TONIX PHARMACEUTICALS

TNX-102 SL

Fibromyalgia, Long COVID, and Acute Stress Disorder

NASDAQ: TNXP

Version P0540 March 13, 2023 (Doc 1399)

Tonmya™ (TNX-102 SL)*
Cyclobenzaprine HCl (Protectic®)

Non-opiate analgesic

A unique, sublingual formulation of cyclobenzaprine designed for bedtime dosing with sublingual delivery and transmucosal absorption, bypassing 1st pass metabolism

Potent binding and antagonist activities at the serotonergic-5-HT_{2A}, adrenergic-α_1, histaminergic-H_1, and muscarinic-M_1 cholinergic receptors to facilitate restorative sleep

Innovative and proprietary PROTECTIC® Rapid drug exposure following once nightly sublingual administration

Differentiators:

Relative to Oral Cyclobenzaprine
- Lower daytime exposure
- Avoids first-pass metabolism
- Reduces risk of pharmacological interference from major metabolite

Relative to Standard of Care
- Potential for better tolerability while maintaining efficacy
- Not scheduled, without recognized abuse potential

Patents Issued

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

Indications Most Recently Pursued

Fibromyalgia

Status: Two potential pivotal Phase 3 studies completed
- Positive Phase 3 study (RELIEF) completed
- Second Phase 3 study (RALLY) missed primary endpoint
- Positive confirmatory Phase 3 study (RESILIENT) completed

Next Steps: Type B Pre-NDA meeting with FDA scheduled for 2Q 2024

Fibromyalgia-Type Long COVID

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

Next Steps: Meeting with FDA regarding primary endpoint

Acute Stress Reaction/ Acute Stress Disorder

- Phase 2 ready investigator-initiated study
- Department of Defense funded/ UNC will perform study

Next Steps: Expect to start Phase 2 in 1Q 2024

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About Fibromyalgia

*Fibromyalgia is a **chronic pain disorder** resulting from amplified sensory and pain signaling within the CNS*[1]

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

[1]American Chronic Pain Association (www.theacpa.org, 2019)
[3]CFS/ME = chronic fatigue syndrome/myalgic encephalomyelitis
[3]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)

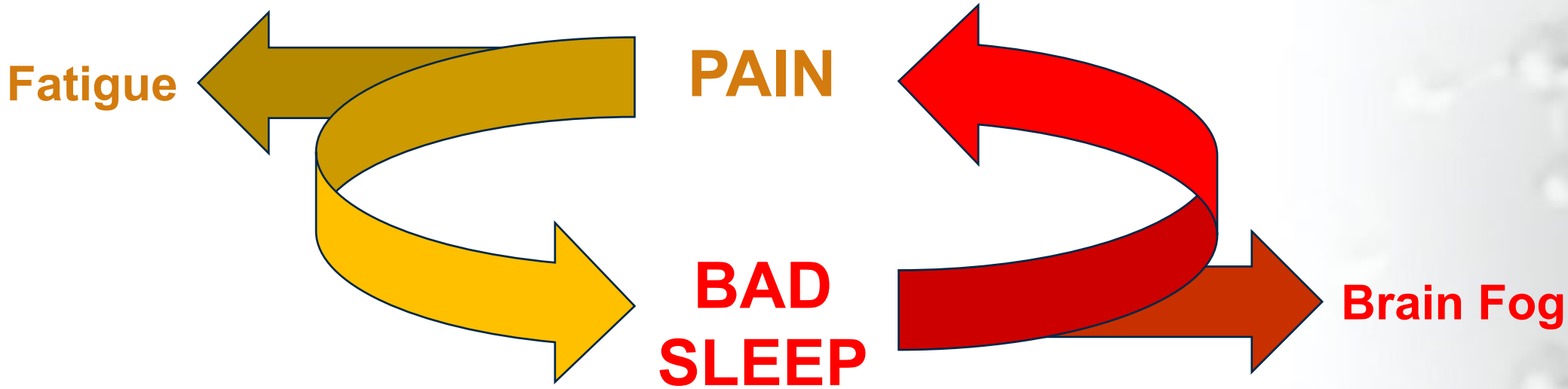
Fibromyalgia is a Large, Underserved and Dissatisfied population

- **~10 million U.S. adults are affected – predominantly women[1,2]**
  - Debilitating and life altering condition
  - Significant economic cost
- **Patients are dissatisfied, despite three FDA approved drugs[3,4]**
  - Average patient has 20 physician office visits per year[2]
  - Typical for patients to rotate between drugs[3]
  - Polypharmacy (multiple drugs at the same time) common[3]
  - Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[5,6]
- **Prescription opiate use declining because of availability**
  - Unknown number of patients using 'street drugs'
- **No new R*x* product since 2009**

[1]American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
[2]Vincent 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
[3]Robinson RL, et al. *Pain Med*. 2012 13(10):1366-76. doi: 10.1111; ; 85% received drug treatment
[4]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)
[5]Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.
[6]Market research by Frost & Sullivan, commissioned by Tonix, 2011

Poor Sleep and Pain have Bi-directional Reinforcing Effects[1]

- **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]



[1]Moldofsky H, et al. *J Rheumatol*. 1996;23:529–533.
[2]Grönbald M, et al. *Clin Rheumatol*. 1993;12(2):186–191

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Fibromyalgia Program Status

Tonmya™*
(TNX-102 SL)

Cyclobenzaprine Protectic®
Sublingual Tablets

Fibromyalgia

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

- **Positive Phase 3 study (*RELIEF*) reported – December 2020**[1]
- Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021
- **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**

*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.

[1]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

RESILIENT Study

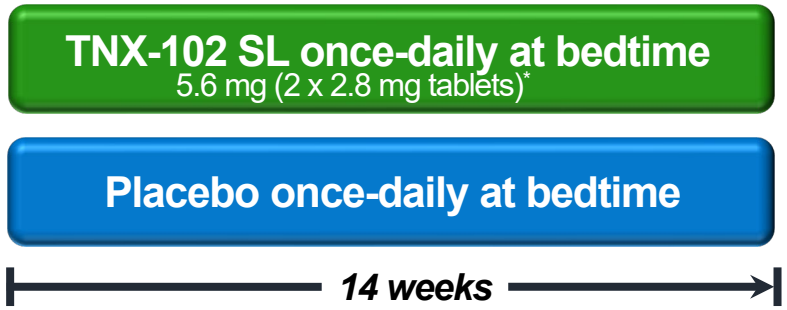
CNS PORTFOLIO

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[1]

Primary Endpoint:

- Change from baseline to Week 14 (TNX-102 SL vs. placebo) in weekly averages of daily diary average pain severity score
- ***Primary Endpoint, p-value = 0.00005***



*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')

[1]Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, Mease PJ, Russell AS, Russell IJ, Walitt B. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016; 46(3):319-329.

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RESILIENT Summary of Endpoints

RESILIENT Study

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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

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RESILIENT Primary Outcome Measure
Reduction in Widespread Pain

RESILIENT Study

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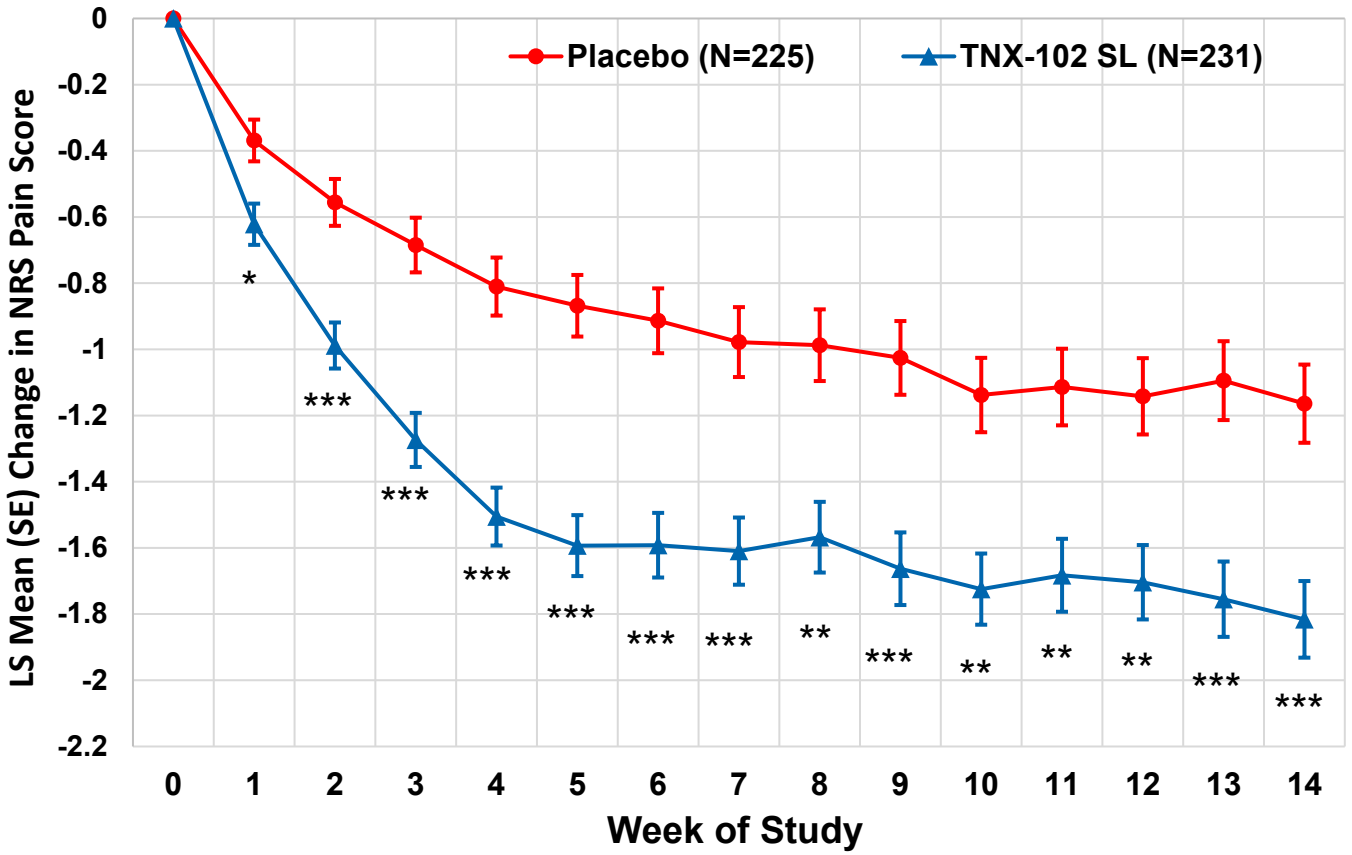
Weekly Average of Daily Diary NRS Ratings of Average Pain Over Prior 24 Hours



*p<0.01; **p<0.001; ***p<0.0001

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

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RESILIENT Continuous Pain Responder Graph

RESILIENT Study

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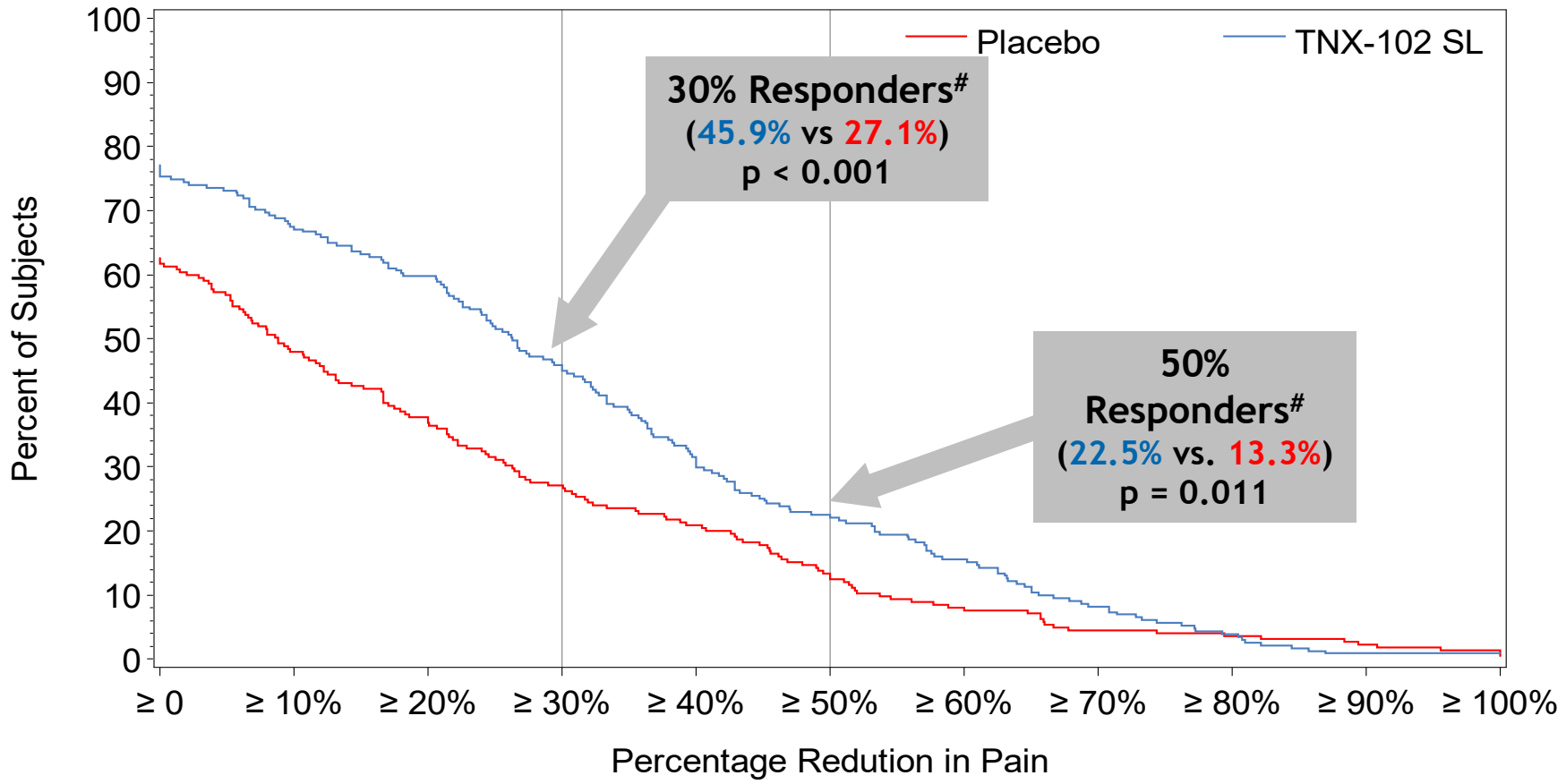

#Analyses: Pearson's Chi Squared test for equality of proportions
Abbreviations: CI, confidence interval; DIP, difference in proportions
^pre-specified analyses but not key secondary analyses

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RESILIENT Patient Global Impression of Change
Key Secondary Outcome Measure

