



Controversies in Fibromyalgia - Brussels

**Tonmya™* (TNX-102 SL) in
Development for the Management
of Fibromyalgia**

March 7, 2024
NASDAQ: TNXP

*Tonmya is conditionally accepted by FDA as the tradename for TNX-102 SL for the management of fibromyalgia

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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 drugs³

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®)
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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.



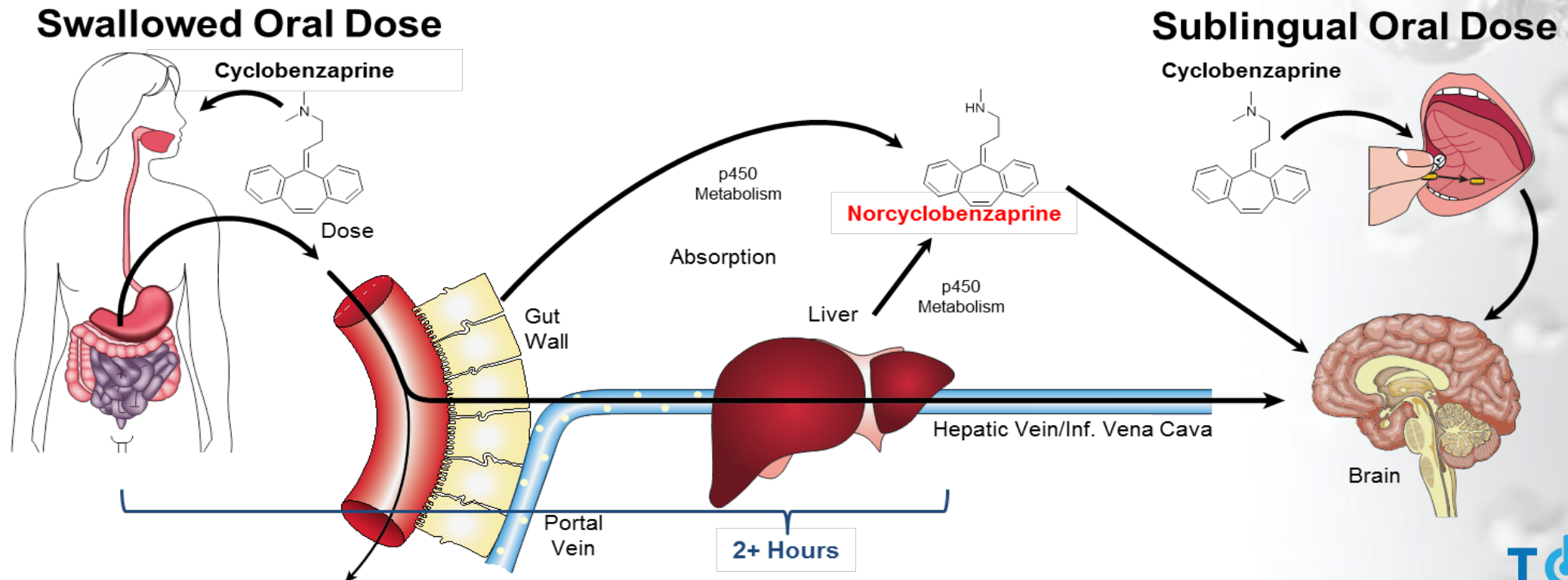
Tonmya™ (TNX-102 SL, Cyclobenzaprine HCl Sublingual Tablets)¹

- **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.

