



# 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

Version P0535 March 7, 2024 (Doc 1389)

© 2024 Tonix Pharmaceuticals Holding Corp.

# 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, 2022, as filed with the Securities and Exchange Commission (the “SEC”) on March 13, 2023, 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.



# About Fibromyalgia

Fibromyalgia is a **chronic pain disorder** resulting from amplified sensory and pain signaling within the CNS<sup>1</sup>

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<sup>3</sup>**

**Fibromyalgia is the prototypic nociplastic syndrome**

<sup>1</sup>American Chronic Pain Association (www.theacpa.org, 2019)  
<sup>3</sup>CFS/ME = chronic fatigue syndrome/myalgic encephalomyelitis  
<sup>3</sup>The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)  
© 2024 Tonix Pharmaceuticals Holding Corp.



# Fibromyalgia: Unrefreshing Sleep and Cyclobenzaprine Treatment

- **Non-restorative sleep<sup>1,2</sup>**
  - Harvey Moldofsky – recognition of unrefreshing/non-restorative sleep:
    - Symptom
    - Potential causative or potentiating factor
- **Cyclobenzaprine<sup>3,9</sup>**
  - 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 sleep<sup>10-11</sup>**
  - Recognition of unrefreshing sleep as a target of therapy
  - Primitive oral, swallowed formulation – “flat” pharmacokinetics
- **Bedtime, sublingual transmucosal cyclobenzaprine targeting non-restorative sleep<sup>12</sup>**
  - 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.

<sup>1</sup>Moldofsky H et al. *Psychosom Med*. 1975. 37:341-51.

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

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

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

<sup>5</sup>Reynolds WJ, et al. *J Rheumatol*. 1991.18:452-4.

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

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

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

<sup>9</sup>Tofferi JK, et al. *Arthritis Rheum*. 2004. 51:9-13.1

<sup>10</sup>Iglehart IW. 2003; US Patent 6,541,523.

<sup>11</sup>Moldofsky et al. *J Rheumatol*. 2011. 38:2653-2663

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



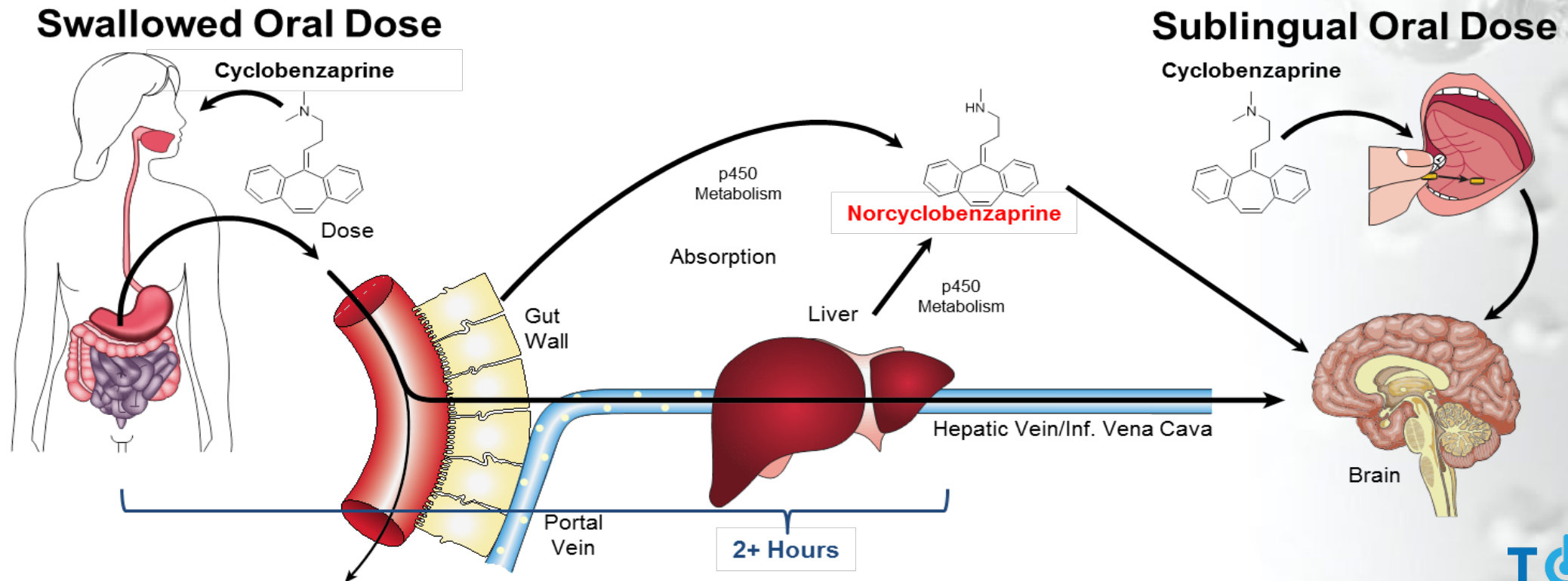
# Tonmya™ (TNX-102 SL, Cyclobenzaprine HCl Sublingual Tablets)<sup>1</sup>

