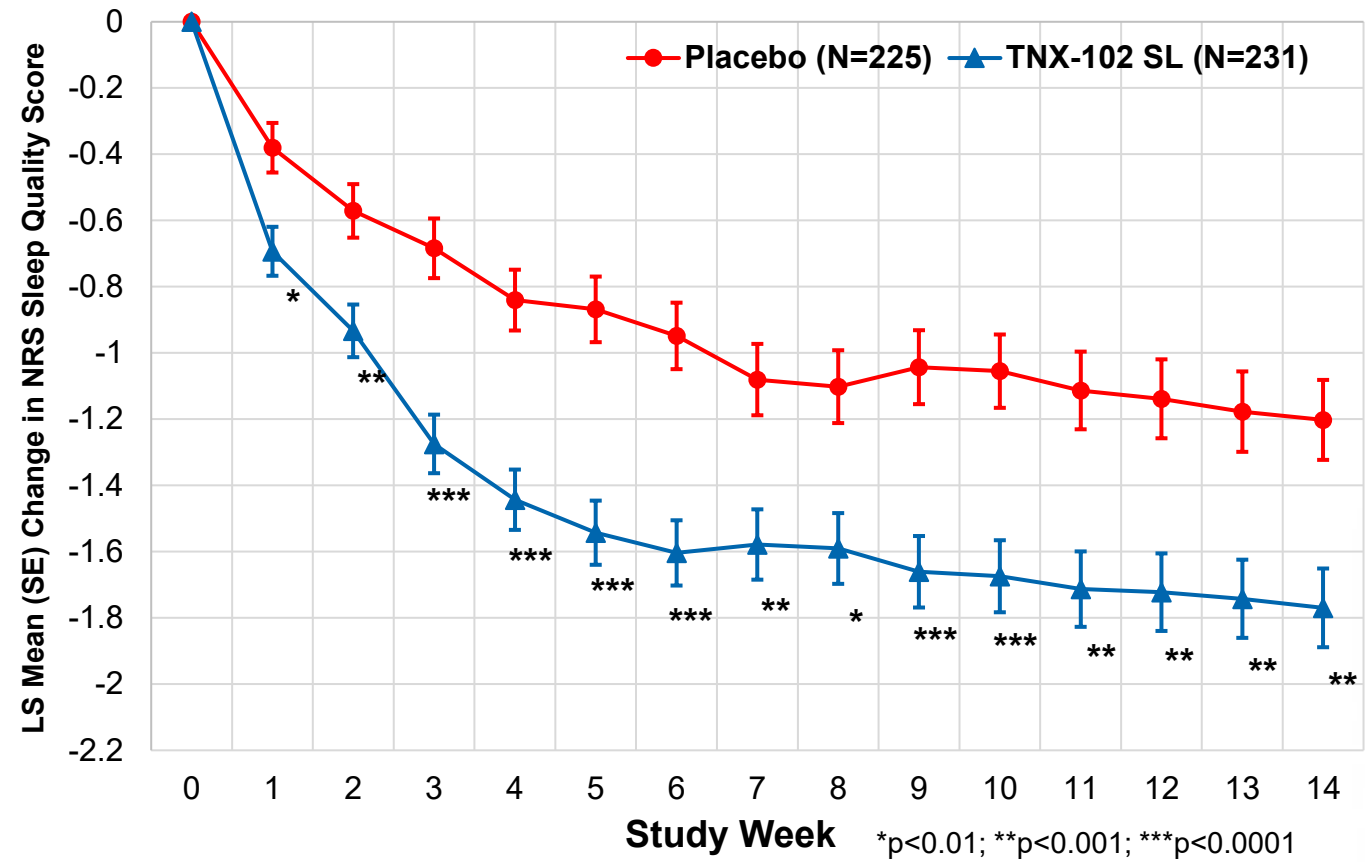
Week 14 LS mean (SE) change from baseline for TNX-102 SL -7.2 (0.55) and for placebo -4.2 (0.56); LSMD from placebo -3.0 (0.77); **p=0.00009#**

#Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT Sleep Quality by Daily Diary

Key Secondary Outcome Measure

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



Week 14 LS mean (SE) change from baseline for TNX-102 SL -1.77 (0.12) and for placebo -1.20 (0.12); LSMD from placebo -0.57 (0.17); **p=0.0007[#]**

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT Summary of Efficacy



Fibromyalgia is the prototypic noicplastic *syndrome* composed of *symptoms*

- Widespread pain
- Fatigue
- Sleep disturbance

Efficacy across symptoms of pain, fatigue and sleep

- Pain: primary endpoint, daily pain diary: p -value of 0.00005
- Fatigue: PROMIS fatigue: p -value of 0.00009
- Sleep: PROMIS sleep disturbance: p -value of 0.0000001

Conclusion: Tonmya has “broad spectrum” or “syndromal activity”

- Broad spectrum: across several symptoms
- Syndromal: improves the syndrome (most of the symptoms)
- Potential for a broad-spectrum drug to reduce the use of multiple drugs or “polypharmacy”

Treatment-Emergent Adverse Events (TEAEs) at Rate of $\geq 3\%$ 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%)



RESILIENT Safety, Continued

No Signals for Clinically Meaningful Changes in Systolic or Diastolic Blood Pressure or in Weight

*No clinically meaningful difference in mean **systolic blood pressure** between groups*

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.7 (12.38) mmHg

Placebo = 0.5 (10.42) mmHg

*No clinically meaningful difference in mean **diastolic blood pressure** between groups*

Week 14 mean (SD) change from baseline:

TNX-102 SL = 1.1 (8.60) mmHg

Placebo = 0.2 (8.22) mmHg

*No clinically meaningful difference in mean **weight** between treatment groups*

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.02 (2.940) kg

Placebo = 0.20 (2.932) kg

Large Need for New Fibromyalgia Therapies that Provide Broad Symptom Improvement with Better Tolerability

- Currently-approved medications may have side effects that limit long-term use¹
 - Many patients skip doses or discontinue altogether within months of treatment initiation
- Medication-related side effects may be similar to fibromyalgia symptoms
- High rates of discontinuation, switching and augmentation
 - Attempt to treat multiple symptoms and/or avoid intolerable side effects
 - Average of 2-3 medications used simultaneously²
 - The typical patient has tried six different medications³
- Substantial off-label use of narcotic painkillers and prescription sleep aids³
 - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment⁴
- Tonmya™ (TNX-102 SL) is a non-opioid, centrally-acting analgesic that could provide a new therapeutic option for fibromyalgia patients

¹ Nuesch et al, Ann Rheum Dis 2013;72:955-62.

² Robinson RL et al, Pain Medicine 2012;13:1366.

³ Patient Trends: Fibromyalgia", Decision Resources, 2011.

⁴ Berger A, Dukes E, Martin S, Edelsberg J, Oster G, Int J Clin Pract, 2007; 61(9):1498–1508.





Tonmya™ Showed Broad-Spectrum Activity and was Well Tolerated

		Lyrica®	Cymbalta® Savella®	Tonmya™
Activity	Pain	+	+	+
	Sleep	+	-	+
	Fatigue	-	+	+
Systemic Tolerability Issues	Insomnia	-	+	-
	Fatigue	+	-	-
	Weight	+	-	-
	Blood Pressure	-	+	-
	Sexual function	-	+	-
	GI issues	-	+	-

- Tonmya showed activity in all three measures of pain, sleep, and fatigue
- Tonmya is not associated with any of the commonly reported side effects of the FDA-approved approved drugs

The image is a composite graphic. The left half has a solid blue background with a faint, large-scale molecular structure graphic. The right half features a photograph of a family (a man, a woman, and two young children) walking through a grassy field at sunset. The image is divided by a diagonal white line. The top right corner has an orange triangular overlay, and the bottom left corner has a green triangular overlay.

THANK YOU