Tonix Pharmaceuticals

TNX-102 SL (sublingual cyclobenzaprine)

Fibromyalgia Phase 3 RESILIENT Study (TNX-CY-F307) Topline

December 20, 2023

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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.

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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

Internally developed - Patents Issued – No royalties owed

*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: Pre-NDA Meeting with FDA

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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TNX-102 SL: Phase 3 RESILIENT Study Design

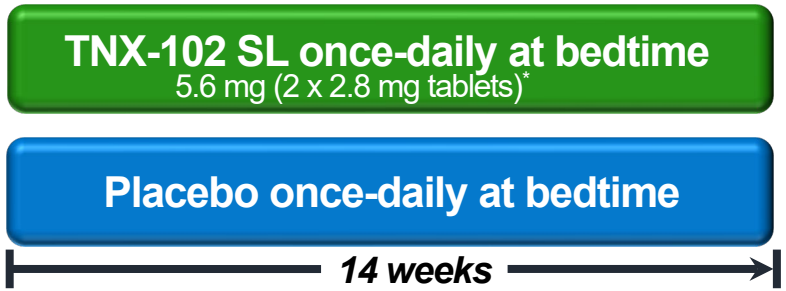
RESILIENT Study

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^

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 ('F307')

^ 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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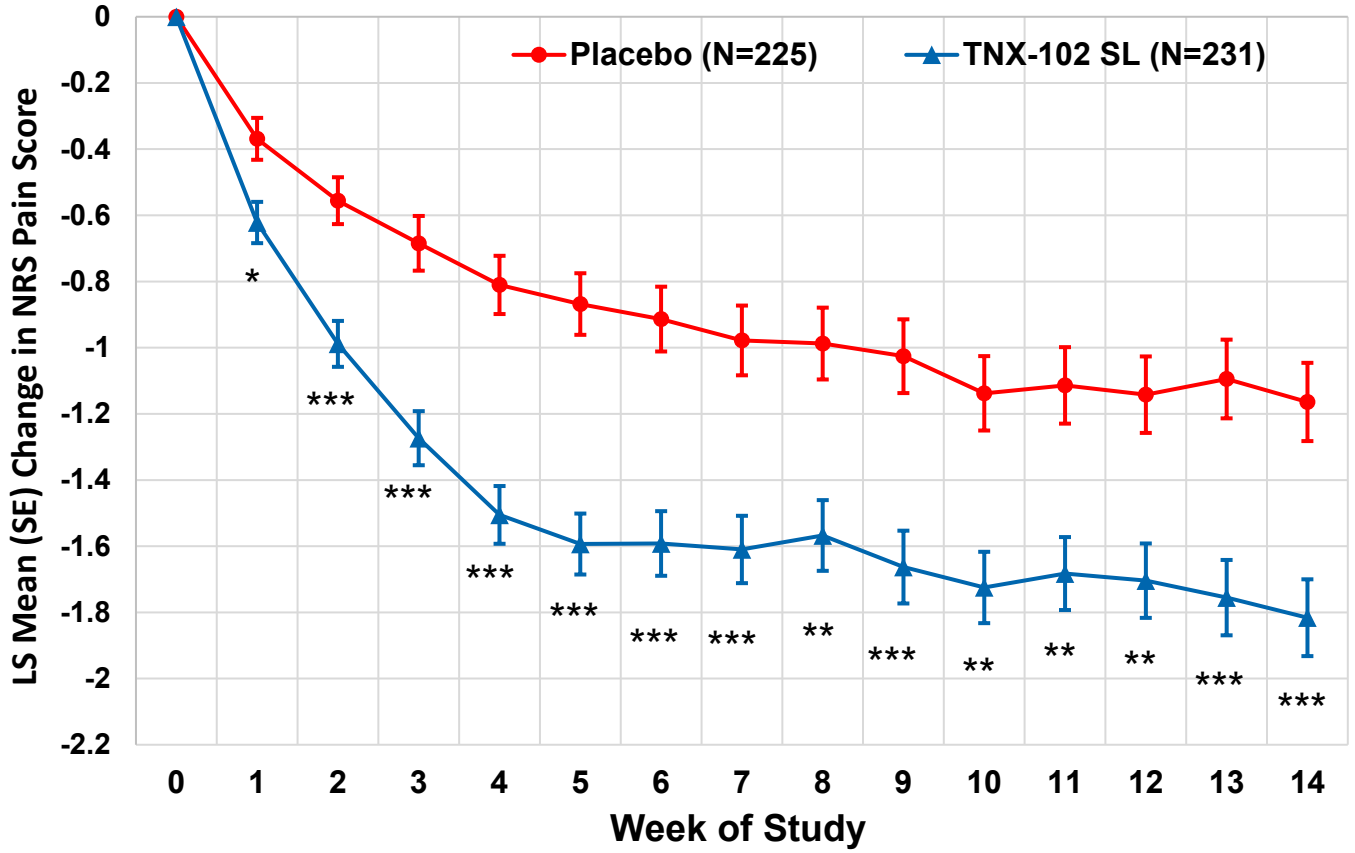
F307 Primary Outcome Measure
Reduction in Widespread Pain