- **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<sub>2A</sub>,  $\alpha$ <sub>1</sub>-adrenergic, histaminergic-H<sub>1</sub>, and muscarinic-M<sub>1</sub> 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

<sup>1</sup>Tonmya™ 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<sup>®</sup> Fibromyalgia Program Status

Tonmya<sup>™</sup>

(TNX-102 SL)

Cyclobenzaprine Protectic<sup>®</sup>  
Sublingual Tablets

Fibromyalgia

**Positive 2<sup>nd</sup> Phase 3 Topline Results Reported 4Q'23**

- 1) **Positive Phase 3 study (*RELIEF*) reported – December 2020<sup>1</sup>**
- 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 2<sup>nd</sup> (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***

<sup>1</sup>Lederman 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

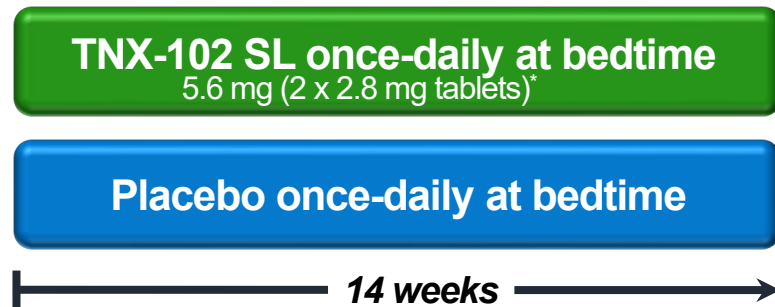


## General study characteristics:

- 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 Criteria<sup>1</sup>

## Primary Endpoint:

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



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')