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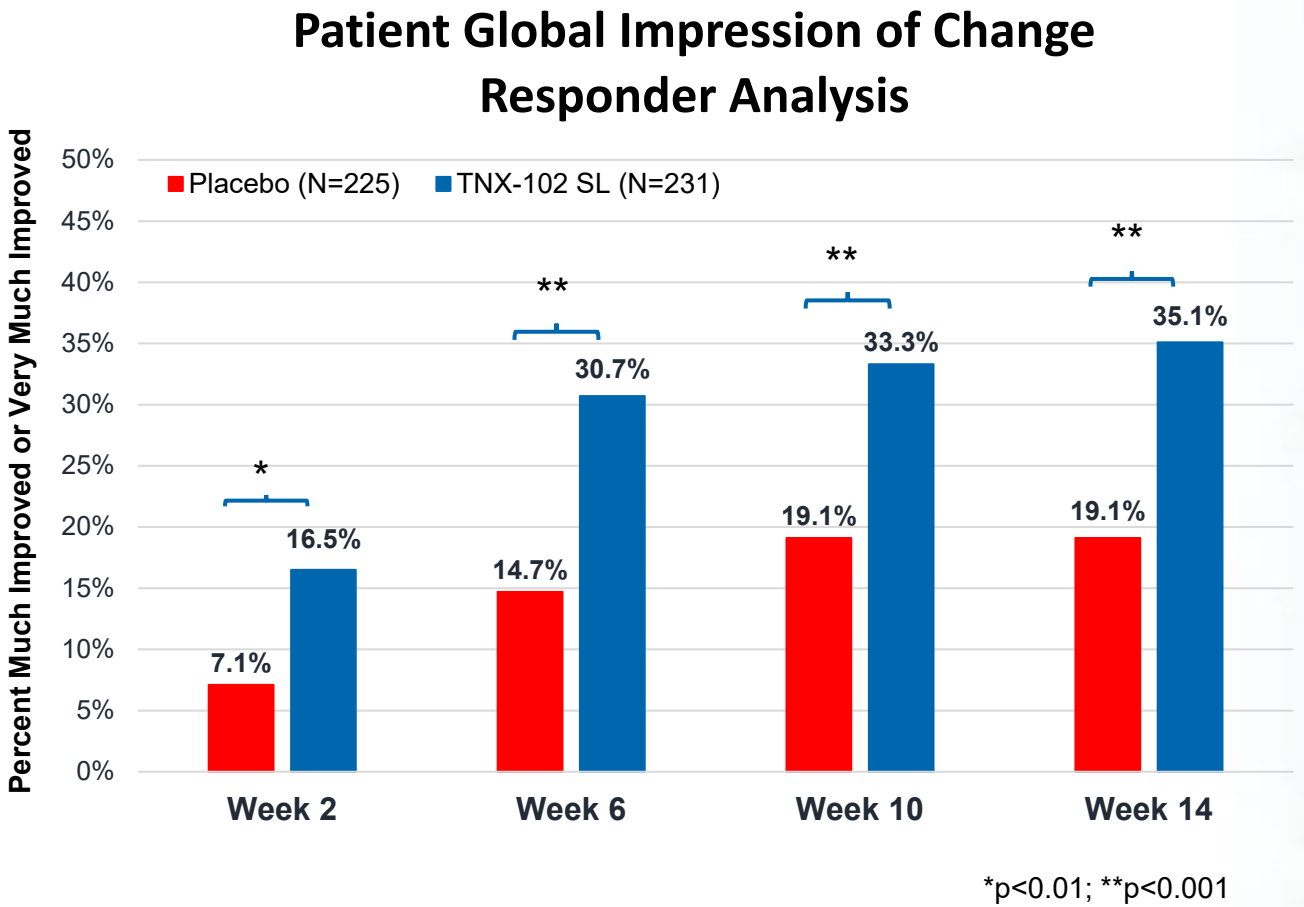

Week 14 TNX-102 SL responders 35.1%, and placebo responders 19.1%; difference in proportions (95% CI) 16% (7.9%, 24.0%); **p=0.00013#**

#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

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RESILIENT FIQ-R Symptoms Domain

Key Secondary Outcome Measure

RESILIENT Study

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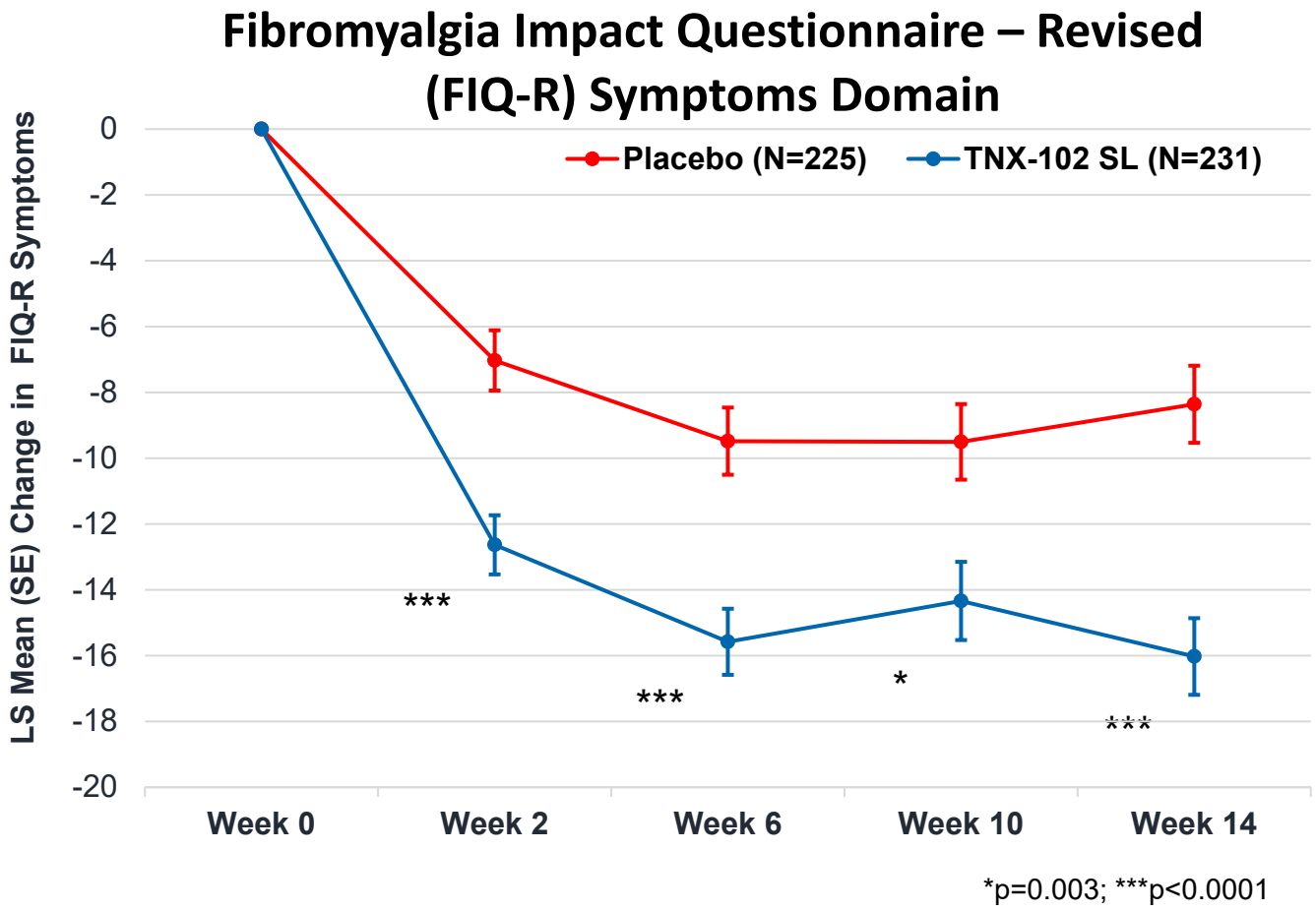

Week 14 LS mean (SE) change from baseline for TNX-102 SL -16.0 (1.17) and for placebo -8.4 (1.17); LSMD from placebo -7.7 (1.62); **p=0.000002**[#]

[#]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.

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RESILIENT FIQ-R Function Domain
Key Secondary Outcome Measure

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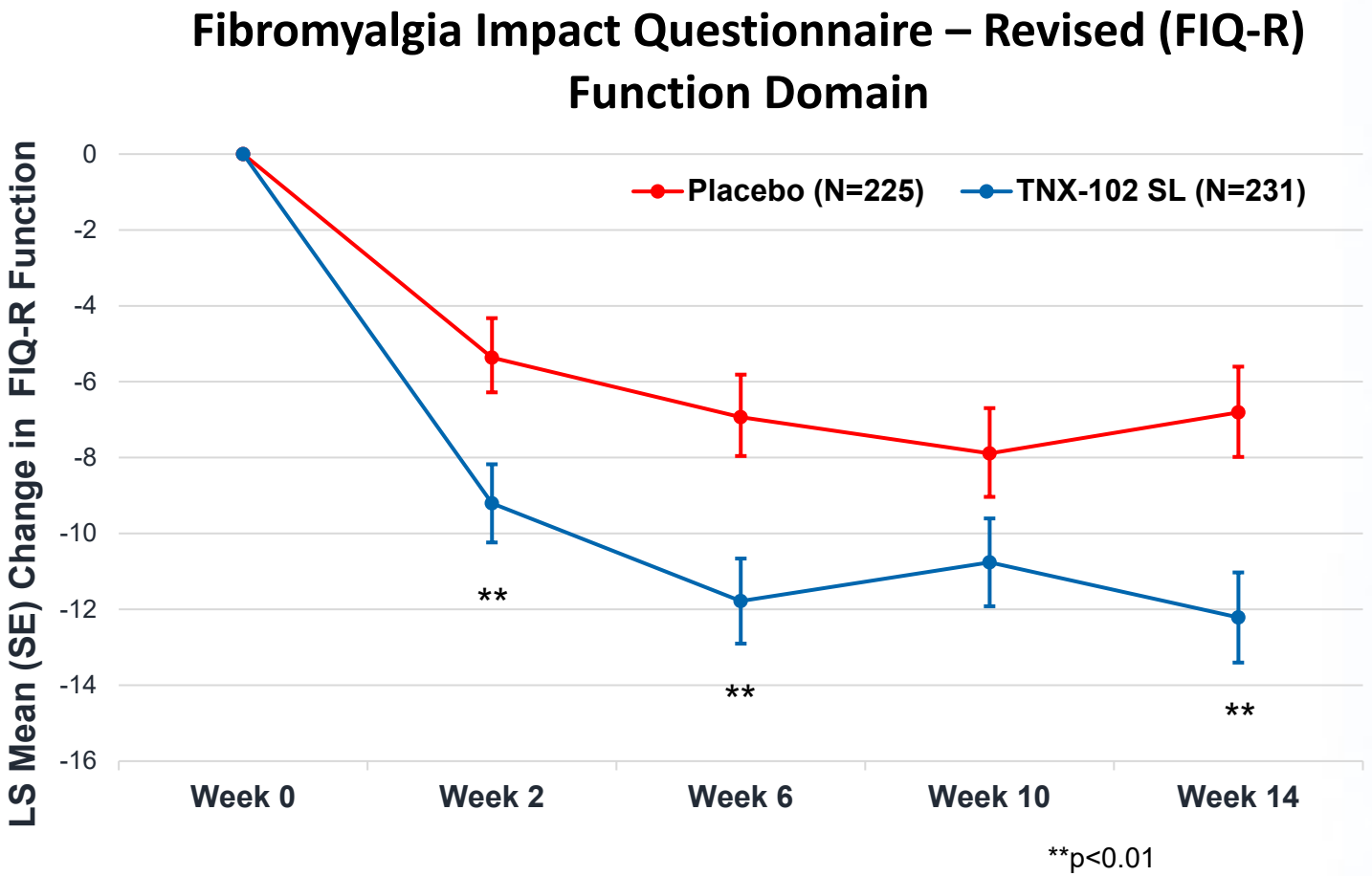

Week 14 LS mean (SE) change from baseline for TNX-102 SL -12.2 (1.19) and for placebo -6.8 (1.21); LSMD from placebo -5.4 (1.66); **p=0.001**[#]

[#]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.

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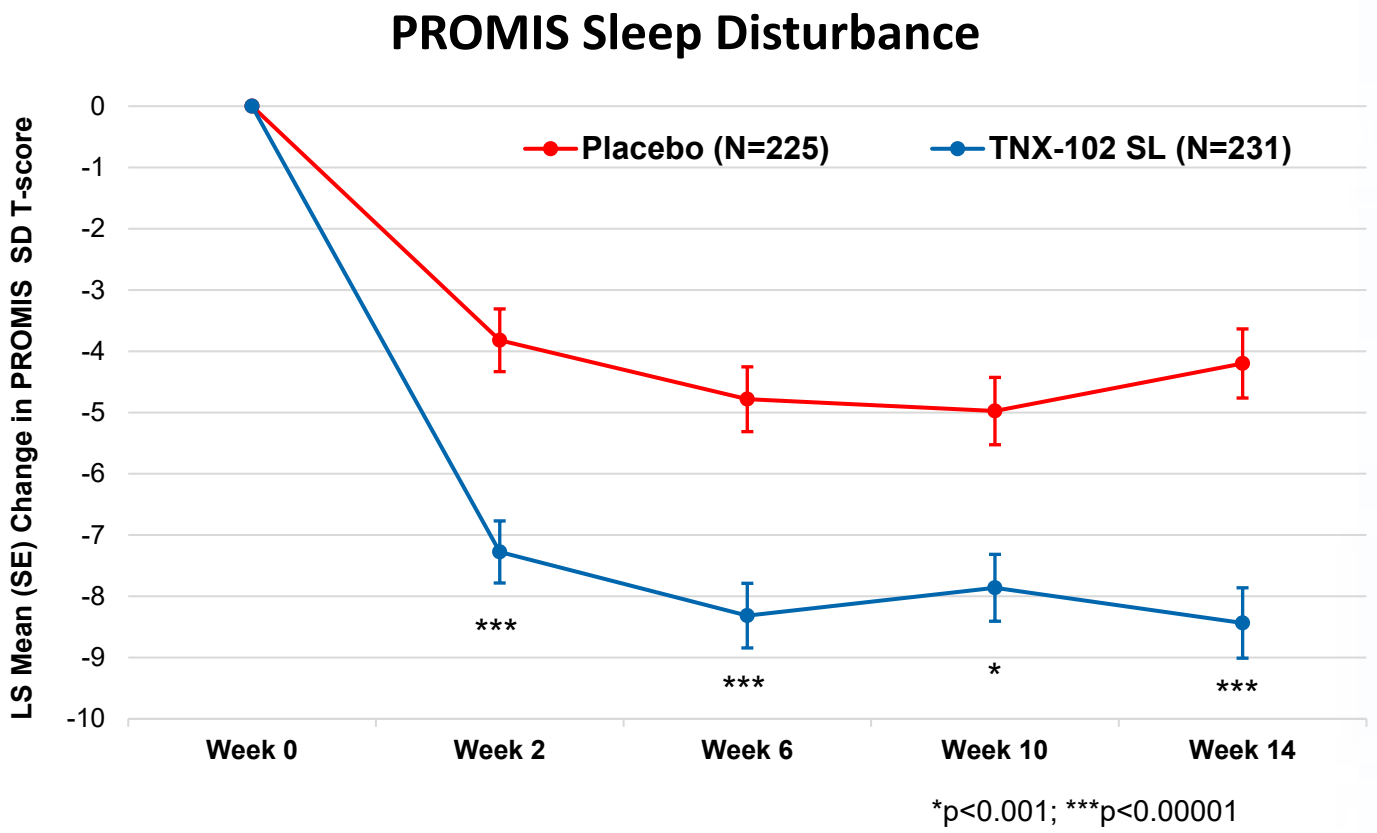
RESILIENT PROMIS Sleep Disturbance Inventory
Key Secondary Outcome Measure



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

RESILIENT Study

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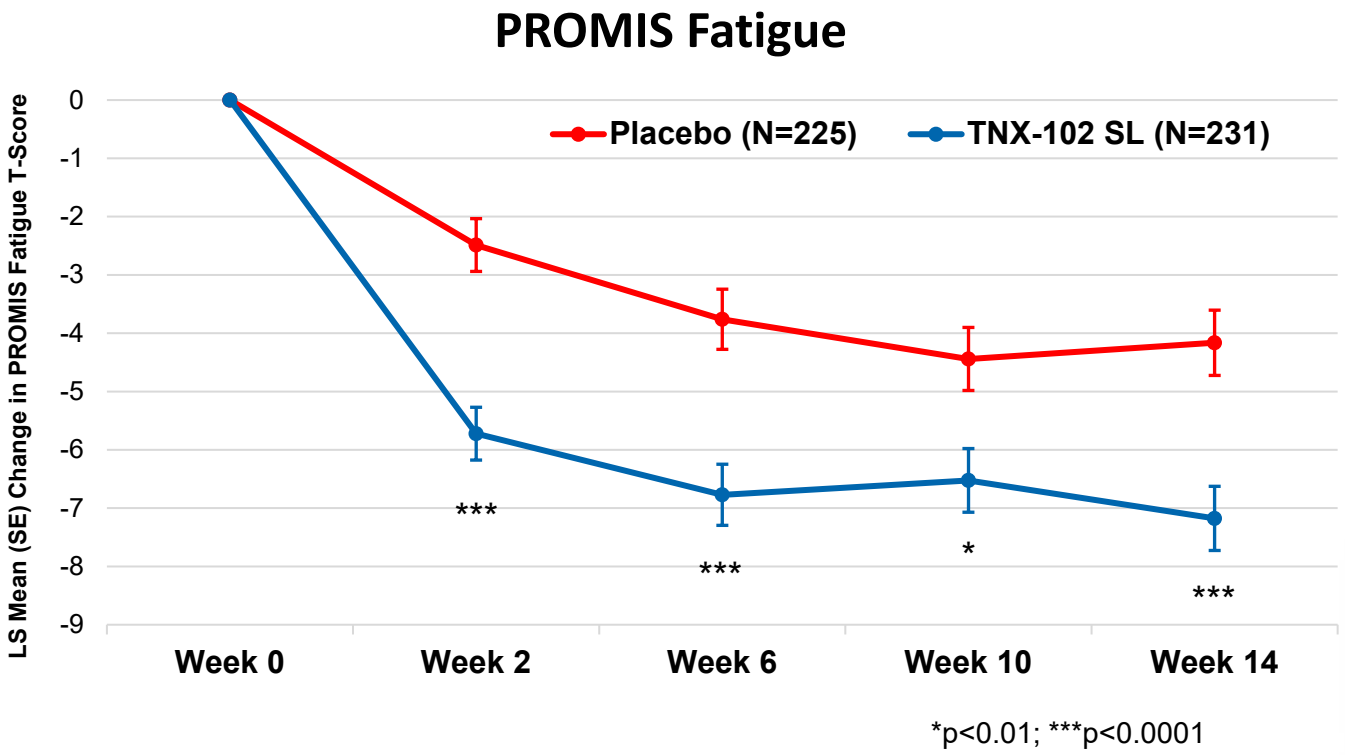

*p<0.01; ***p<0.0001

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.