TNX-102 SL – Sublingual Administration and Transmucosal Delivery

- Advantages of the sublingual route
- Faster absorption provides PK that is ideal for bedtime dosing
- Bypasses “first-pass” hepatic metabolism
- Reduced metabolism of parent CBP to active metabolite norcyclobenzaprine (nCBP)





Tonmya[®] Fibromyalgia Program Status

Tonmya[™]

(TNX-102 SL)

Cyclobenzaprine Protectic[®]
Sublingual Tablets

Fibromyalgia

Positive 2nd Phase 3 Topline Results Reported 4Q'23

- 1) **Positive Phase 3 study (*RELIEF*) reported – December 2020¹**
- 2) **Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021**
 - Unexpected increase in adverse event-related discontinuations in both drug and placebo arms, potentially due to recruiting during COVID-19
- 3) **Positive 2nd (confirmatory) Phase 3 study (*RESILIENT*) reported – December 2023**

Next Steps:

Type B Pre-NDA meeting scheduled with FDA in 2Q'24

NDA filing expected 2H'24

FDA decision on NDA approval expected 2H'25

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 Pre-Specified Primary Endpoint

Summary¹

- Tonmya™ (TNX-102 SL) demonstrated statistically significant improvement in mean weekly pain scores over placebo at Week 14
- [P-value of 0.00005](#) is *highly* statistically significant

Additional Findings

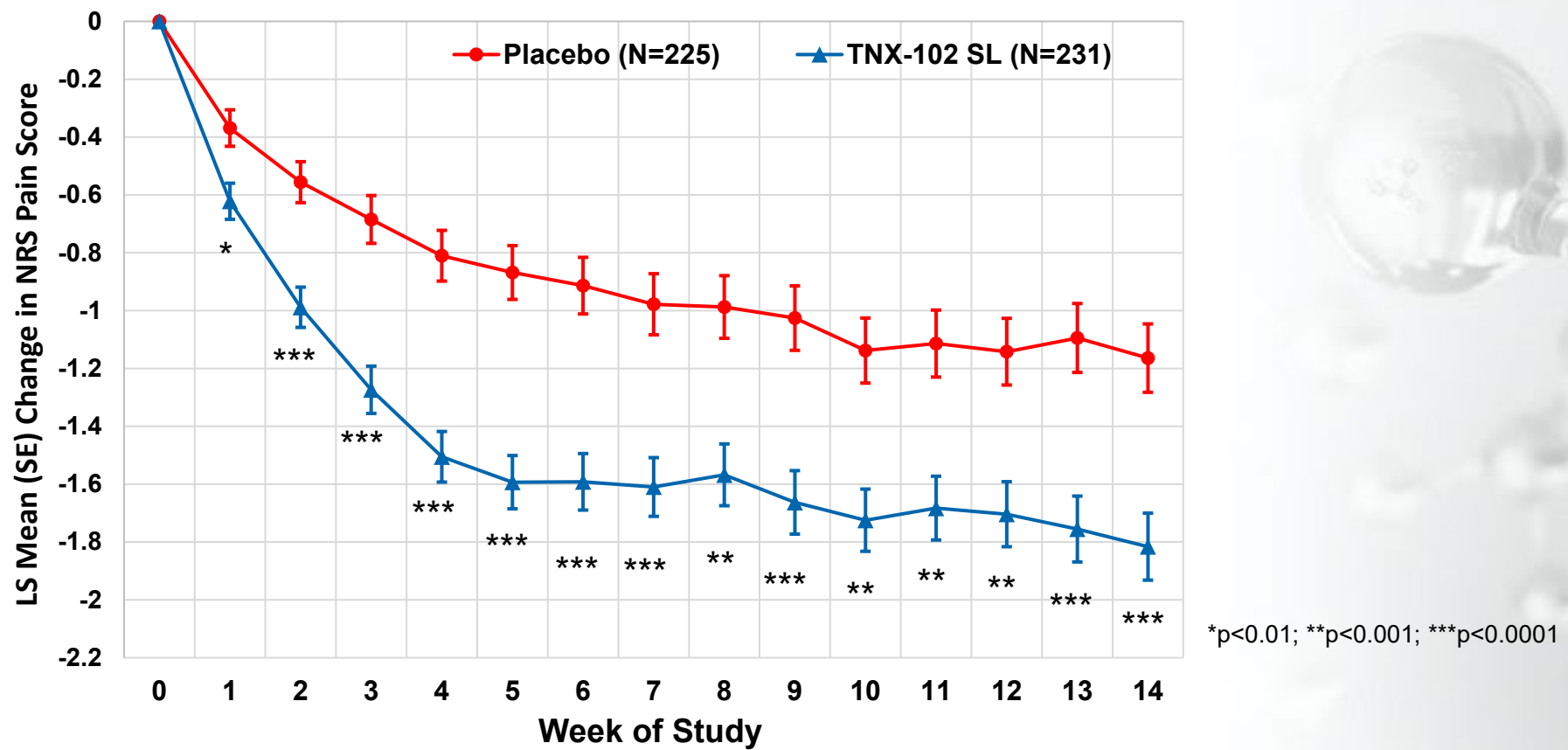
- Cohen's *d* effect size 0.38
- All pre-specified sensitivity analyses of the primary endpoint show statistical significance ($p \leq 0.001$)
- Rapid onset of action: *p*-values <0.01 at each weekly time point, including Week 1