RESILIENT Study

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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Pre-Specified Primary Endpoint

RESILIENT Study

Summary

- **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

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

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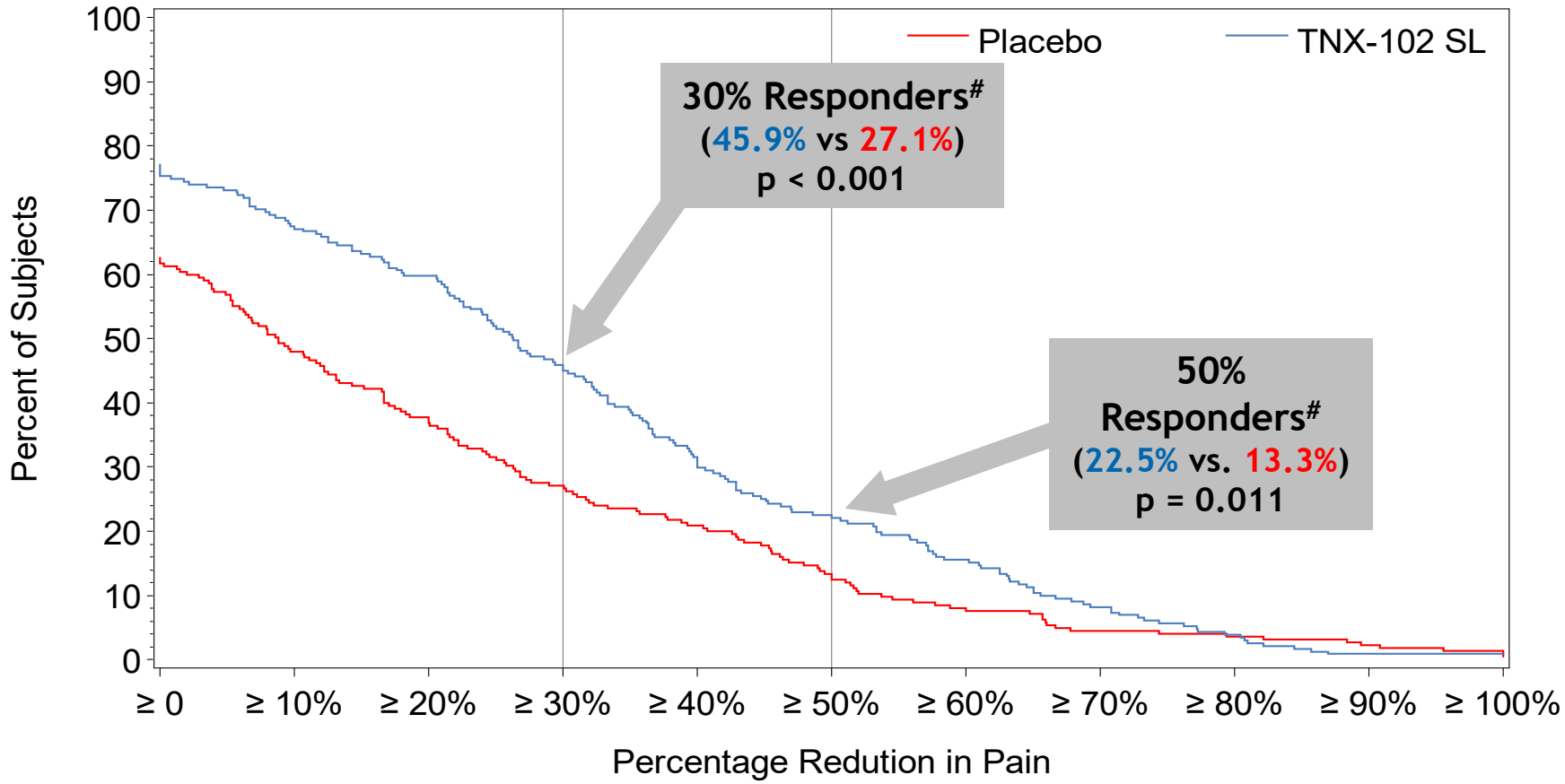
F307 Continuous Pain Responder Graph