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RESILIENT Sleep Quality by Daily Diary
Key Secondary Outcome Measure

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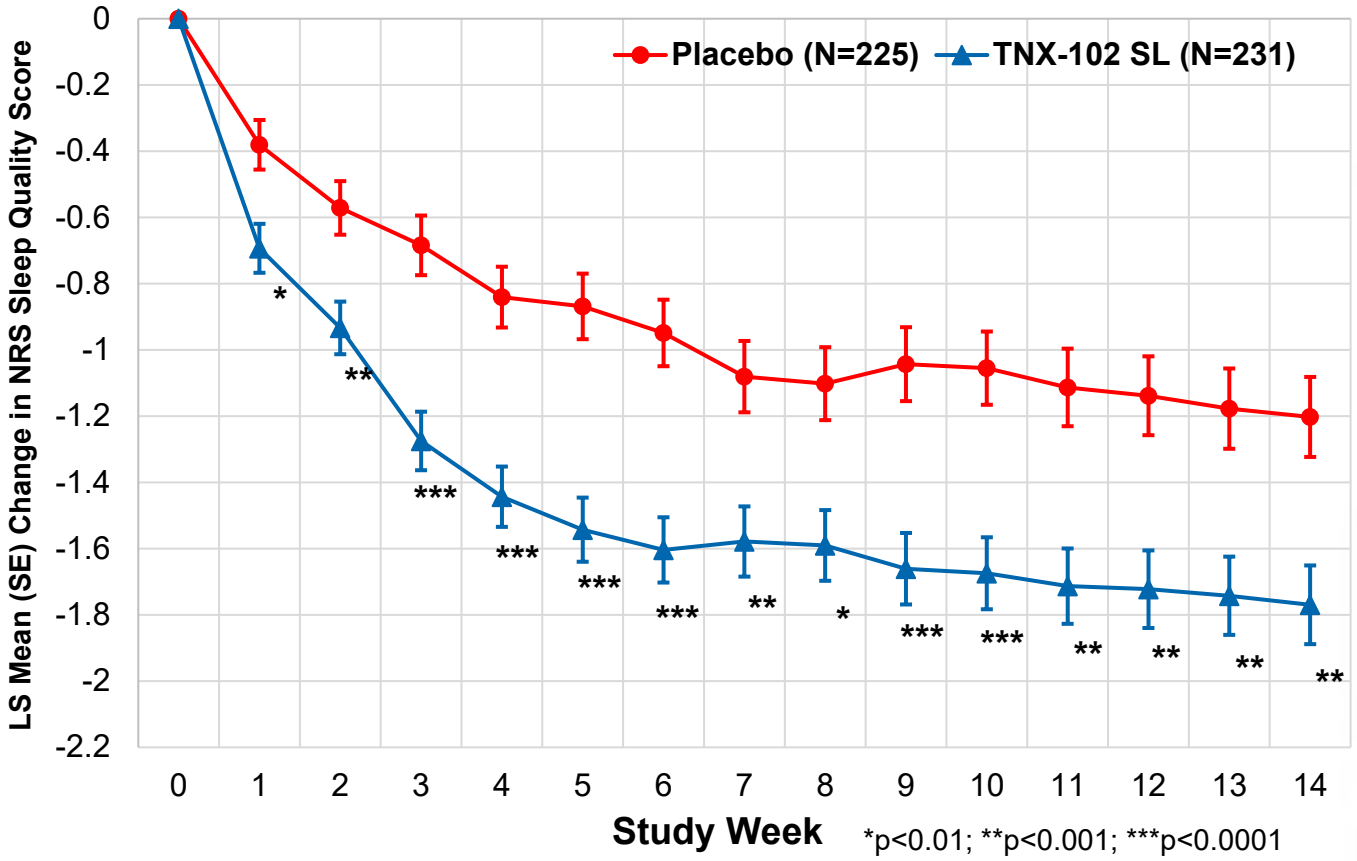
Weekly Average of Daily Diary NRS Ratings of Prior Night Sleep Quality



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.

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RESILIENT – Cognitive Dysfunction or "Brain Fog"

RESILIENT Study

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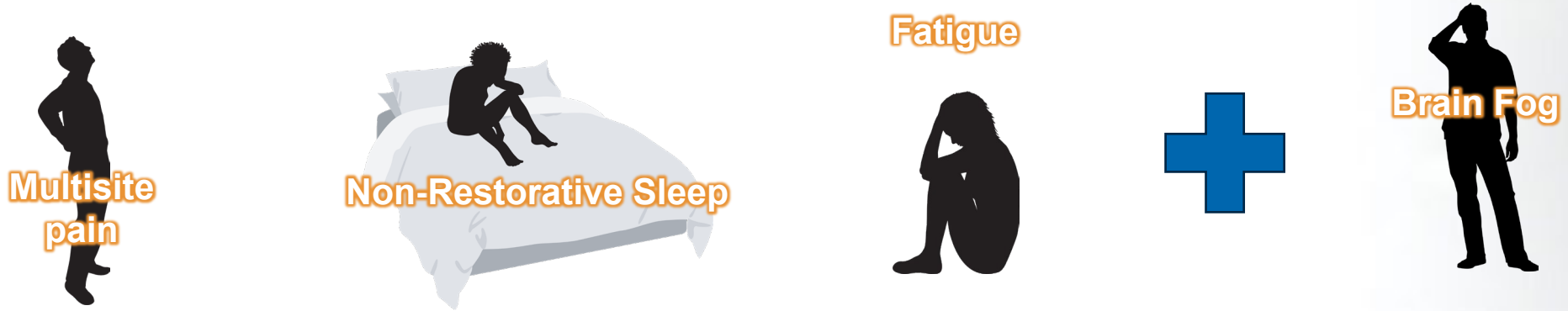
Brain Fog assessed by the FIQ-R[1] item on memory

- 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



[1]FIQ-R = Fibromyalgia Impact Questionnaire - Revised

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RESILIENT Summary of Efficacy

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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"

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RESILIENT Subject Disposition

	Placebo	TNX-102 SL	Total
Randomized	**226**	**231**	**457**
Completed	**179** (79.2%)	**187** (81.0%)	**366** (80.1%)
Discontinued	**47** (20.8%)	**44** (19.0%)	**91** (19.9%)
Adverse Event	8 (3.5%)	14 (6.1%)	22 (4.8%)
Lack of Efficacy	8 (3.5%)	2 (0.9%)	10 (2.2%)
Investigator Decision	2 (0.9%)	0 (0.0%)	2 (0.4%)
Withdrew Consent	16 (7.1%)	14 (6.1%)	30 (6.6%)
Lost to Follow Up	10 (4.4%)	10 (4.3%)	20 (4.4%)
Pregnancy	0 (0.0%)	1 (0.4%)	1 (0.2%)
Non-Compliance	2 (0.9%)	3 (1.3%)	5 (1.1%)
Other	1 (0.4%)	0 (0.0%)	1 (0.2%)

RESILIENT Safety Summary

Among participants randomized to Tonmya™ (TNX-102 SL) and to placebo, 81.0% and 79.6%, respectively, completed the study

Tonmya™ (TNX-102 SL) was generally well tolerated with an adverse event (AE) profile comparable to prior fibromyalgia studies

- No new safety signals were observed
- AE-related study discontinuations occurred in 6.1% and 3.6% of patients in the TNX-102 SL and placebo groups, respectively
- Events rated as mild or moderate made up 97.2% of AEs on placebo and 99.1% on TNX-102 SL
- As observed in prior studies with TNX-102 SL, oral administration site AEs were higher in TNX-102 SL than placebo, 42.9% and 10.2%, respectively
  - Most common oral AEs were oral hypoaesthesia, product taste abnormal, oral paraesthesia, and tongue discomfort (see table on next slide)
  - Nearly all of these common oral AEs were temporally related to dosing and lasted <60 minutes
- Serious Adverse Events (SAEs)
  - Three placebo participants experienced an SAE:
    - 1. Pneumonia, 2. Muscular weakness, and 3. Hypertension/Angina/Coronary Artery Disease
  - Two TNX-102 SL participants experienced an SAE
    - 1. Renal carcinoma deemed not related to study drug
    - 2. Acute pancreatitis with onset 14 days after completion of treatment phase, deemed ‘possibly related’* to study drug
      - Outcome: ‘Recovered/Resolved’
      - *Note: participant was non-compliant with end of treatment study visits, and the last dose before onset of SAE was not known at the time that relationship with study drug was assessed by Investigator and Sponsor

RESILIENT Safety Summary

RESILIENT Study

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Treatment-Emergent Adverse Events (TEAEs) at Rate of ≥ 3% in Either Treatment Group

System Organ Class Preferred Term	TNX-102 SL N=231	Placebo N=226	Total* N=457
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%)
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%)

*Safety Population

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RESILIENT Demographics and Baseline Characteristics

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	TNX-102 SL (N=231)	**Placebo** (N=225)
Age (years)	49.3 (10.45)*	49.5 (11.35)*
Female	224 (97.0%)†	211 (93.8%)†
Hispanic or Latino	36 (15.6%)†	35 (15.6%)†
White	194 (84.0%)†	192 (85.3%)†
Black	32 (13.9%)†	26 (11.6%)†
Pain Score (0-10 NRS)	5.9 (1.05)*	5.9 (1.08)*
Employed Yes	147 (63.6%)†	150 (66.7%)†
FM Duration (years)	8.6 (8.44)*	9.9 (9.53)*
BMI (kg/m^2)	31.1 (6.34)*	31.1 (6.32)*

* Mean (standard deviation)
† N (%)

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RESILIENT Prior Medication Use

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Summary of Lifetime and Prior Fibromyalgia Pharmacotherapy*

System Organ Class Preferred Term	TNX-102 SL N=231	Placebo N=226	Total* N=457
At least one lifetime medication	124 (53.7%)	133(58.8%)	257 (56.2%)
Gabapentin/Pregabalin	72 (31.2%)	75 (33.2%)	147 (32.2%)
Gabapentin	46 (19.9%)	50 (22.1%)	96 (21.0%)
Pregabalin**	46 (19.9%)	45 (19.9%)	91 (19.9%)
Antidepressants	60 (26.0%)	66 (29.2%)	126 (27.6%)
Duloxetine**	47 (20.3%)	52 (23.0%)	99 (21.7%)
Amitriptyline	12 (5.2%)	13 (5.8%)	25 (5.5%)
Milnacipran**	5 (2.2%)	10 (4.4%)	15 (3.3%)

*Safety population, shown are medicines >3% reported in any group
**Indicated for management of fibromyalgia

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RESILIENT Washout Medications

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Summary of Prior Washout Medications (at least two patients)*

System Organ Class Preferred Term	TNX-102 SL N=231	Placebo N=226	Total* N=457
At least one washout medication	14 (6.1%)	12 (5.3%)	26 (5.7%)
Nervous System Drug	10 (4.3%)	10 (4.4%)	20 (4.4%)
Gabapentin	5 (2.2%)	1 (0.4%)	6 (1.3%)
Amfetamine (different salts)	1 (0.4%)	2 (0.9%)	3 (0.7%)
Duloxetine**	1 (0.4%)	2 (0.9%)	3 (0.7%)
Trazodone	1 (0.4%)	2 (0.9%)	3 (0.7%)
Amitriptyline	0 (0.0%)	2 (0.9%)	2 (0.4%)

*Safety population
**Indicated for management of fibromyalgia

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RESILIENT Characteristics of Study Population

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Pain Scores

- Patients are asked to record “their average pain” for each day
  - ‘Average’ pain for the day will almost always be lower than ‘worst’ pain for a patient’s day
- Baseline pain for randomization
  a) A mean pain intensity score ≥4 and ≤9 on the 11-point (0-10) NRS scale for the 7 days immediately preceding Visit 2, and
  b) No more than 2 individual days with a score <4 on the 7 days immediately preceding Visit 2, and
  c) No score of 10 on any of the 7 days immediately preceding Visit 2, and
  d) Pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2
- Mean Pain score for Baseline (BL) for the RESILIENT study was 5.9
  - Using the same method, BL for F304 (RELIEF) was 6.1 and BL for F306 (RALLY) was 6.0
- Breakthrough pain
  - No explicit rescue algorithm
  - 10 participants took an opiate during the study (6 on TNX-102 SL and 4 on placebo)

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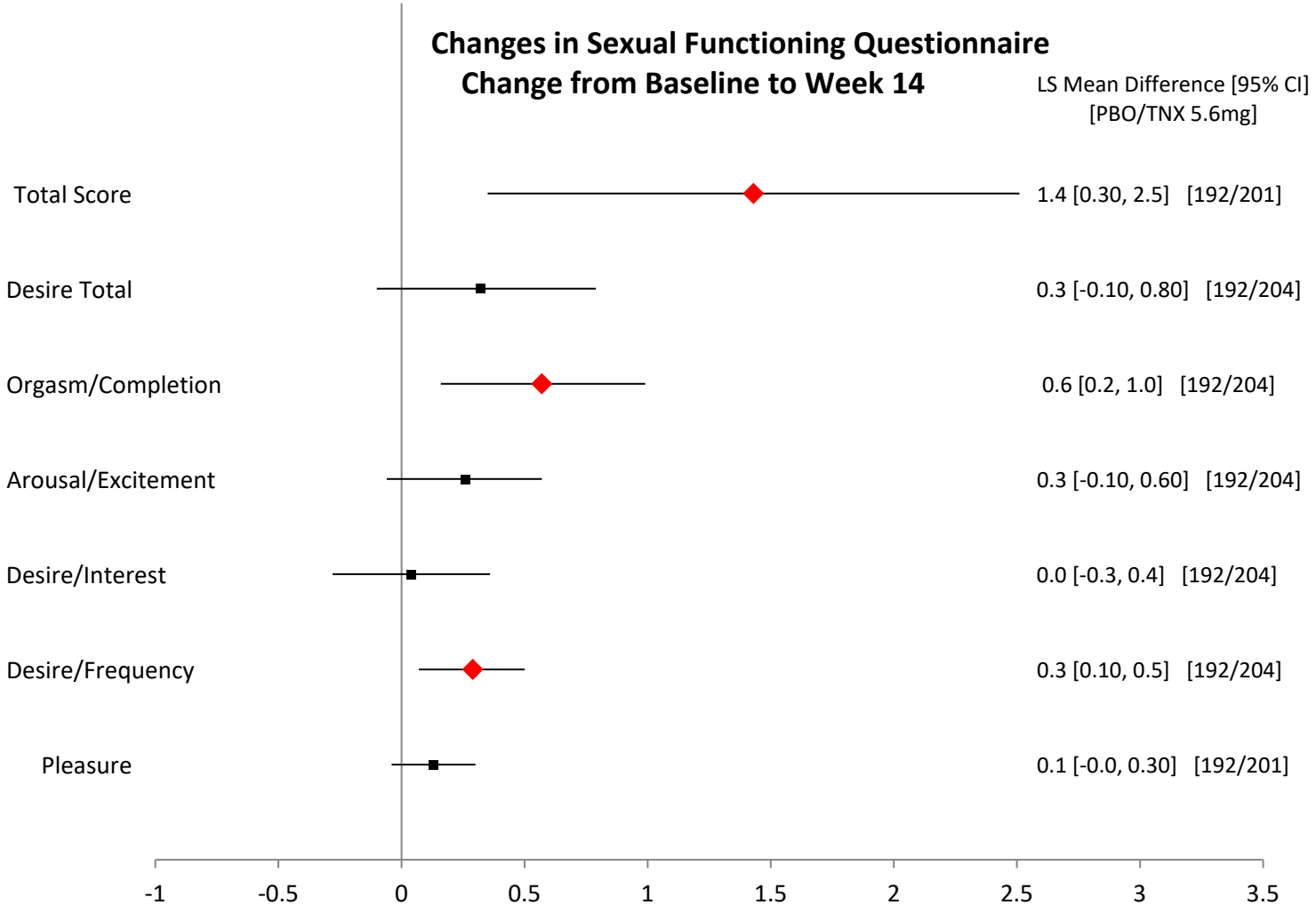
RESILIENT CSFQ-14 Females
Safety Measure