¹The Company plans to publish the results in a journal later this year

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

Summary of Key Secondary Endpoints



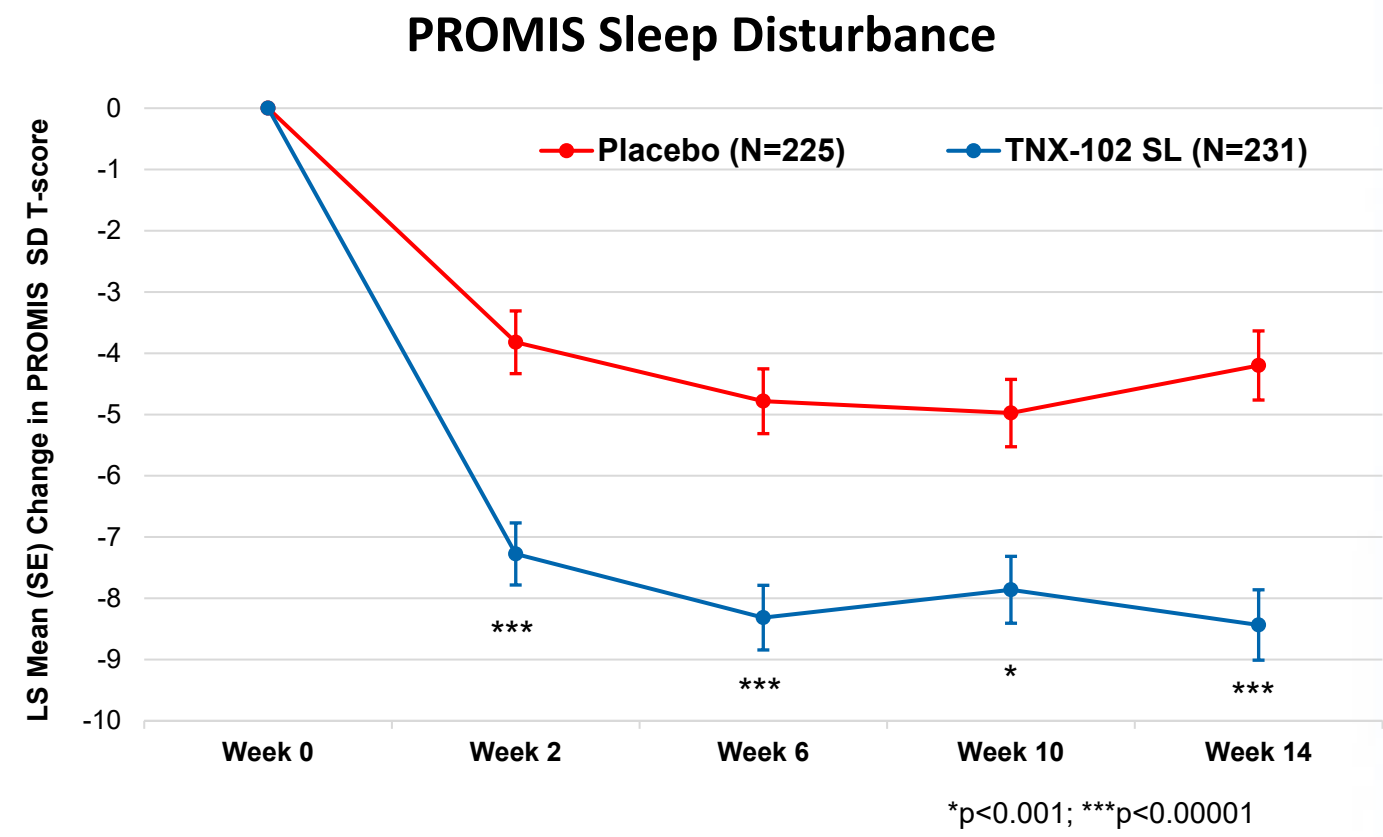
Endpoint ¹	P-value	Effect Size ²
Patient Global Impression of Change (PGIC)	$p = 0.00013$	--
Fibromyalgia Impact Questionnaire – Symptoms Domain	$p = 0.000002$	ES = 0.44
Fibromyalgia Impact Questionnaire – Function Domain	$p = 0.001$	ES = 0.30
PROMIS Sleep Disturbance Instrument	$p = 0.0000001$	ES = 0.50
PROMIS Fatigue Instrument	$p = 0.00009$	ES = 0.37
Diary Sleep Quality Ratings	$p = 0.0007$	ES = 0.32