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

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

# RESILIENT Pre-Specified Primary Endpoint

## Summary<sup>1</sup>

- 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

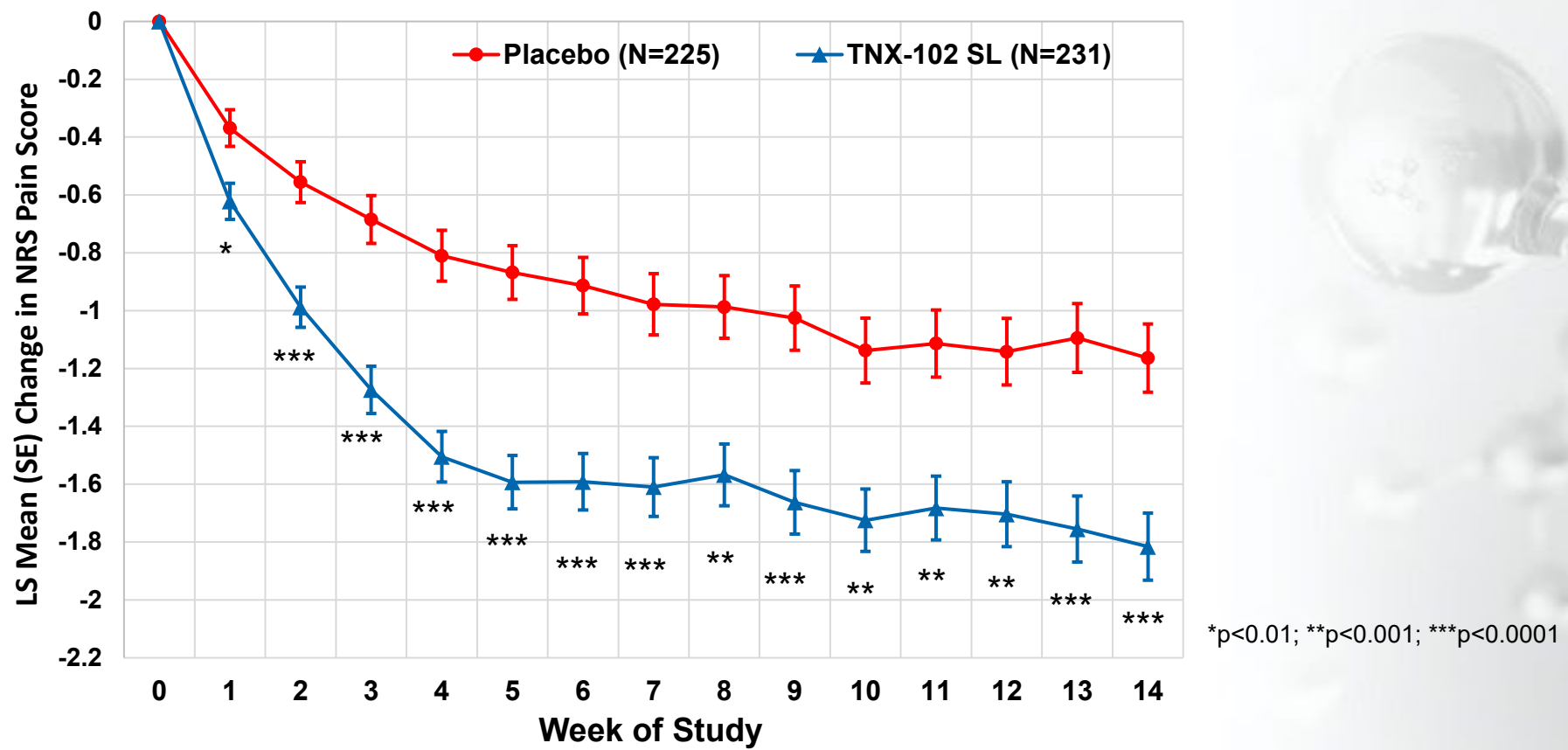
- Cohen's *d* effect size 0.38
- All pre-specified sensitivity analyses of the primary endpoint show statistical significance ( $p \leq 0.001$ )
- Rapid onset of action: *p*-values  $<0.01$  at each weekly time point, including Week 1