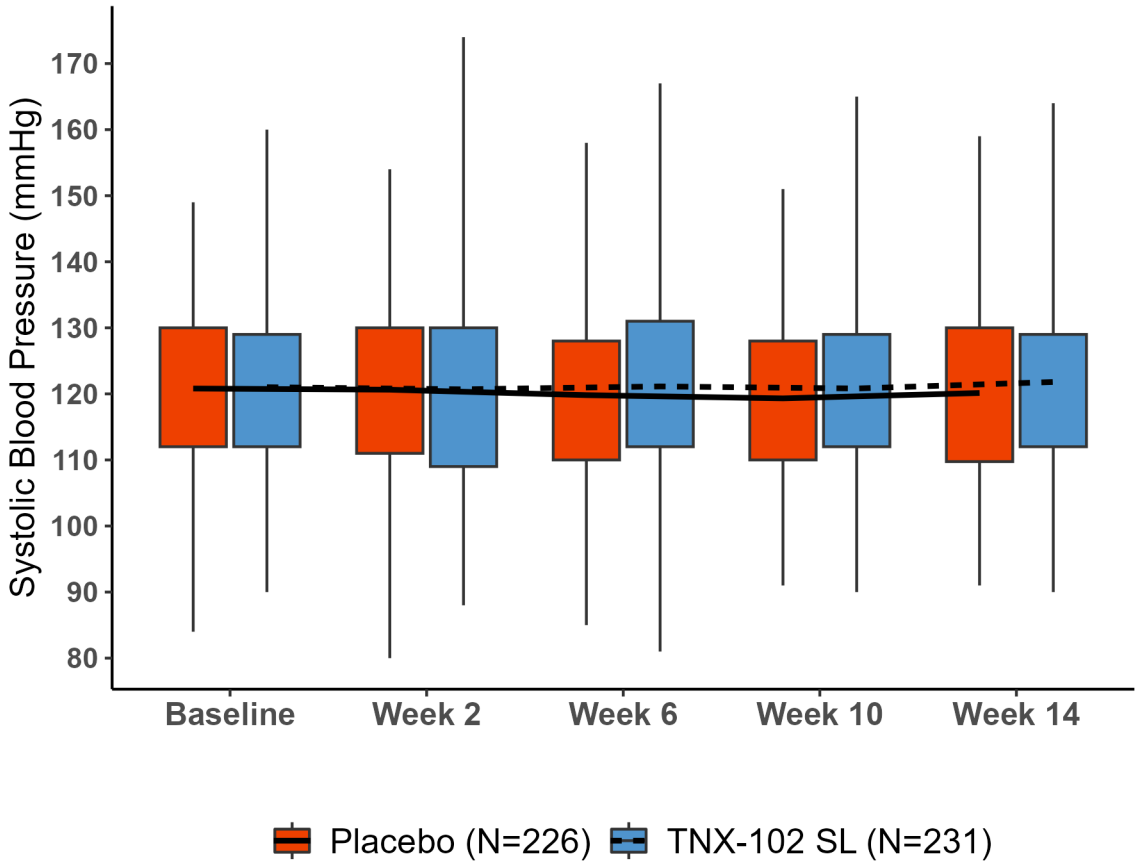
ANCOVA analysis: comparison between groups (TNX-102 SL 5.6 mg vs. Placebo)
Red Diamond refers to treatment differences with p <0.05, not corrected for multiple comparisons

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
- Potential tolerability advantage over pharmacotherapeutics with potent serotonin reuptake inhibition

CNS PORTFOLIO

RESILIENT Systolic blood pressure
Safety Measure



No clinically meaningful difference in mean systolic blood pressure between groups

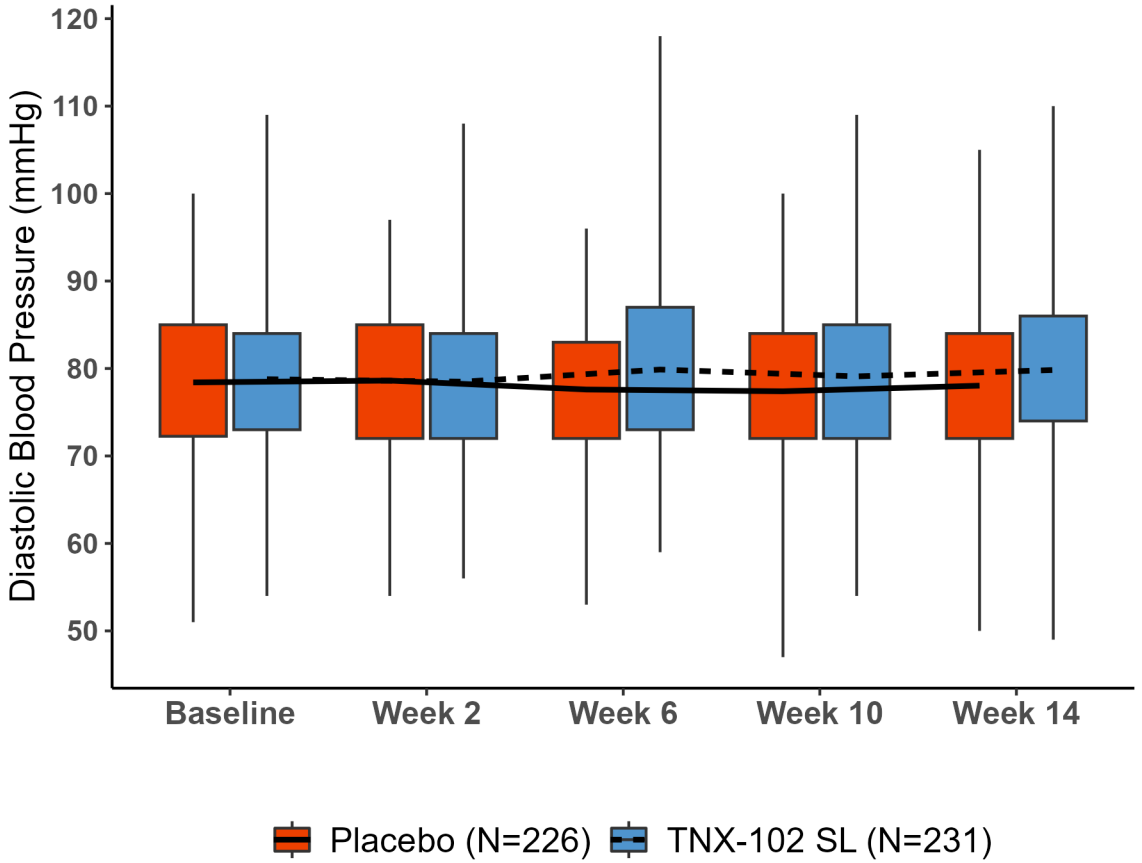
Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.7 (12.38) mmHg

Placebo = 0.5 (10.42) mmHg

Horizontal lines are the mean for each group; boxes are the 25th and 75th percentiles; and vertical lines begin and end at the 5th and 95th percentiles.

RESILIENT Diastolic blood pressure
Safety Measure



No clinically meaningful difference in mean diastolic blood pressure between groups

Week 14 mean (SD) change from baseline:

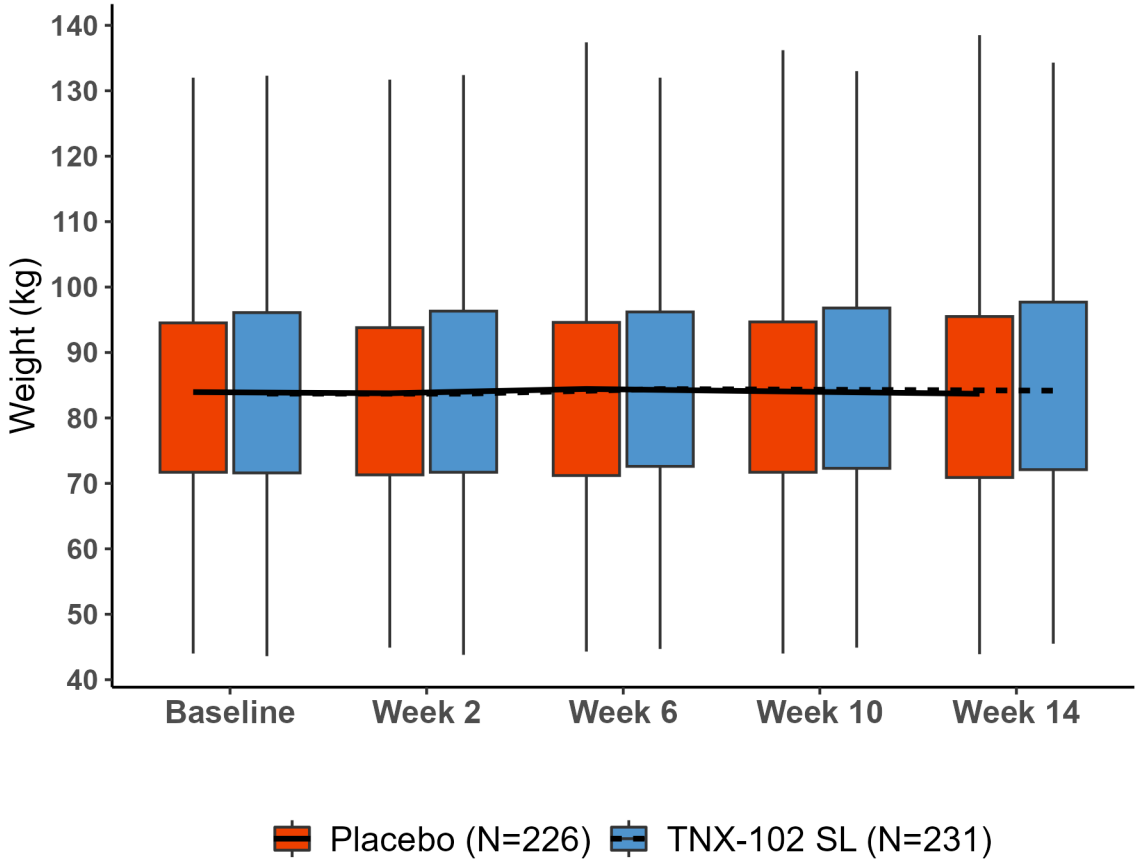
TNX-102 SL = 1.1 (8.60) mmHg

Placebo = 0.2 (8.22) mmHg

Horizontal lines are the mean for each group; boxes are the 25th and 75th percentiles; and vertical lines begin and end at the 5th and 95th percentiles.

CNS PORTFOLIO

RESILIENT Weight
Safety Measure



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

Horizontal lines are the mean for each group; boxes are the 25th and 75th percentiles; and vertical lines begin and end at the 5th and 95th percentiles.

Tonmya™ (TNX-102 SL): Patents and Patent Applications

- **U.S. Composition:***
  - A 75:25 cyclobenzaprine HCl - mannitol eutectic (dependent claims add a basifying agent).
    - 5 US Patents (Expire November 2034)
    - 1 Pending US Application (Would expire November 2034)
  - A composition of a cyclobenzaprine HCl and a basifying agent suitable for sublingual absorption.
    - 1 Pending US Application (Would expire June 2033)

- **U.S. Methods of Use* (Specific Indications):**
  - Fibromyalgia
    - Pain, Sleep Disturbance, Fatigue
      - 1 Pending US Application (Would expire December 2041)
    - Early Onset Response
      - 1 Pending US Provisional Application (Would expire December 2044)
    - Depressive Symptoms
      - 1 Pending US Application (Would expire March 2032)
  - Sexual Dysfunction
    - 1 Pending US Application (Would expire October 2041)
  - PASC
    - 1 Pending US Application (Would expire June 2043)
  - PTSD
    - 1 US Patent (Expires November 2030)
  - Agitation (Dementia)
    - 1 US Patent (Expires December 2038)
    - 1 Pending US Application (Would expire December 2038)
  - Alcohol Use Disorder
    - 1 Pending US Application (Would expire November 2041)

- **Foreign Filings**
  - Corresponding foreign patents have been filed and some have issued:
    - Composition (25 patents, 3 allowed applications, 16 pending applications)
    - Methods of Use (9 patents, 54 pending applications)

*US Patents: Issued: US Patent Nos. 9,636,408; 9,956,188; 10,117,936; 10,864,175; 11,839,594; 9,918,948; 11,826,321. Pending: US Patent Application Nos. 13/918,692; 18/385,468; 13/412,571; 18/265,525; 63/612,352; 18/382,262; 18/037,815; 17/226,058; 18/212,500.