RESILIENT Study



#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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Summary of ALL Key Pre-Specified Secondary Outcome Measures

RESILIENT Study

Rating Scale	Week 14	Met**
Patient Global Impression of Change (PGIC)	*p < 0.001*	✓
Fibromyalgia Impact Questionnaire - Symptoms	*p < 0.001*	✓
Fibromyalgia Impact Questionnaire - Function	*p = 0.001*	✓
PROMIS Sleep Disturbance	*p < 0.001*	✓
PROMIS Fatigue	*p < 0.001*	✓
Weekly average of daily Sleep Quality scores	*p < 0.001*	✓

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

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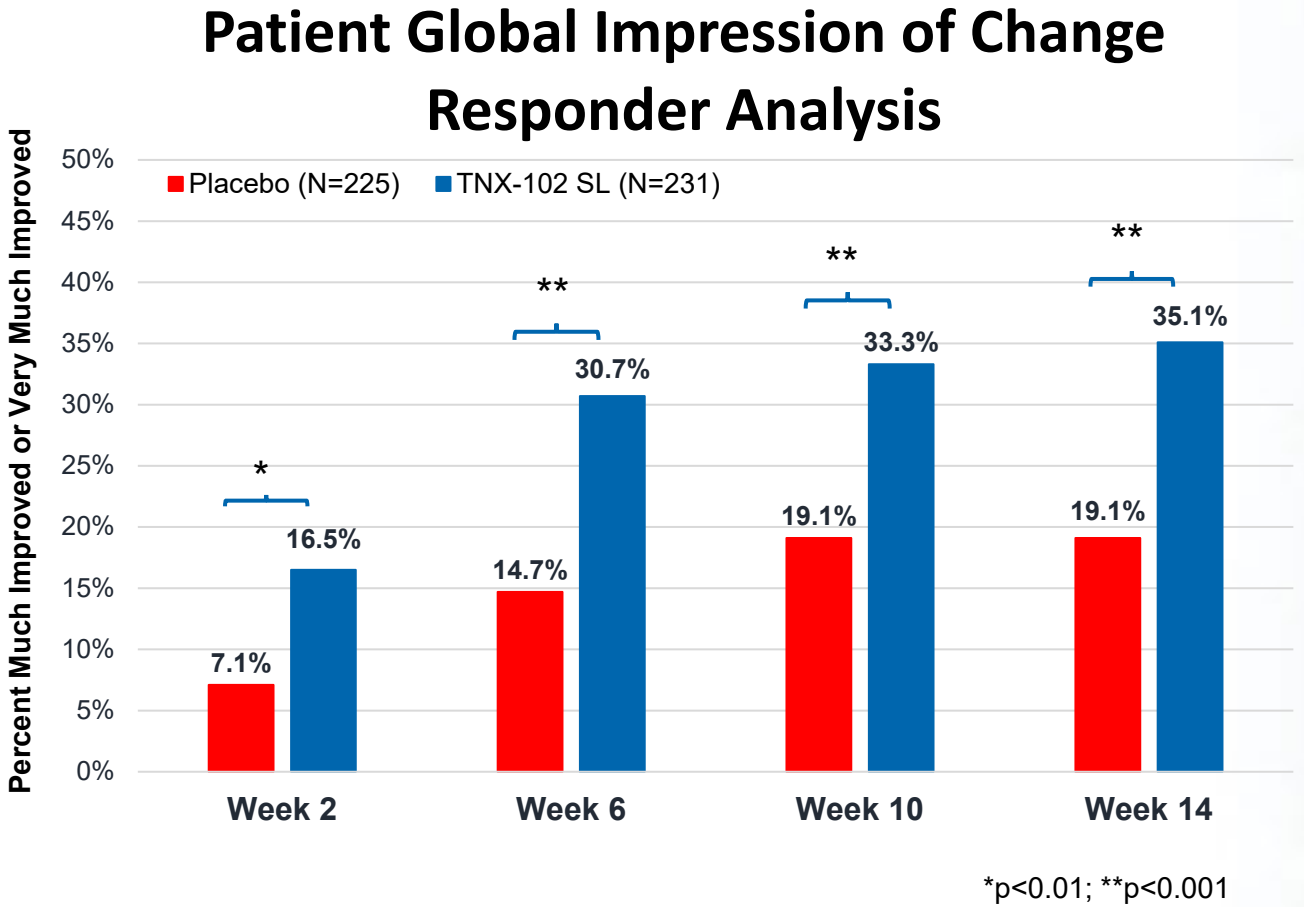
F307 Patient Global Impression of Change
Key Secondary Outcome Measure