<sup>1</sup>The 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**<sup>#</sup>

<sup>#</sup>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



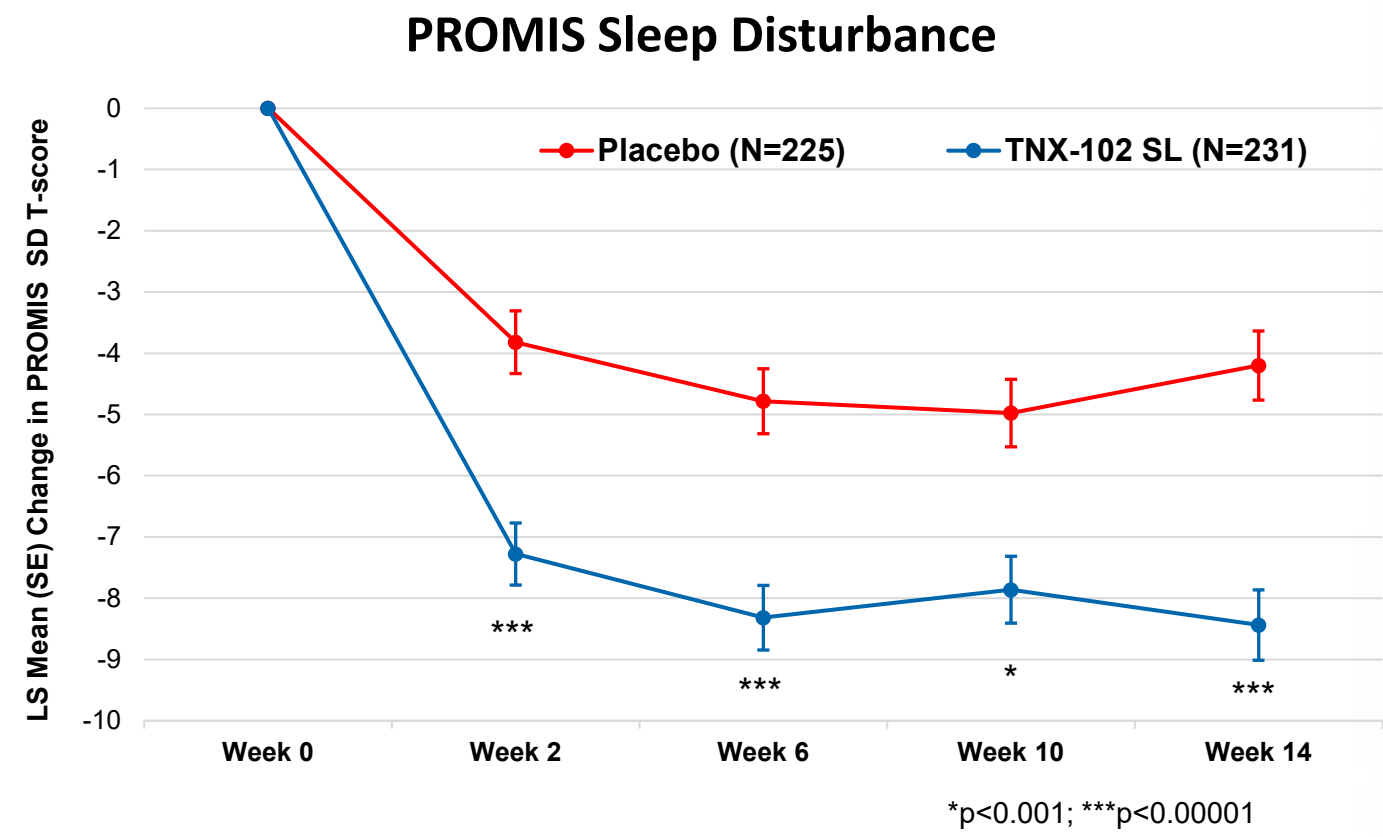
Endpoint <sup>1</sup>	P-value	Effect Size <sup>2</sup>
Patient Global Impression of Change (PGIC)	$p = 0.00013$	--
Fibromyalgia Impact Questionnaire – Symptoms Domain	$p = 0.000002$	ES = 0.44
Fibromyalgia Impact Questionnaire – Function Domain	$p = 0.001$	ES = 0.30
PROMIS Sleep Disturbance Instrument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