Fibromyalgia: Market Characteristics

Prevalence

- One of the more common chronic pain disorders (2-4% of US Population)[1]

Diagnosed population

- Large population but underdiagnosed[2] relative to prevalence rate
- Majority receive drug treatment[3]

Treatment Pattern

- Polypharmacy the norm - average 2.6 drugs/patient[3]
- Rotation through therapy common: average ~5 drugs/year[3]
- Estimated that >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[4,5]

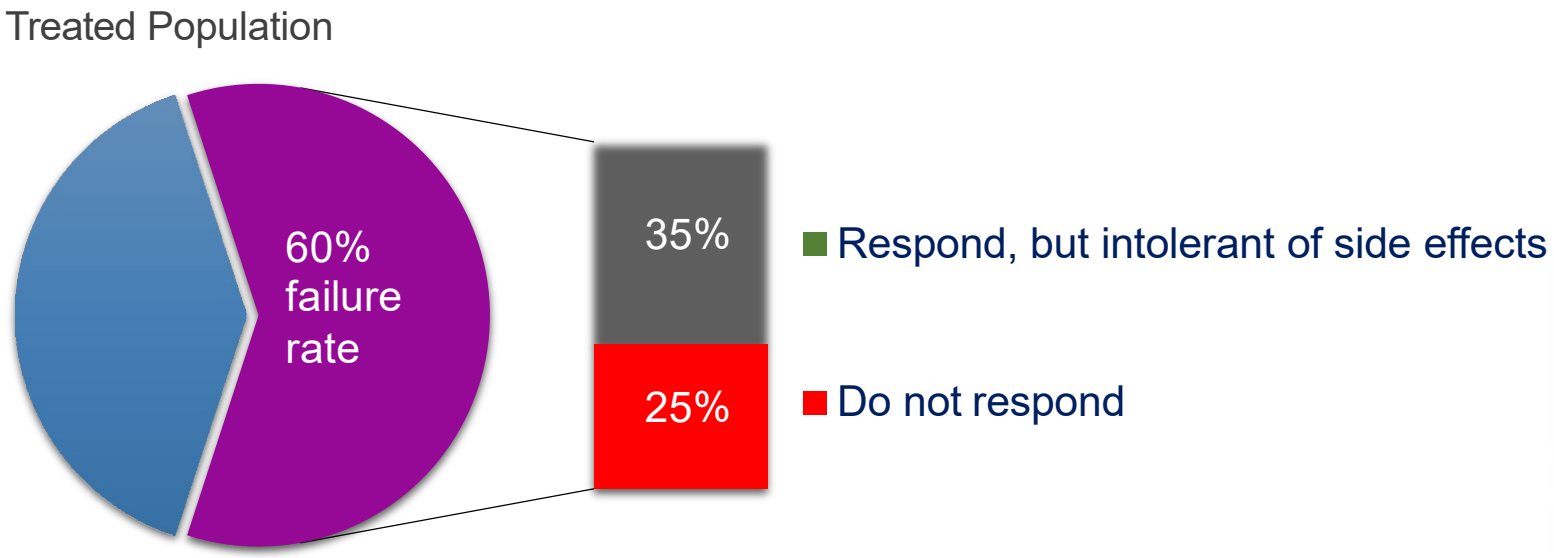
Unmet Need

- Majority of patients do not respond or cannot tolerate therapy[6]

[1]American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
[2]Vincent et al., 2013; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population
[3]Robinson, et al., 2012; 85% received drug treatment
[4]Vincent et al, Arthritis Care Res 2013;65:786
[5]Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.
[6]Market research by Frost & Sullivan, commissioned by Tonix, 2011

Fewer than Half of Those Treated for Fibromyalgia Receive Sustained Benefit from the Three FDA-Approved Drugs[1]

- The treatment objective is to **restore functionality** and **quality of life** by broadly improving symptoms while avoiding significant side effects
- The majority fail therapy due to **lack of a response** or **poor tolerability**[2]



[1] The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)
[2] Market research by Frost & Sullivan, commissioned by Tonix (2011)

Current FDA-Approved Fibromyalgia Drugs were Repurposed[1]

Human investigation was required to find drugs that improve pain in fibromyalgia

- No current product addresses pain, poor sleep and fatigue

Drug		Lyrica® - Pfizer	Cymbalta® - Lilly Savella® - AbbVie
Initial Indication Sought		Epilepsy	Depression
Class		Gabapentinoid	SNRI
Mechanism		Slow neuron firing	Block NE reuptake
Fibromyalgia Activity	Pain	+	+
	Sleep	+	-
	Fatigue	-	+
Tolerability Issues	Sleep	-	+
	Fatigue	+	-
		Weight gain	Blood Pressure increases
			Sexual function impairment
			GI issues

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

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 use[1]
  - 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 simultaneously[2]
  - The typical patient has tried six different medications[3]
- Substantial off-label use of narcotic painkillers and prescription sleep aids[3]
  - Among those diagnosed, more than one-third have used prescription opioids as a means of treatment[4]
- 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

		Pregabablin	Duloxetine Milnacipran	Tonmya™
Activity	Pain	**YES**	**YES**	**YES**
	Sleep	**YES**	**-**	**YES**
	Fatigue	**-**	**YES**	**YES**
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 gabapentinoids or SNRIs

TONIX PHARMACEUTICALS

Potential for Tonix to Launch and Market Tonmya™

Decline in personal promotion ("Detailing") of prescription drugs

- The pandemic accelerated transition to non-personal promotion
  - Omnichannel is more important and more sophisticated
    - Tele-sales
    - Digital
    - Direct mail
- Growth in need to support patients with payers to seek reimbursement

Fibromyalgia experts are a subset of Rheumatologists

- New prescriptions for fibromyalgia drugs originate in a subset of doctors
  - Refills may be written by general practitioners

Channels for distribution of prescription drugs are evolving

- Growth of specialty pharmacies who distribute products by mail

Planning for Tonmya™ Launch and Marketing

Several companies that successfully developed CNS drugs have launched them

- Big Pharma wants the commercial launch de-risked before acquisition (*e.g.*, Nurtec®)

Company		Mkt Cap[1]	Product	Indication	FDA Approval	Exit
Axsome	AXSM	$4.4 B	Auvelity®	Depression	8/2022	
Biohaven	BHVN	$3.8 B	Nurtec®	Migraine	2/2020	Sold to PFE for $12 B in Oct 2022
IntraCellular	ITCI	$7.1 B	Caplyta®	Schizophrenia	12/2019	
Supernus	SUPN	$1.5 B	Oxtella-XR®	Seizures	1/2019	
Neurocrine	NBIX	$13.2 B	Ingrezza®	Tardive Dyskinesia	4/2017	
Acadia	ACAD	$4.1 B	Nuplazid®	Parkinson's psychosis	4/2016	

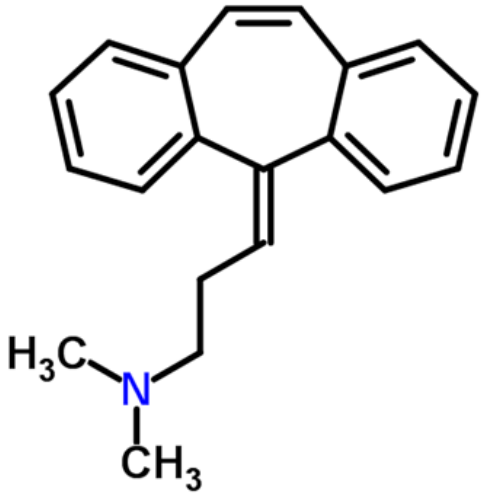
To prepare for the launch of Tonmya, Tonix acquired two marketed Rx drugs: Zembrace® and Tosymra®

- Both are indicated for the acute treatment of migraine

[1] Feb 21, 2024

About Cyclobenzaprine and Tonmya™ Formulation

Cyclobenzaprine Long-Term Utilization



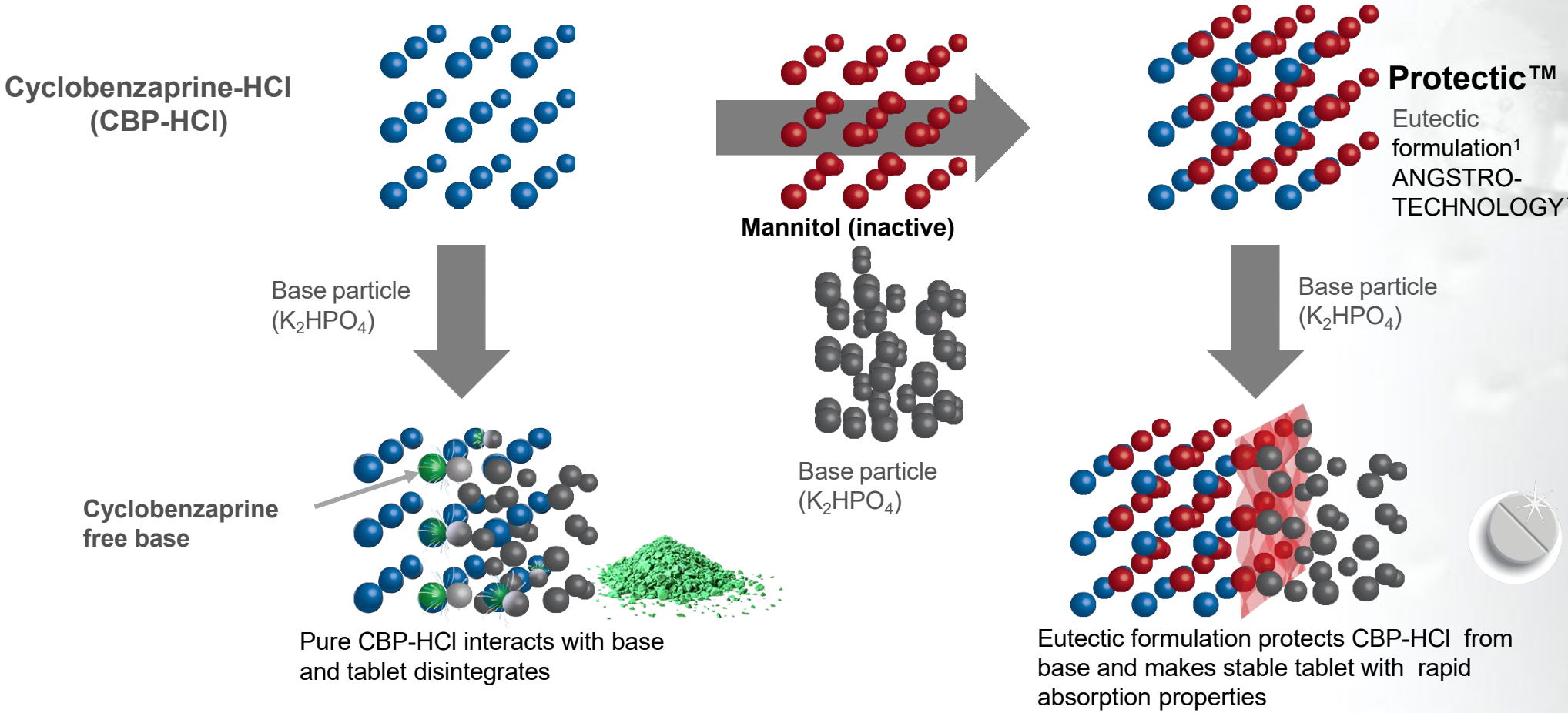
- **Flexeril® approved in 1977 by Merck for the treatment of muscle spasm**
  - 10 mg T.I.D. for acute use (2-3 weeks)
  - 1999 OTC AdCom Briefing Package: original NDA included "*8 long term safety studies* in which patients with various neurologic disorders received cyclobenzaprine up to *80 mg per day for 1 month up to 3 years*."

  6 published studies in fibromyalgia
  - N=246, placebo controlled, 4-24 week treatment period
  - Generally well tolerated, no new or unexpected AEs

  Extensive safety record in humans for over 30 years
  - In recent years, ~20 million prescriptions and ~ 1 billion tablets dispensed *per year*
  - Chronic cyclobenzaprine use is common *(*~12% of users)
- **Post-marketing surveillance program**
  - 7,607 patients included 297 patients treated with 10 mgs for ≥ 30 days
  - Incidence of most common AEs was much lower than in controlled studies

Tonmya™ (TNX-102 SL): Proprietary Eutectic Formulation

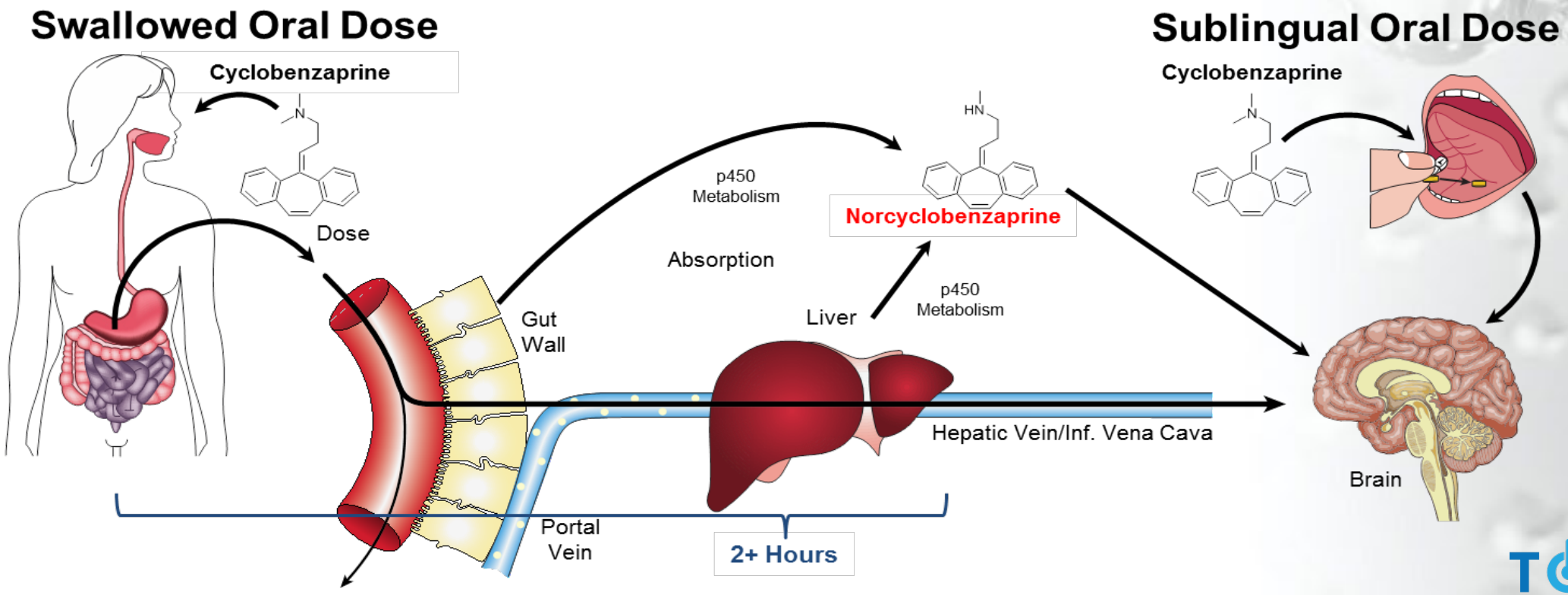
- **Proprietary Cyclobenzaprine HCL Eutectic Mixture Stabilizes Sublingual Tablet Formulation**



[1] U.S. Patent issued May 2, 2017

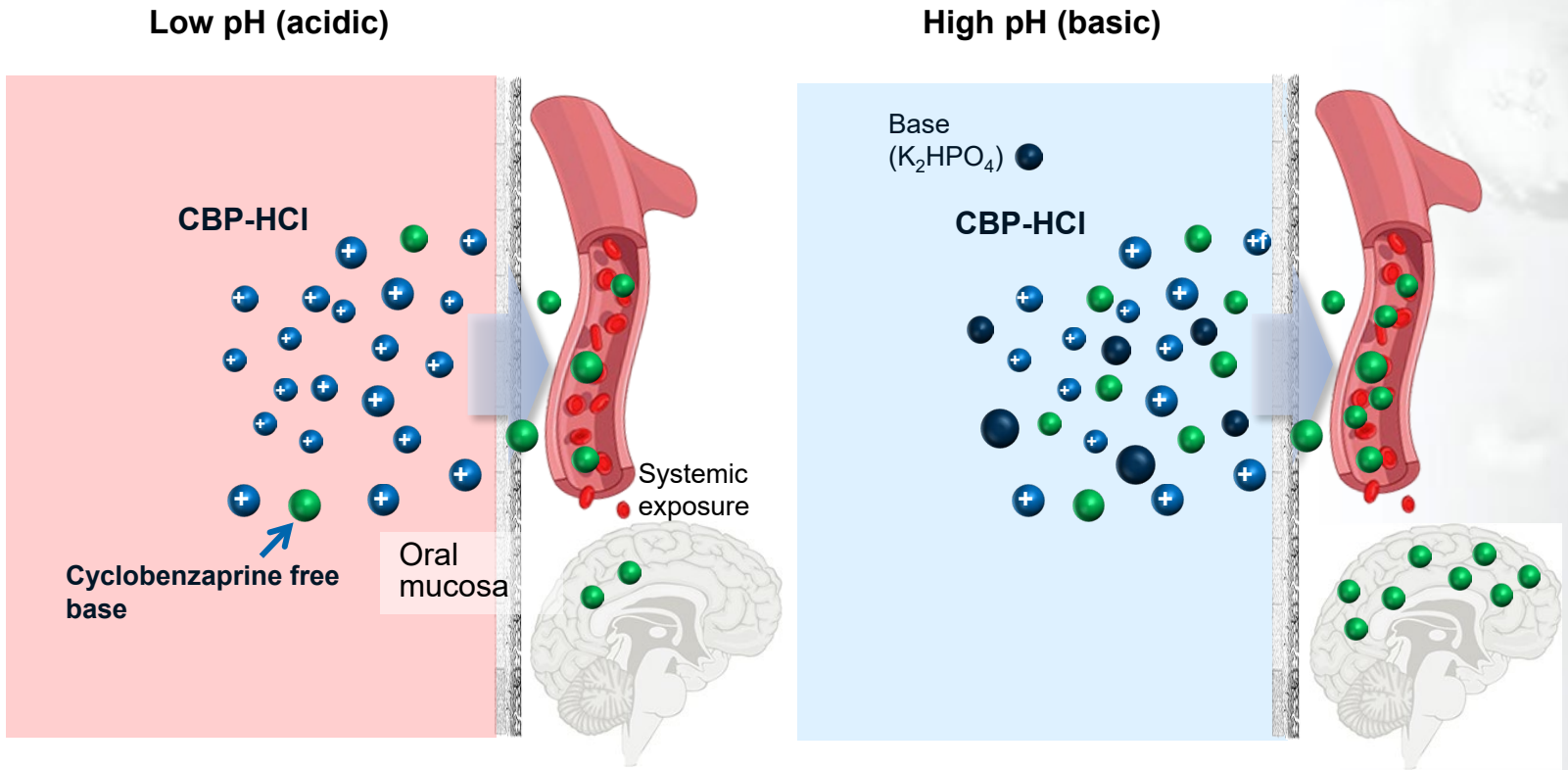
Tonmya™ (TNX-102 SL): Sublingual Administration and Transmucosal Delivery