RESILIENT Study



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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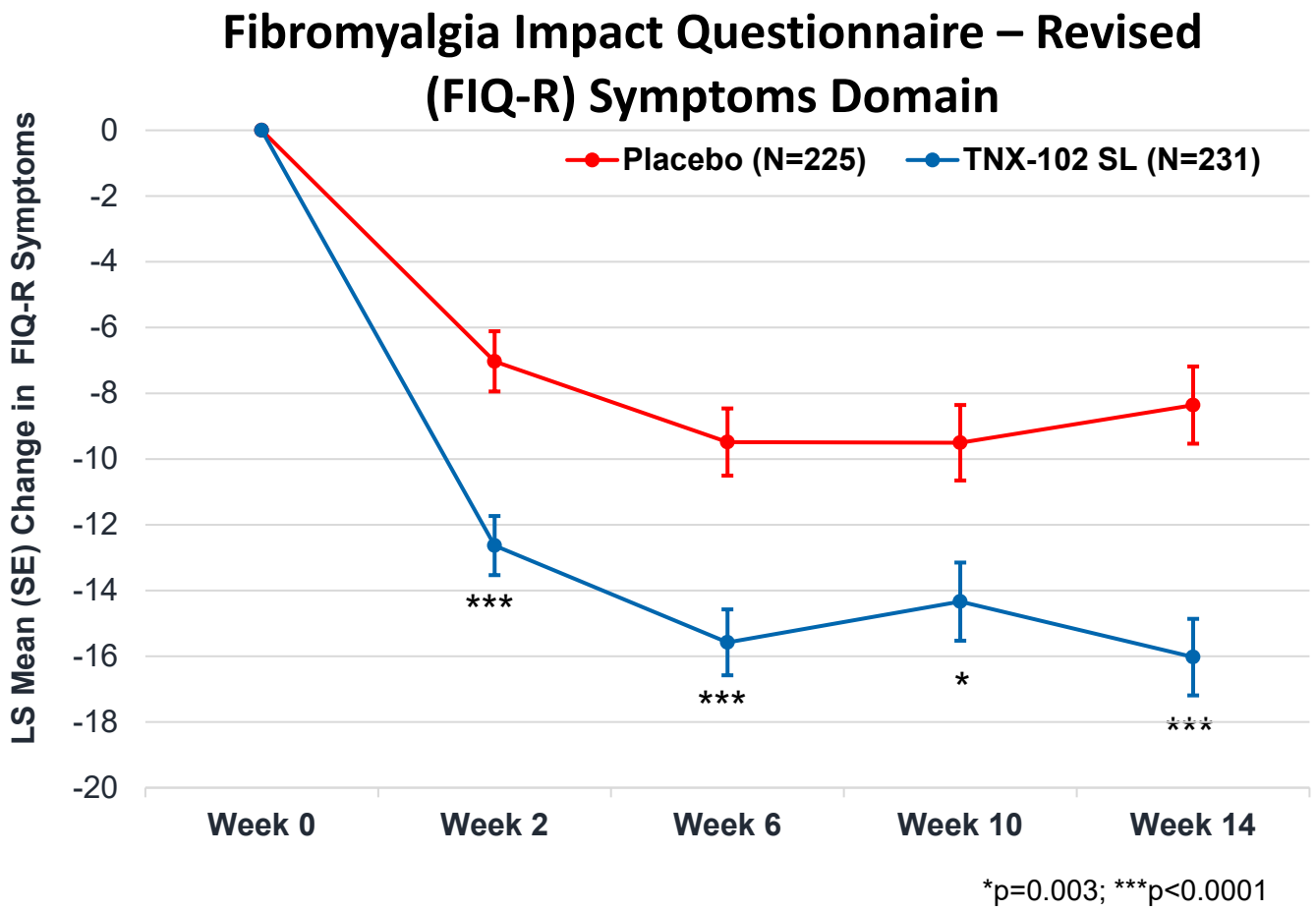
F307 FIQ-R Symptoms Domain
Key Secondary Outcome Measure