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

²Cohen’s *d*

RESILIENT PROMIS Sleep Disturbance Inventory

Key Secondary Outcome Measure

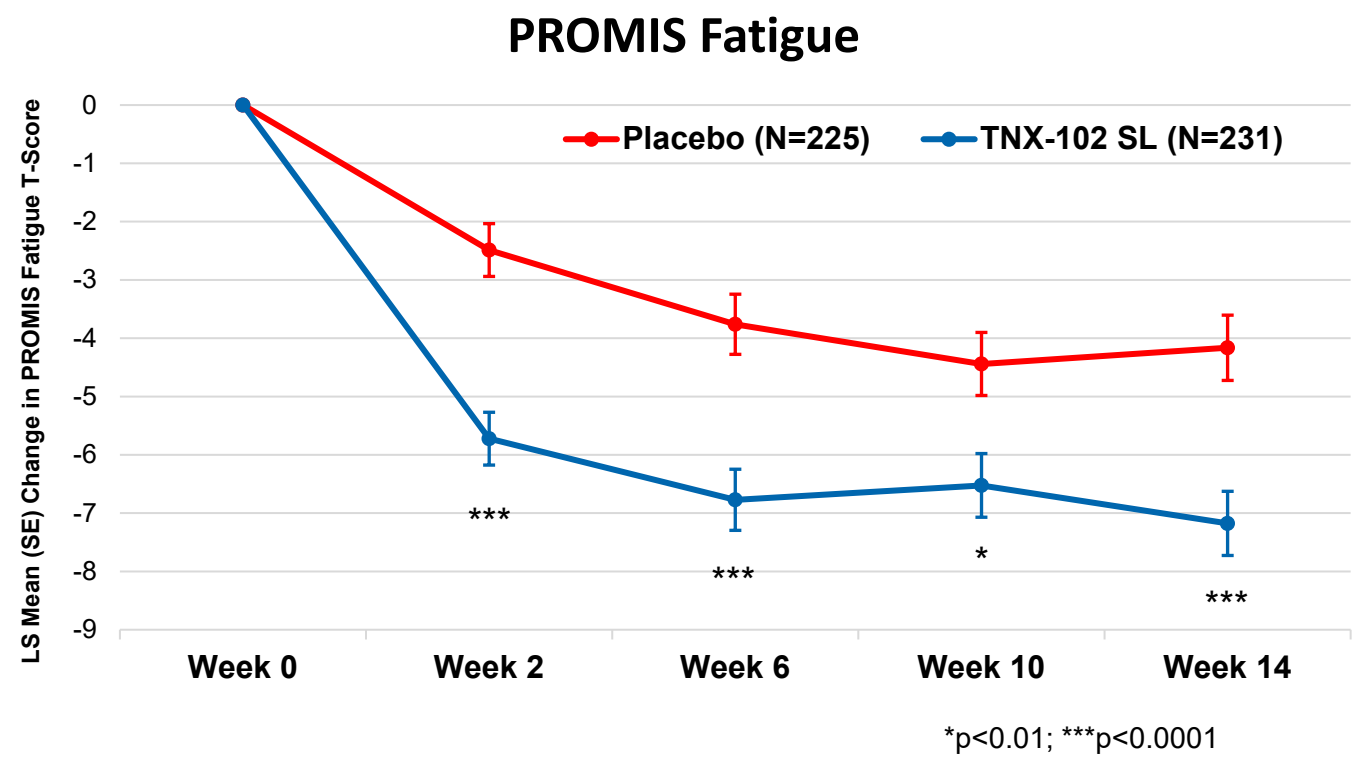


Week 14 LS mean (SE) change from baseline for TNX-102 SL -8.4 (0.57) and for placebo -4.2 (0.56); LSMD from placebo -4.2 (0.79); **p=0.0000001**[#]

[#]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 – Cognitive Dysfunction or “Brain Fog”

Brain Fog assessed by the FIQ-R¹ item on memory

- Patients rated their level of memory problems
- 11-pt scale going from “Good Memory” to “Very Poor Memory”
- Prespecified endpoint, but not in the “waterfall” with the key secondary endpoints
- TNX-102 SL patients vs PBO change from baseline LS mean (SE) difference of -0.8 (0.23)
- $p = 0.001$ (not corrected for multiple comparisons)
- Cohen’s d effect size = 0.31



Fatigue



¹FIQ-R = Fibromyalgia Impact Questionnaire - Revised

RESILIENT Summary of Efficacy



Fibromyalgia is a *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”



Safety and Tolerability

- **Completion Rate (safety population): TNX-102 SL 81.0% and Placebo 79.2%**
- **No new safety signals observed**
- **Only systemic adverse events (AEs) at rate $\geq 3.0\%$ (TNX-102 SL v. Placebo)**
 - COVID-19 (4.3% v. 3.1%), somnolence (3.0% v. 1.3%), and headache (3.0% v. 1.8%)