- 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)



Formulation with Base Increases Systemic Absorption of Sublingual Cyclobenzaprine[1]

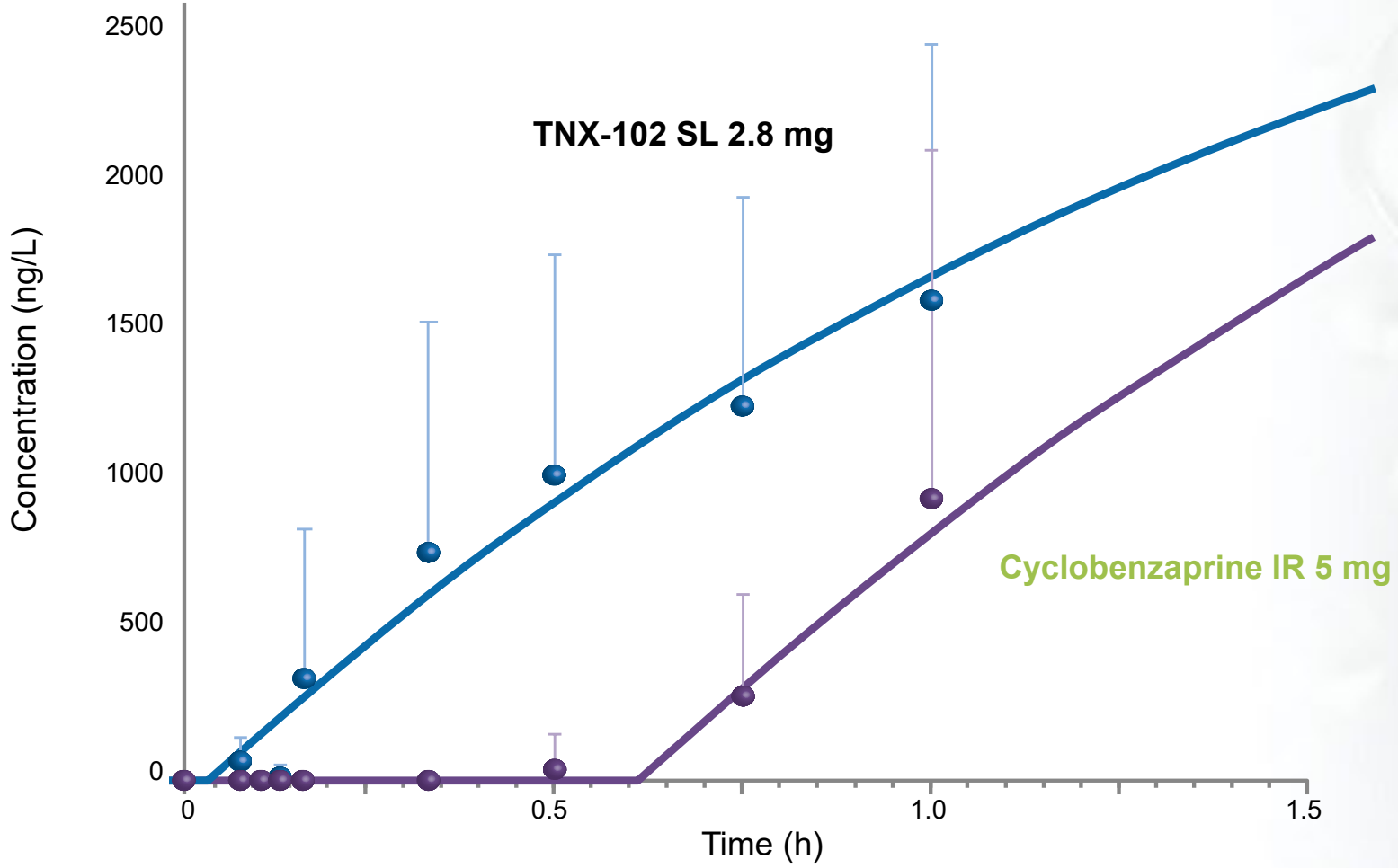
Concentration gradient increases diffusion of free base across oral mucosa (Le Chatelier's Principle)



[1]US Patent applications 13/918,692. 14/214,433 and 14/776,624 - Eutectic Formulations

Tonmya™ (TNX-102 SL): Cyclobenzaprine Detected in Plasma Within Minutes Following Sublingual Administration

Plasma Concentration Versus Time of TNX-102 SL Compared to Cyclobenzaprine IR



Tonmya™ (TNX-102 SL): Single Dose PK Differentiation from Oral IR CBP

TNX-102 SL 2.8 mg v. Oral IR CBP 5 mg: Single Dose Pharmacokinetics

Parameter	TNX-102 SL 2.8 mg	Oral IR CBP 5 mg	TNX-102 SL Compared to Oral IR
	Cyclobenzaprine		
Absorption Lag Time	0.050 hr (3 min)	0.622 hr (37 min)	12x faster
Relative Bioavailability	154%	-	54% higher
C_{max}	3.41 ng/mL	4.26 ng/mL	20% lower
AUC_{0-48}	57.4 ng•hr/mL	69.5 ng•hr/mL	17% lower
	Norcyclobenzaprine		
C_{max}	0.81 ng/mL	1.71 ng/mL	53% lower
AUC_{0-48}	30.5 ng•hr/mL	58.6 ng•hr/mL	48% lower
	Cyclobenzaprine/Norcyclobenzaprine		
Ratio AUC_{0-48}	1.88	1.18	59% higher

PK = pharmacokinetics
IR = immediate release
CBP = cyclobenzaprine
C_{max} = maximum concentration
AUC = Area under the curve

Tonmya™ (TNX-102 SL): Multi-Dose PK Differentiation from Simulated Oral IR CBP

Tonmya™ (TNX-102 SL): Proprietary sublingual formulation of cyclobenzaprine (CBP) with transmucosal absorption

- Rapid systemic exposure
- Increases bioavailability during sleep
- Avoids first-pass metabolism
- Lowers exposure to long-lived active major metabolite, norcyclobenzaprine (norCBP)

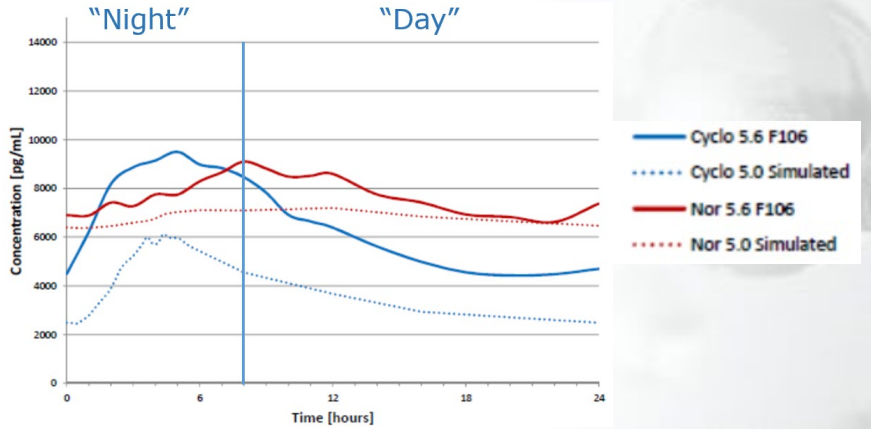
CBP undergoes extensive first-pass hepatic metabolism when orally ingested

- Active major metabolite, norCBP

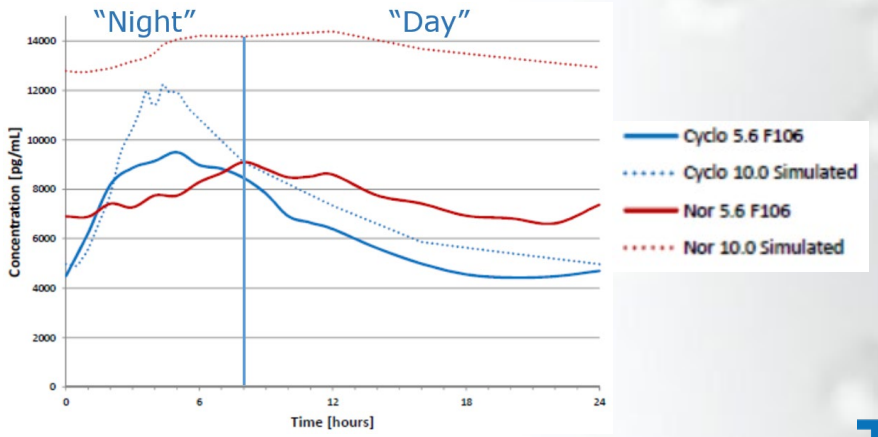
PK = pharmacokinetics
IR = immediate release
CBP = Cyclo = cyclobenzaprine
Nor = norCBP = norcyclobenzaprine

Steady State Pharmacokinetics (after 20 days dosing)

Day 20 TNX-102 SL 5.6 mg v. Simulated Oral IR 5 mg



Day 20 TNX-102 SL 5.6 mg v. Simulated Oral IR 10 mg



Multi-Functional Mechanism Involves Antagonism at Four Neuronal Receptors

Active ingredient, cyclobenzaprine, interacts with four receptors

- Antagonist at 5-HT_{2A} receptors
  - Similar activity to trazodone and Nuplazid® (pimivanserin)
- Antagonist at α_1-adrenergic receptor
  - Similar activity to Prazosin® (prazosin)
- Antagonist at histamine H_1 receptors
  - Similar activity to Benadryl® (diphenhydramine) and hydroxyzine
- Antagonist at muscarinic M_1 receptors
  - Similar activity to Benadryl® (diphenhydramine), Prozac® (fluoxetine), Paxil® (paroxetine), Zyprexa (olanzapine) and Seroquel® (quetiapine).

Cyclobenzaprine Binding Affinities for Receptor and Transporter

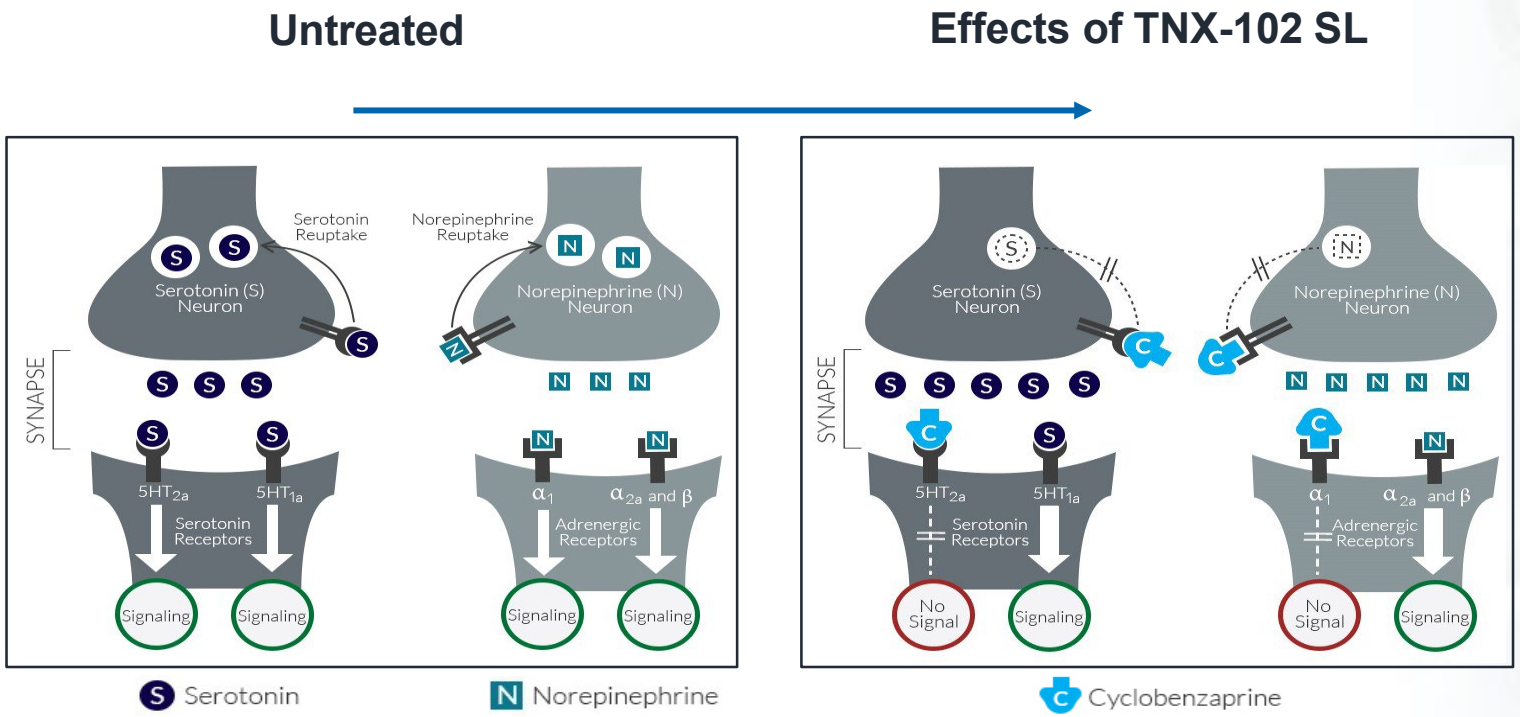
	H_1	5-HT_{2A}	α_{1A}	α_{1B}	M_1	SERT	NET
Cyclobenzaprine (CBP)	1.2	5.4	7.1	8	8.4	29	39
Norcyclobenzaprine (nCBP)	17.8	38	82	71	155	461	12.8

CBP/nCBP Activity	Antagonist	Inhibitor

Cyclobenzaprine Effects on Nerve Cell Signaling

Cyclobenzaprine is a multi-functional drug – SNARI

- inhibits serotonin and norepinephrine reuptake
- blocks serotonin 5-HT_{2A} and norepinephrine$_{\alpha 1}$ receptors



SNARI = Serotonin and Norepinephrine receptor Antagonist and Reuptake Inhibitor

Tonmya™ (TNX-102 SL): No Recognized Abuse Potential in Clinical Studies

Active ingredient is cyclobenzaprine, which is structurally related to tricyclic antidepressants

- Cyclobenzaprine interacts with receptors that regulate sleep quality: 5-HT2A, α1-adrenergic and histamine H1 receptors
- Cyclobenzaprine does NOT interact with the same receptors as traditional hypnotic sleep drugs, benzodiazepines or non- benzodiazepines that are associated with retrograde amnesia
- Cyclobenzaprine-containing product was approved 40 years ago and current labeling (May 2016) indicates no abuse or dependence concern

Tonmya™ (TNX-102 SL) NDA can be filed without drug abuse and dependency assessment studies

- April 2017 meeting minutes from the March 2017 FDA meeting

Tonmya™ (TNX-102 SL): Sublingual Formulation is Designed for Bedtime Administration

Tonmya™ (TNX-102 SL): Proprietary sublingual formulation of cyclobenzaprine (CBP) with transmucosal absorption

- Innovation by design with patent protected CBP/mannitol eutectic
- Rapid systemic exposure
- Increases bioavailability during sleep
- Avoids first-pass metabolism
- Lowers exposure to long-lived active major metabolite, norcyclobenzaprine (norCBP)

CBP undergoes extensive first-pass hepatic metabolism when orally ingested

- Active major metabolite, norCBP1
- Long half-life (~72 hours)
- Less selective for target receptors (5-HT2A, α1-adrenergic, histamine H1)
- More selective for norepinephrine transporter and muscarinic M1