RESILIENT Study



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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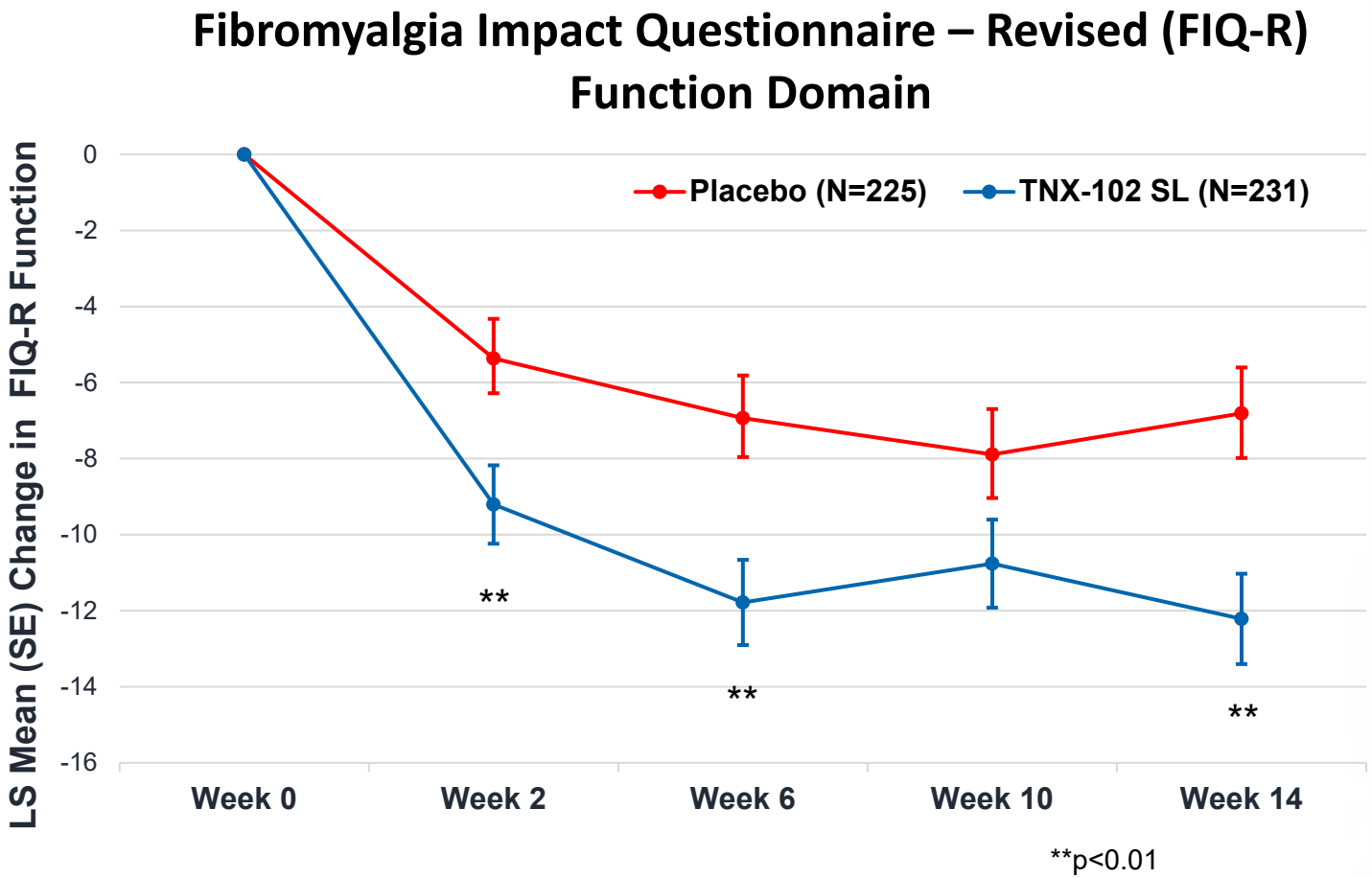
F307 FIQ-R Function Domain
Key Secondary Outcome Measure