- **As previously observed TNX-102 SL associated with administration site reactions**
 - Hypoaesthesia oral (23.8% v. 0.4%), product taste abnormal (11.7% v. 0.9%), paraesthesia oral (6.9% v. 0.9%), and tongue discomfort (6.9% v. 0%)
- **No effect on weight or blood pressure (BP)**
 - Weight: Week 14 change from baseline for TNX-102 SL of +0.04 lbs.; and for Placebo of +0.44 lbs.
 - Systolic BP: Week 14 change from baseline for TNX-102 SL of +0.7 mmHg; and for Placebo of +0.5 mmHg
 - Diastolic BP: Week 14 change from baseline for TNX-102 SL of +1.1 mmHg; and for Placebo of +0.2 mmHg
- **No sexual dysfunction AEs and improved female sexual functioning**
 - No reported AEs of any type of sexual dysfunction
 - Improvement in female sexual function using Changes in Sexual Functioning Questionnaire (p=0.010)

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%)

*Safety Population

Changes in Sexual Functioning Questionnaire short form (CSFQ-14) was a safety measure in the study

- In females, CSFQ-14 total score improved (indicating better sexual functioning) to a greater extent in the TNX-102 SL group compared with placebo, $p=0.010$
- Orgasm/Completion and Desire/Frequency were improved
- Potential tolerability advantage over pharmacotherapeutics with potent serotonin reuptake inhibition