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

<sup>2</sup>Cohen’s *d*

# RESILIENT PROMIS Sleep Disturbance Inventory

## Key Secondary Outcome Measure

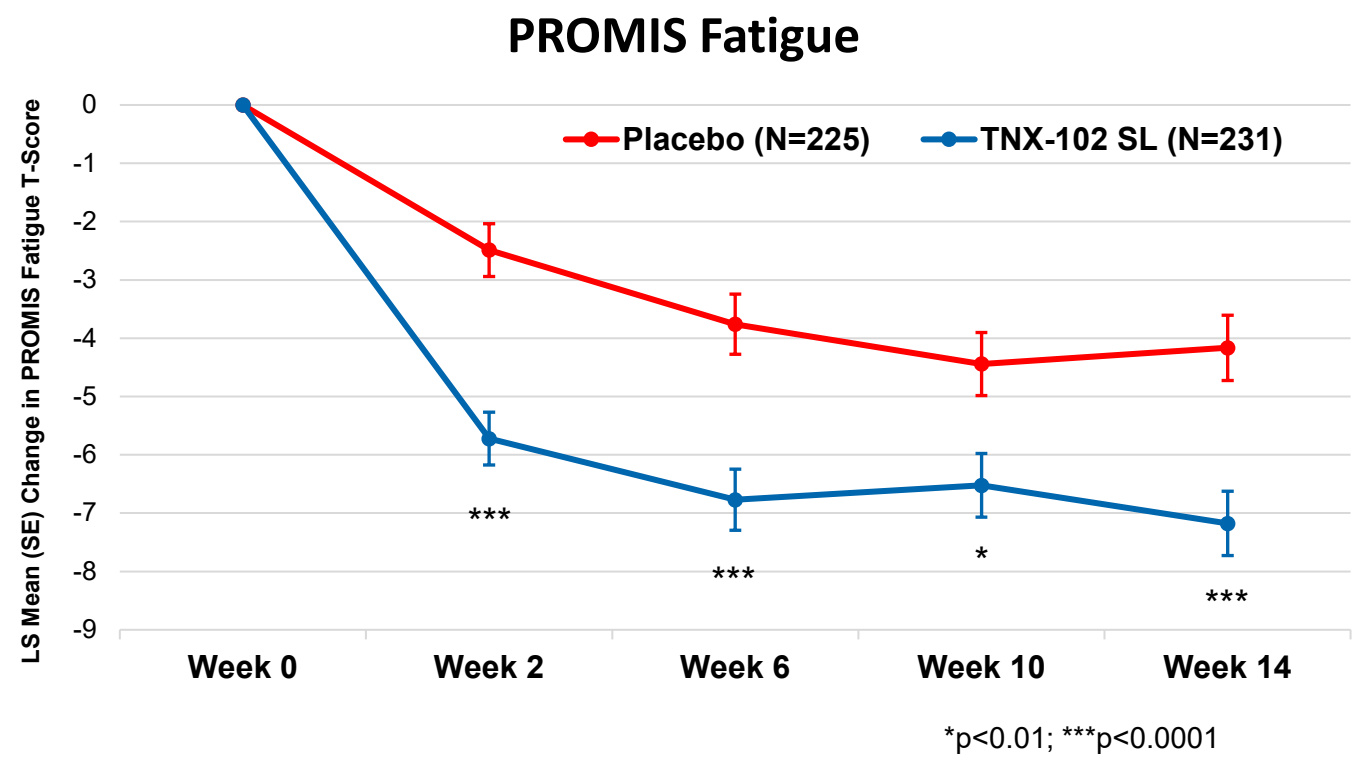


Week 14 LS mean (SE) change from baseline for TNX-102 SL -8.4 (0.57) and for placebo -4.2 (0.56); LSMD from placebo -4.2 (0.79); **p=0.0000001**<sup>#</sup>

<sup>#</sup>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<sup>#</sup>**

<sup>#</sup>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-R<sup>1</sup> 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



<sup>1</sup>FIQ-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
<b>Systemic Adverse Events</b>			
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%)
<b>Oral Cavity Adverse Events</b>			
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

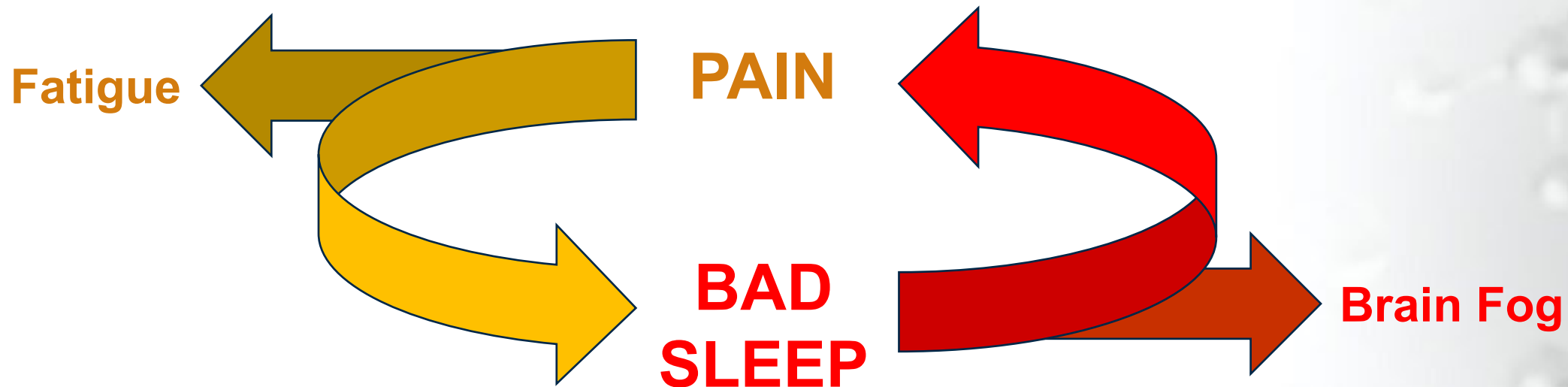


	Symptoms/ <b>Side Effects</b>		Pregabalin		Duloxetine Milnacipran		Tonmya™
Activity	Pain		YES		YES		YES
	Sleep		YES		-		YES
	Fatigue		-		YES		YES
Systemic Tolerability Issues	<b>Sleep</b>		-		<b>YES</b>		-
	<b>Fatigue</b>		<b>YES</b>		-		-
	<b>Weight</b>		<b>YES</b>		-		-
	<b>Blood Pressure</b>		-		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



## Poor Sleep and Pain have Bi-directional Reinforcing Effects<sup>1</sup>

- 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<sup>1,2</sup>



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

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

# Key Clinical Programs

Molecule*	Indication	Phase 1	Phase 2	Phase 3	NDA Submission
<b>Tonmya™</b> <b>TNX-102 SL</b> 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