Multi-functional activity suggests potential for other indications

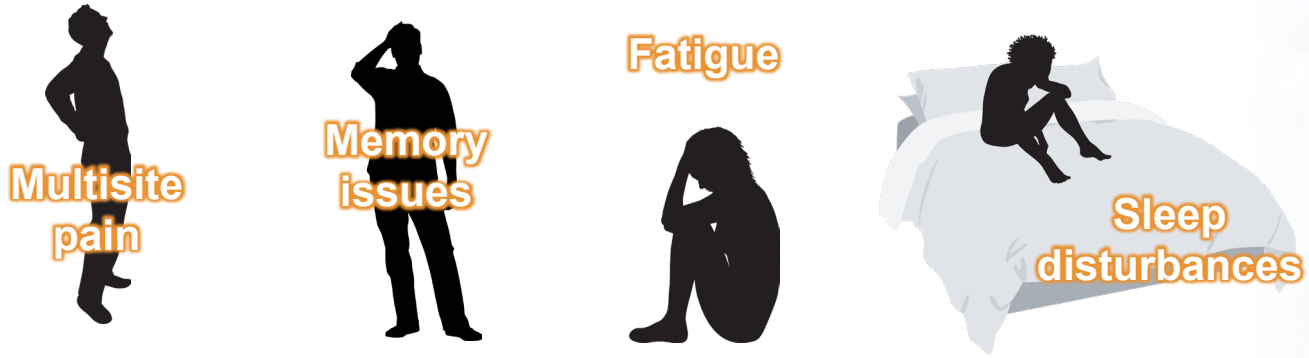
- TNX-102 SL was developed for the management of fibromyalgia (Phase 3)
- Sleep quality is a problem in other conditions

TONIX PHARMACEUTICALS

Tonmya™ for Other Indications: Long COVID and Acute Stress Disorder

About Fibromyalgia-Type Long COVID

Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after acute COVID-19 infection[1]



Many Long-COVID symptoms overlap with core symptoms of fibromyalgia

and are hallmarks of other chronic pain syndromes like myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

19% **Long COVID occurs in approximately 19% of recovered COVID-19 patients[2]**

40% **As many as 40% of Long COVID patients experience multi-site pain[3,4]**

[1]CDC - https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=Some%20people%20who%20have%20been,after%20acute%20COVID%2D19%20infection.
[2]CDC Press Release, June 22, 2022 - https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm
[3]Harris, H, et al. Tonix data on file. 2022
[4]TriNetX Analytics

TONIX PHARMACEUTICALS

TNX-102 SL for Fibromyalgia-Type Long COVID: Phase 2 PREVAIL Study Design

PREVAIL Study

CNS PORTFOLIO

Study characteristics:

- Randomized, double-blind, placebo-controlled study of TNX-102 SL in fibromyalgia-type Long COVID
- U.S. sites only, ***completed enrollment of 63 patients***

Primary Endpoint:

- Daily diary pain severity score change from baseline to Week 14 (TNX-102 SL vs. placebo)
  - Weekly averages of the daily numerical rating scale scores

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

Placebo once-daily at bedtime

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

ClinicalTrials.gov Identifier: NCT05472090
"A Phase 2 Study to Evaluate the Efficacy and Safety of TNX-102 SL in Patients With Multi-Site Pain Associated With Post-Acute Sequelae of SARS-CoV-2 Infection (PREVAIL)"

Next Steps: ***End of Phase 2 Meeting with FDA***

TONIX PHARMACEUTICALS

TNX-102 SL: Phase 2 PREVAIL Topline Results[1]

Did not meet the primary endpoint of multi-site pain reduction at Week 14

However, findings fulfill the objectives of proof-of-concept study, supporting the decision to advance the program based on a proposed primary endpoint using the PROMIS Fatigue scale

- TNX-102 SL showed robust effect size in improving fatigue and consistent activity across secondary measures of sleep quality, cognitive function, disability and Patient Global Impression of Change (PGIC)
- Was generally well tolerated with an adverse event (AE) profile comparable to prior studies with TNX-102 SL:
  - AE-related discontinuations were similar in drug and placebo arms
  - No new safety signals were observed

Fatigue is the signature symptom of Long COVID and has been identified as the dominant symptom contributing to disability[2]

- We observed numerical improvement in the PROMIS fatigue score (in RELIEF p=0.007 MMRM and in RALLY p=0.007 MMRM) in both prior Phase 3 studies of TNX-102 SL in fibromyalgia,
- We believe the results of PREVAIL, together with extensive data from studies in other chronic conditions[3-5], makes PROMIS Fatigue a solid candidate for the primary endpoint of future Long COVID registrational studies

[1]Tonix Press Release, September 5, 2023 - https://bit.ly/3Z6FQHQ
[2]Walker S, *et al*. *BMJ Open* 2023;13:e069217. doi:10.1136/ bmjopen-2022-069217
[3]Cook, K.F., et al. 2016. *Journal of Clinical Epidemiology*, 73, 89- 102
[4]Cella, D., et al. 2016. *Journal of Clinical Epidemiology*, 73, 128–134
[5]Lai, J.S., et al. 2011. *Archives of Physical Medicine and Rehabilitation*, 92(10 Supplement), S20-S27.

TONIX PHARMACEUTICALS

Acute Stress Reaction (ASR)/ Acute Stress Disorder (ASD)

ASR/ASD are acute stress conditions resulting from trauma which can affect both civilian and military populations.

Large unmet need:

- According to National Center for PTSD, about 60% of men and 50% of women in the US are exposed least one traumatic experience in their lives[1]
- In the US alone, one-third of emergency department visits (40-50 million patients per year) are for evaluation after trauma exposures[2]

Current standard of care:

- No medications are currently available at or near the point of care to treat patients suffering from acute traumatic events and support long-term health

[1]National Center for PTSD. How Common is PTSD in Adults? https://www.ptsd.va.gov/understand/common/common_adults.asp
[2]Wisco et al. *J Clin Psychiatry*. 2014.75(12):1338-46

TNX-102 SL for ASR/ASD: Program Status

Status: Expect to start Phase 2 in 2Q 2024

Phase 2 Trial Funded by DoD grant to University of North Carolina (UNC)

- UNC Institute for Trauma Recovery awarded a $3M grant from the Department of Defense (DoD)
- OASIS trial will build upon infrastructure developed through the UNC-led, $40M AURORA initiative
  - AURORA study is a major national research initiative to improve the understanding, prevention, and recovery of individuals who have experienced a traumatic event
  - Supported in part by funding from the National Institutes of Health (NIH) and the health care arm of Google's parent company Alphabet
- Opportunity to investigate the correlation between motor vehicle collisions and the emergence of ASD and PTSD
- Supported by multiple clinical trials:
  - Phase 2 trial in military-related PTSD (AtEase or NCT02277704)
  - Phase 3 trial in military-related PTSD (HONOR or NCT03062540)
  - Phase 3 trial in primarily civilian PTSD (RECOVERY or NCT03841773)
- In each of these studies, early and sustained improvements in sleep were associated with TNX-102 SL treatment by the PROMIS sleep disturbance (SD) scale and the Clinician Administered PTSD Scale (CAPS-5) "sleep disturbance" item.

Together these studies provide preliminary evidence that TNX-102 SL is well-tolerated and may promote recovery from PTSD via a pharmacodynamic facilitation of sleep-dependent emotional memory processing

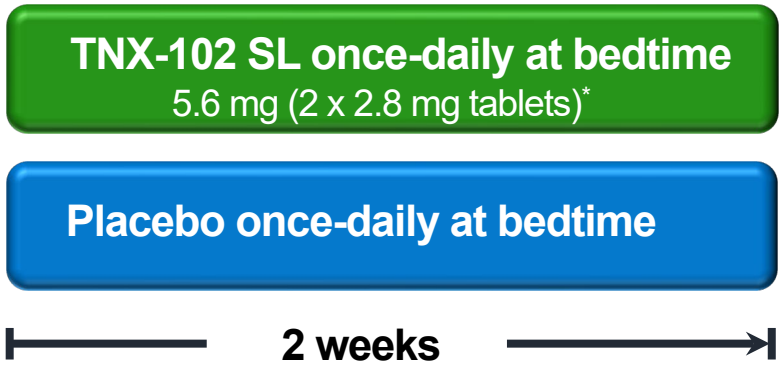
TNX-102 SL for ASR/ASD: Phase 2 OASIS Study Design

General study characteristics:

- Randomized, double-blind, placebo-controlled study in Acute Stress Reaction (ASR) / Acute Stress Disorder (ASD)
- The proposed Optimizing Acute Stress reaction Interventions with TNX-102 SL (OASIS) trial will examine the safety and efficacy of TNX-102 SL to reduce adverse posttraumatic neuropsychiatric sequelae among patients presenting to the emergency department after a motor vehicle collision (MVC)
- The trial will enroll approximately 180 individuals who acutely experienced trauma at study sites across the US
- Participants will be randomized in the emergency department to receive a two-week course of either TNX-102 SL or placebo
- Investigator-initiated IND

Objective:

- Investigate the potential of Tonix's TNX-102 SL (cyclobenzaprine HCl sublingual tablets) to reduce the frequency and severity of the adverse effects of traumatic exposure, including acute stress reaction (ASR), acute stress disorder (ASD), and posttraumatic stress disorder (PTSD).
- ASR refers to the body's immediate response to trauma, whereas ASD is the short-term effects of trauma (within 1 month), and PTSD is the long-term effects of trauma (beyond 1 month)



*First dose of TNX-102 SL 5.6 mg versus placebo taken in the emergency department, and then daily at bedtime to finish 2 weeks of treatment

A Phase 2 Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily in Patients With ASR/ ASD (OASIS)

- Primary outcome measure: Acute Stress Disorder Scale (ASDS) assessed at 7 and 21 days post MVC
- Posttraumatic stress symptom severity assessed at 6 and 12 weeks post MVC using the PTSD Checklist for DSM-5 (PCL-5)
- Standardized survey instruments of sleep disturbances, anxiety and depression symptoms, general physical and mental health, and clinical global improvement also employed
- Detailed and brief neurocognitive assessments are performed from baseline to 12 weeks after MVC at specific timepoints throughout study participation period

TONIX PHARMACEUTICALS

THANK YOU

APPENDIX

Tonmya™ (TNX-102 SL): RALLY Study
Increased Adverse Event-Related Discontinuations

Increases in AE-Related discontinuations in RALLY study compared with RELIEF study in both placebo and TNX-102 SL groups

	RALLY (F306)	RELIEF (F304)	RALLY (F306)	RELIEF (F304)
	Placebo		TNX-102 SL	
Patients with at least one TEAE leading to early discontinuation	6.2%	3.5%	15.2%	8.5%
Ratio of patients with at least one TEAE leading to early discontinuation in F306 to F304 (F306/F304)	1.77		1.79	

TEAE = treatment-emergent adverse event

Adverse events in RALLY

- TNX-102 SL 5.6 mg was well tolerated.
- Among participants randomized to drug and placebo groups, 73.8% and 81.4%, respectively, completed the 14-week dosing period.
- As expected, based on prior TNX-102 SL studies, oral administration site reactions were higher in the drug treatment group, including rates of tongue/mouth numbness, pain/discomfort of tongue/mouth, and product taste abnormal (typically a transient bitter aftertaste)
- Tongue/mouth numbness or tingling and product aftertaste were local effects nearly always temporally related to dose administration and transiently expressed (<60 minutes) in most occurrences.
- Adverse events resulted in premature study discontinuation in TNX-102 SL and placebo groups at rates of 15.2% and 6.2%, respectively
- Approximately 95% of adverse events in both the drug treatment and placebo groups were rated as mild or moderate.

TONIX PHARMACEUTICALS

Tonmya™ (TNX-102 SL): RALLY Study
Impact of Missing Data on *p*-Values in RALLY

Since 2010, FDA has generally required that "missing data" be accounted for by using a statistical method called "multiple imputation" or MI

- MI data approach can attenuate *p*-values in the setting of missing data

RALLY (F306) results without MI treatment for missing data are comparable to prior positive RELIEF (F304) study

- Efficacy results in the table without MI are labelled "MMRM"

MI missing data treatment attenuated *p*-values in RALLY

- At the current time, we expect MI will be part of the statistical analysis for the RESILIENT trial

Endpoints	RALLY (F306)			
	MMRM+MI*		MMRM**	
	LSMD (SE)	*p*-value	LSMD (SE)	*p*-value
Pain by Diary#	-0.2 (0.16)	**0.115**	-0.4 (0.16)	0.014
FIQR Symptom domain	-1.9 (1.52)	0.216	-3.4 (1.55)	0.030
FIQR Function domain	-0.4 (1.46)	0.797	-1.6 (1.48)	0.266
PROMIS Sleep Disturbance	-2.3 (0.80)	0.004	-3.3 (0.73)	<0.001
PROMIS Fatigue	-1.2 (0.74)	0.101	-2.0 (0.73)	0.007
Sleep Quality by Diary	-0.3 (0.16)	0.094	-0.4 (0.16)	0.008
Endpoints	**RELIEF (F304)**			
	MMRM+MI*		MMRM**	
	LSMD (SE)	*p*-value	LSMD (SE)	*p*-value
Pain by Diary#	-0.4 (0.16)	**0.010**	-0.5 (0.16)	0.004
FIQR Symptom domain	-4.3 (1.60)	0.007	-5.6 (1.60)	<0.001
FIQR Function domain	-4.4 (1.69)	0.009	-5.2 (1.63)	0.001
PROMIS Sleep Disturbance	-2.9 (0.82)	<0.001	-3.3 (0.82)	<0.001
PROMIS Fatigue	-1.8 (0.76)	0.018	-2.1 (0.79)	0.007
Sleep Quality by Diary	-0.6 (0.17)	<0.001	-0.7 (0.17)	<0.001

FIQR = Fibromyalgia Impact Questionnaire-Revised; LSMD = least squares mean difference (between TNX-102 SL and placebo); MMRM = mixed model repeated measures; MI = multiple imputation; PROMIS = Patient-Reported Outcomes Measurement Information System; SE = standard error

* MMRM with MI was the pre-specified primary analysis

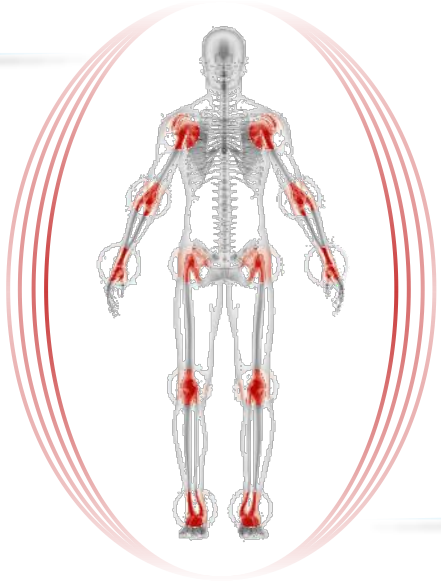
**MMRM without MI was a pre-specified analysis

Primary efficacy endpoint: change from baseline in the weekly average of daily diary pain severity numerical rating scale scores

Chronic Overlapping Pain Conditions (COPC) Believed to Result from Shared Brain Processes

- COPC is a set of disorders that coaggregate; these disorders can include but are not limited to[1,2]:

- Temporomandibular disorder
- Fibromyalgia
- Irritable bowel syndrome
- Vulvodynia
- CFS/ME[3]
- Interstitial cystitis/painful bladder syndrome



- Endometriosis
- Chronic tension-type headache
- Migraine headache
- Chronic lower back pain

- Similar central mechanisms play significant roles in all pain conditions, even those with known peripheral contributions[1,2]

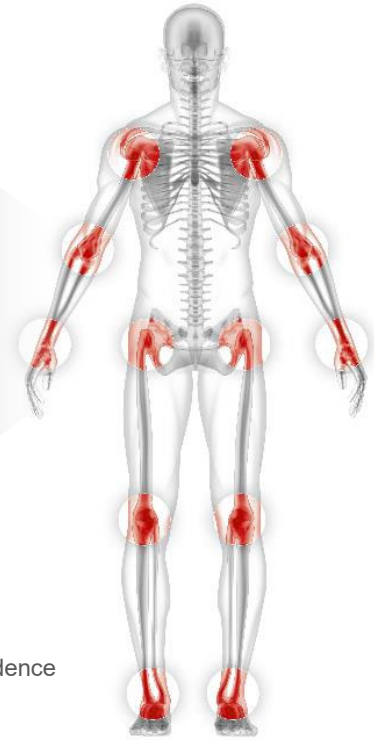
[1]Maixner W, et al. *J Pain*. 2016;17(9 Suppl):T93-T107.
[2]Veasley C, et al. http://www.chronicpainresearch. org/public/CPRA_WhitePaper_2015-FINAL-Digital.pdf. Published May 2015. Accessed July 26, 2021.
[3]CFS/ME – chronic fatigue syndrome/myalgic encephalomyelitis

Role of Infections in Triggering Fibromyalgia or Chronic fatigue (CFS)-Like Illnesses

- Symptoms of Long COVID, like multi-site pain, fatigue and insomnia, are the hallmarks of chronic pain syndromes like fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).
- In August 2022, the HHS released the *National Research Action Plan on Long COVID*[1] which endorses the connection between Long COVID and chronic fatigue syndrome.