Tonmya™ Showed Broad-Spectrum Activity and was Well Tolerated

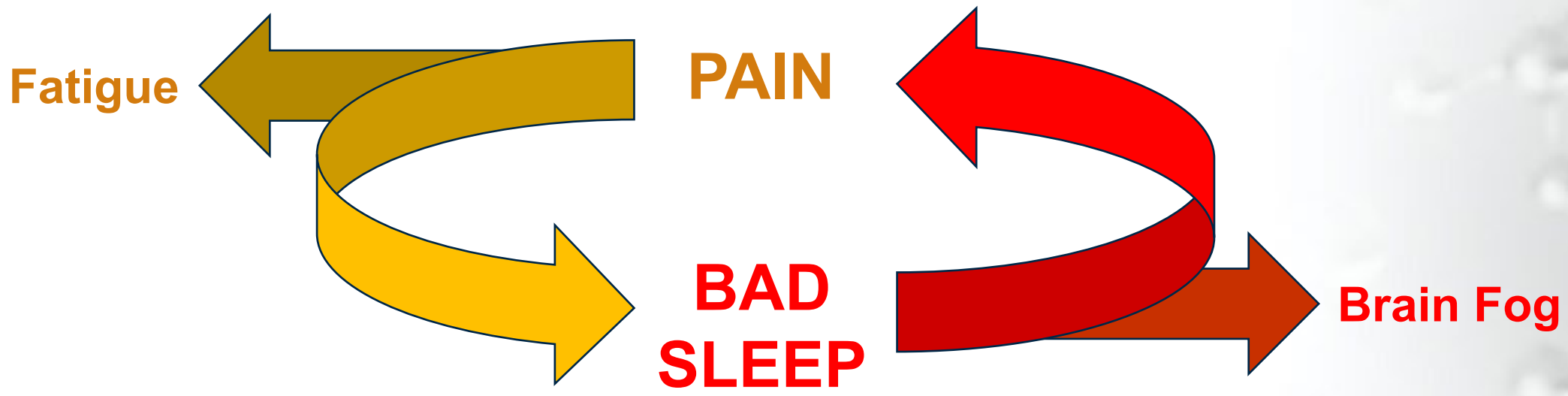
No current product addresses pain, poor sleep and fatigue

	Symptoms/ Side Effects		Pregabalin		Duloxetine Milnacipran		Tonmya™
Activity	Pain		YES		YES		YES
	Sleep		YES		-		YES
	Fatigue		-		YES		YES
Systemic Tolerability Issues	Sleep		-		YES		-
	Fatigue		YES		-		-
	Weight		YES		-		-
	Blood Pressure		-		YES		-
	Sexual function		-		YES		-
	GI issues		-		YES		-
Class			Gabapentinoid		SNRI		Tricyclic
Mechanism			Slow neuron firing		Block NE reuptake		Targets sleep disturbance



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

Key Clinical Programs

Molecule*	Indication	Phase 1	Phase 2	Phase 3	NDA Submission
Tonmya™ TNX-102 SL Cyclobenzaprine HCl Protectic® Sublingual Tablets	Fibromyalgia	Positive Phase 3 Topline Results Reported 4Q'23			Submission expected 2H'24
	Long COVID	Phase 2 Topline Results Reported 3Q'23			
	Acute Stress Disorder	Phase 2** Study Start Expected 2Q'24			

*All of Tonix's product candidates are investigational new drugs or biologics and none has been approved for any indication..

**Investigator-initiated study



Additional Potential Indications for Tonmya™ (TNX-102 SL)

Fibromyalgia-Type Long COVID

- Status: Phase 2
- Phase 2 study (*PREVAIL*) completed
- Topline results reported 3Q 2023

Next Steps: Meet with FDA

Acute Stress Reaction/ Acute Stress Disorder

- Phase 2 ready investigator-initiated study
- Department of Defense funded
- UNC will perform study
- Received IND clearance from FDA

Next Steps: Expect to start Phase 2 in 2Q 2024



THANK YOU