RESILIENT Study



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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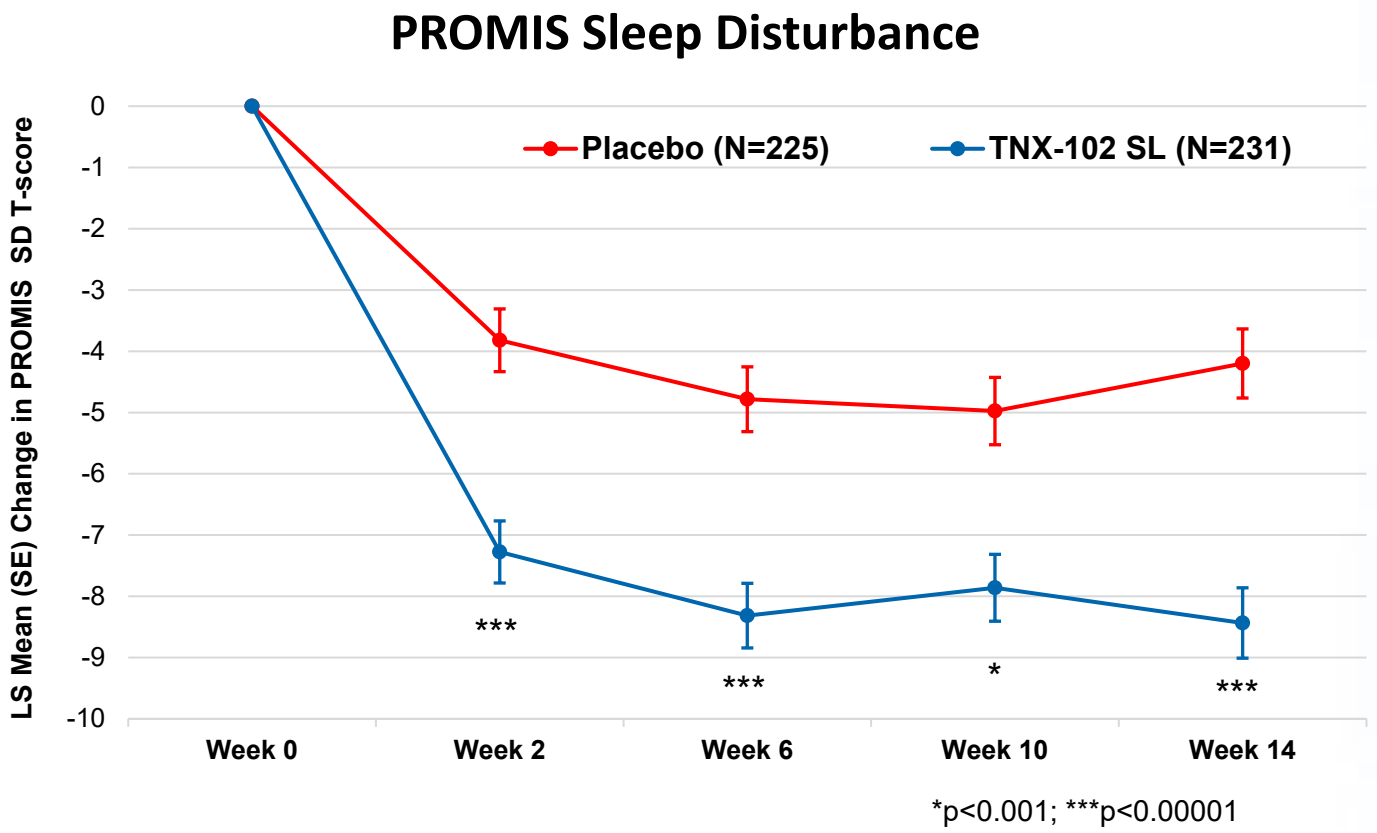
F307 PROMIS Sleep Disturbance Inventory
Key Secondary Outcome Measure