Infection initiates an autoreactive process, which affects several functions, including brain and energy metabolism[2-7]

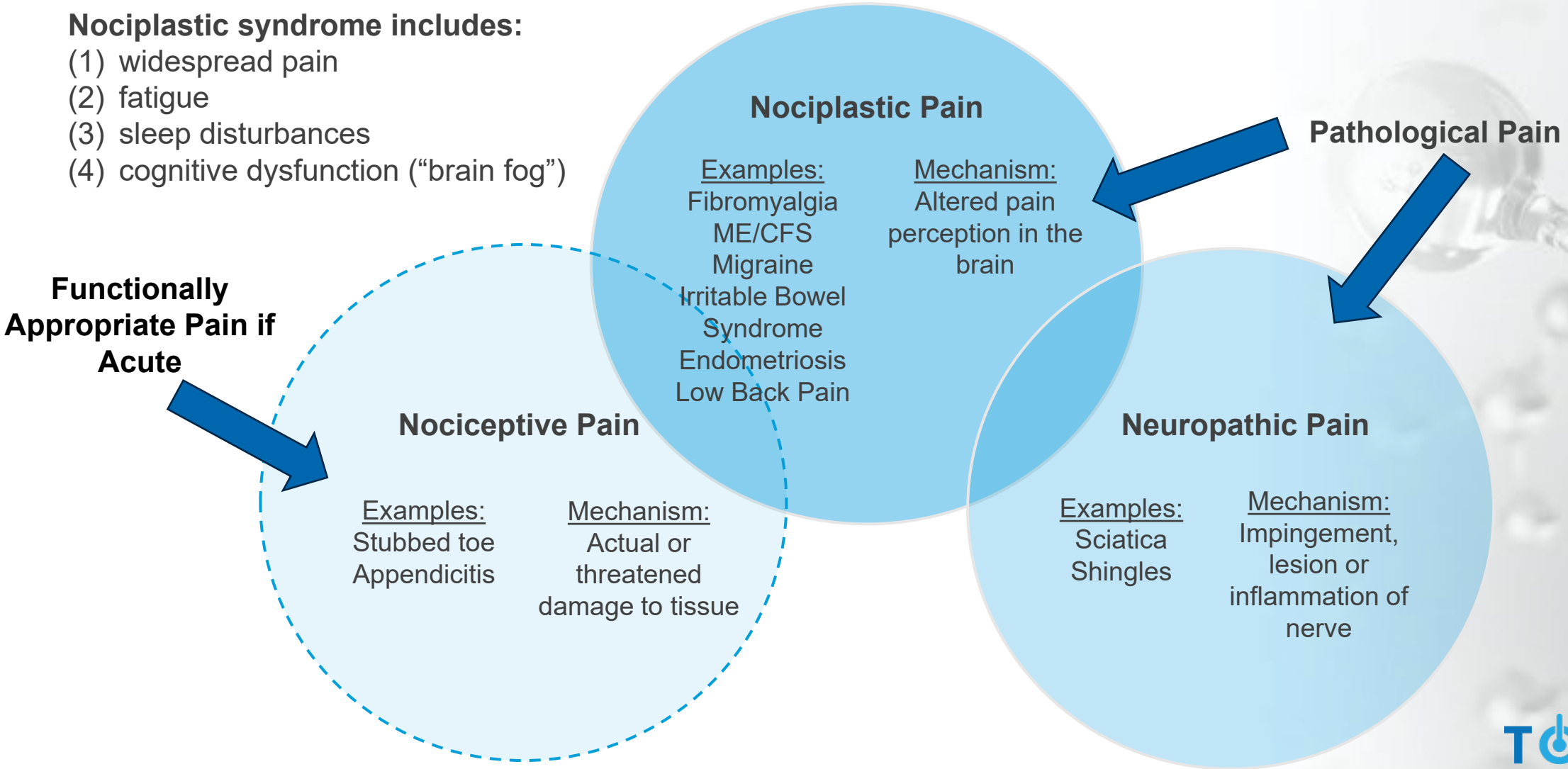
- Infections can trigger any of these conditions in approximately 10% of exposed individuals
- The initial location of the infection determines the subsequent pain syndrome
- Any type of infectious diarrhea will trigger irritable bowel syndrome (IBS) in 10% to 20% of those exposed



[1]Department of Health and Human Services, Office of the Assistant Secretary for Health. 2022. National Research Action Plan on Long COVID, 200 Independence Ave SW, Washington, DC 20201.
[2]Blomberg J, et al. Front Immunol. 2018;9:229. Published 2018 Feb 15.
[3]Warren JW, et al. Urology. 2008;71(6):1085-1090.
[4]Buskila D, et al. Autoimmun Rev. 2008;8(1):41-43.
[5]Hickie I, et al. BMJ. 2006;333(7568):575.
[6]Parry SD, et al. Am J Gastroenterol. 2003;98(9):1970-1975.
[7]Halvorson HA, et al. Am J Gastroenterol. 2006;101(8):1894-1942.

The Third Type of Pain: Nociplastic Pain[1]

Nociplastic syndrome includes:
(1) widespread pain
(2) fatigue
(3) sleep disturbances
(4) cognitive dysfunction (“brain fog”)



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

Fibromyalgia is Believed to Result from Chronic Pain or Prior Stress Experiences

The pain system evolved to detect acute pain

- The body's "check engine" light

Chronic pain breaks down the system that determines whether a sensory experience is painful

- Chronic pain results in nociplastic syndromes
- Nociplastic syndrome was formerly known as "Central and Peripheral Sensitization"

Chronic Overlapping Pain Conditions (COPCs) are Nociplastic Syndromes:

- Fibromyalgia
- ME/CFS
- Migraine
- Irritable Bowel Syndrome
- Endometriosis
- Low Back Pain

Stresses that may precede or precipitate FM include:

Chronic nociceptive pain
- *e.g.*, osteoarthritis

Chronic neuropathic pain
- *e.g.*, diabetic neuropathy

Infectious
- *e.g.*, viral illness

Cancer
- *e.g.*, breast cancer

Chemical
- e.g., cancer chemotherapy

Traumatic
- *e.g.*, motor vehicle accident

Physiologic
- *e.g.*, disturbed sleep

Common Chronic Conditions are a Challenge for Pharma

Fibromyalgia is a common chronic disease[1]

- Chronic pain syndrome that persists for years or decades

No animal model is recognized for nociplastic syndromes or its component symptoms

- Widespread pain
- Fatigue
- Sleep disturbance
- Cognitive impairment

Nociplastic symptoms are subjective

- Humans need to report symptoms using scales

Clinical trials measuring subjective symptoms are challenging

- Placebo response is typically observed
- Long-term therapy means requires long-term tolerability

[1]The U.S. Centers for Disease Control defines chronic diseases as “conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both.” www.cdc.gov/chronicdisease/about/index.htm. (accessed Jan 28, 2024)

Common Chronic Conditions are a Challenge for Society

The Opiate Crisis in the U.S. was driven by mistreatment of chronic pain, which was often nociplastic pain

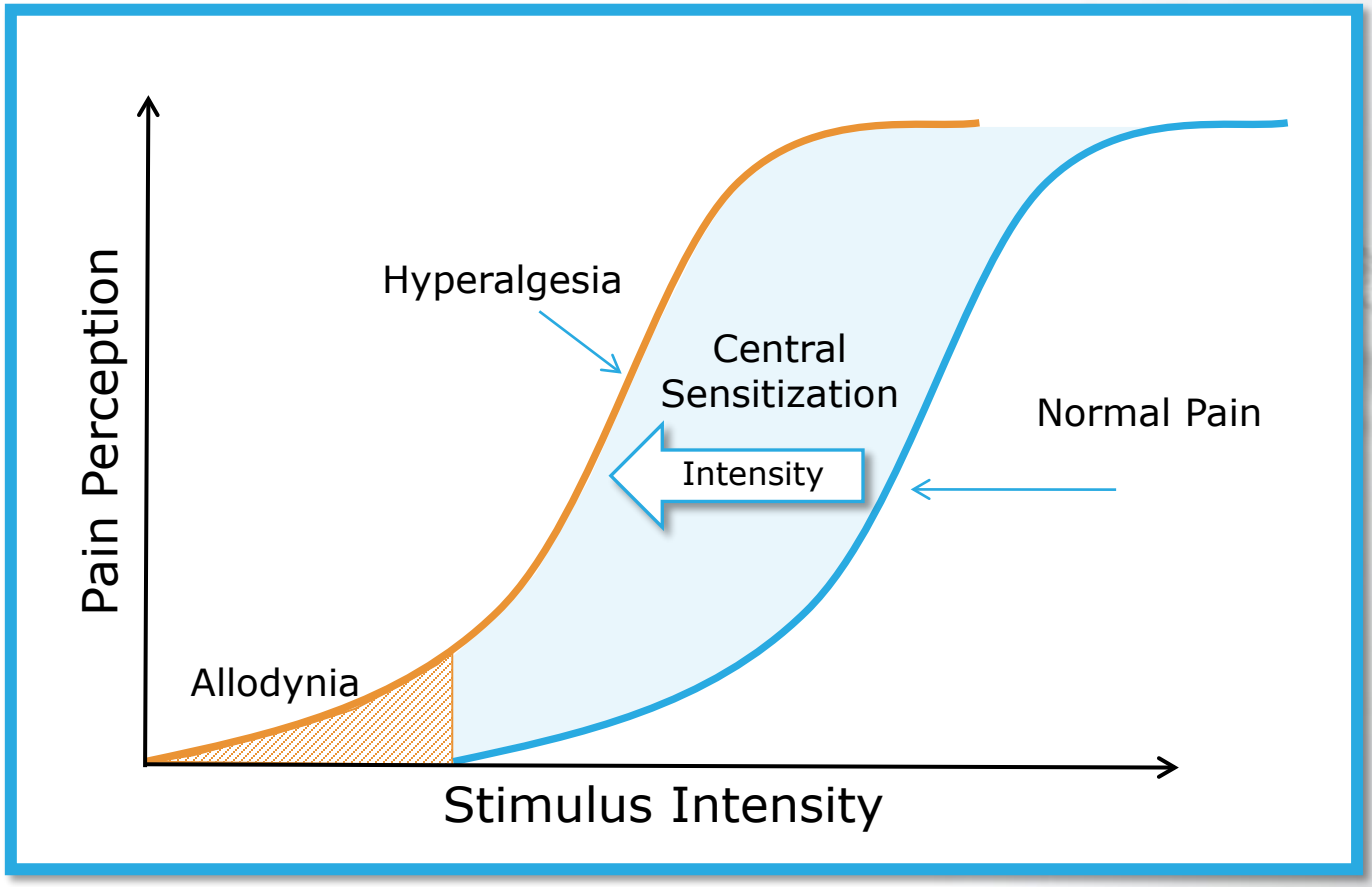
- The epidemic of prescription pain killers was addressed by regulations which limited the availability of opiates
- Mandy individuals who are opiate dependent have transitioned to illegal street heroin and fentanyl
- Illegal drugs contribute to homelessness

There is an unmet need for non-opiate analgesics that address nociplastic pain

- No new drug for fibromyalgia has been approved since 2009

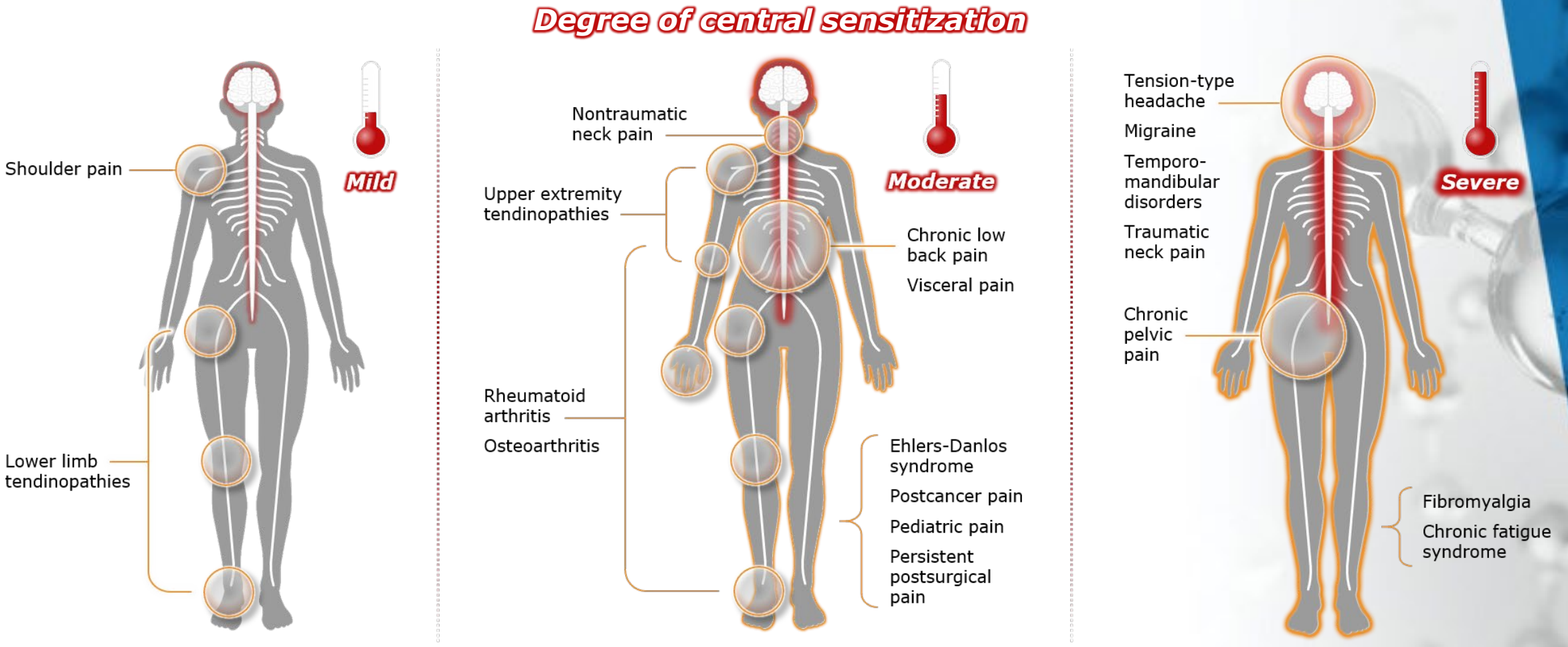
Central Sensitization (CS)
A Feature of Many Nociplastic Pain Syndromes

- CS is caused by amplified neural signaling in CNS pain circuits[1-3]
- Patients with CS perceive higher pain to a slightly noxious stimuli than in non-CS individuals (hyperalgesia)[1]
- Severe CS can lead to hypersensitivity to stimuli that are not typically painful (allodynia)[2]
- CS varies in severity and is observed in syndromes including FM and ME/CFS[1,3]



[1]CFS/ME – chronic fatigue syndrome/myalgic encephalomyelitis
[2]FM - fibromyalgia
[3]Nijs J, et al. *Lancet*. 2021;3(5):e383-e392.

Central Sensitization (CS)
Can Occur in a Range of Diseases and Conditions



Nijs J, et al. *Lancet*. 2021;3(5):e383-e392.