RESILIENT Study



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.

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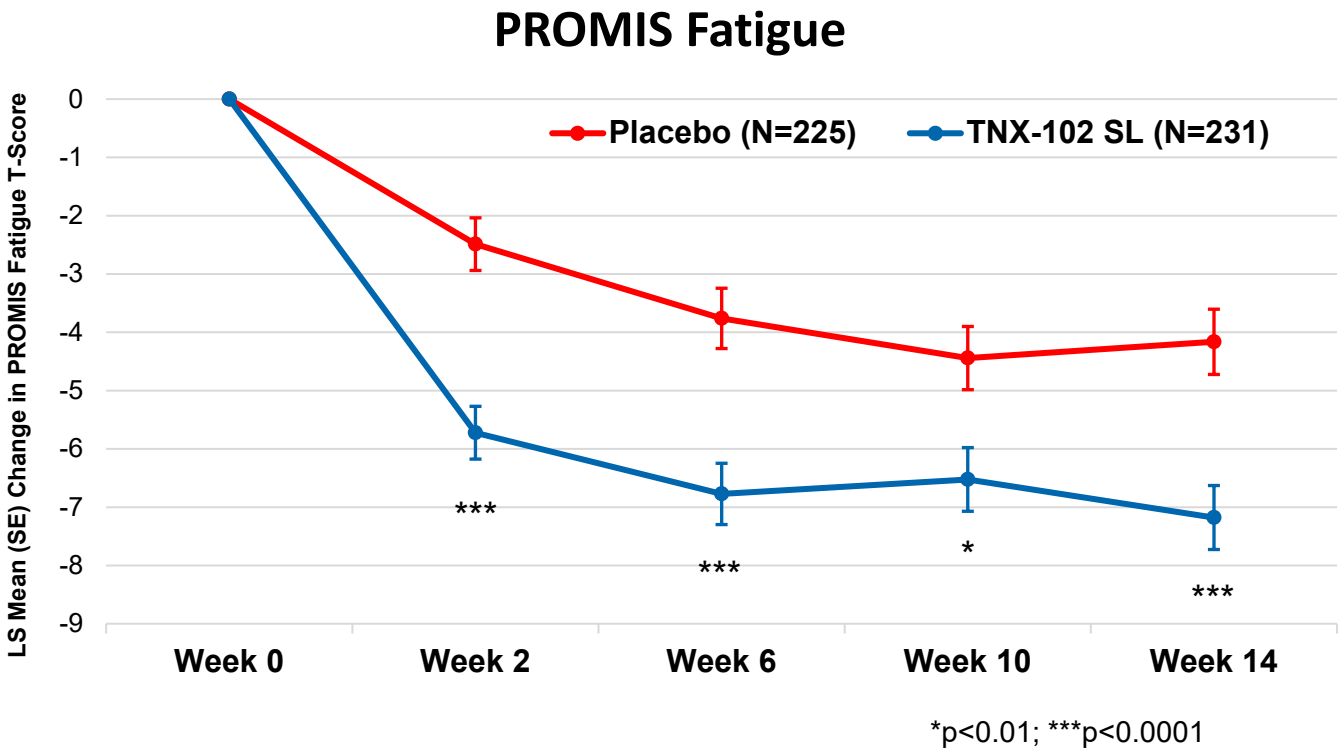
F307 PROMIS Fatigue Inventory
Key Secondary Outcome Measure

RESILIENT Study



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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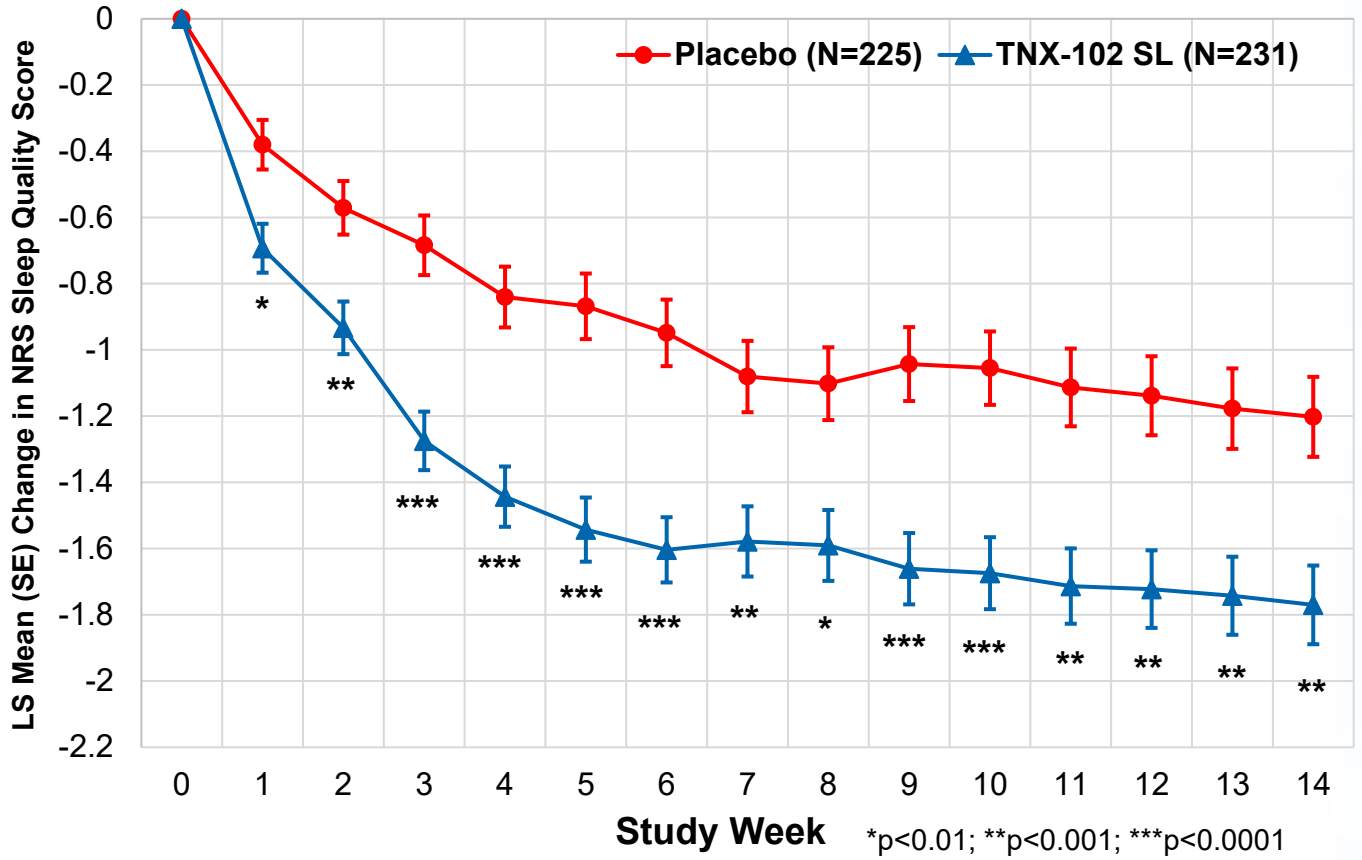
F307 Sleep Quality by Daily Diary
Key Secondary Outcome Measure

RESILIENT Study

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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F307 Subject Disposition

RESILIENT Study

	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%)

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F307 Safety Summary

RESILIENT Study

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

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

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F307 Safety Summary - Continued

RESILIENT Study

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

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

- In females, CFSQ-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
- 7 males on TNX-102 SL and 12 on placebo had Week 14 CSFQ-14 completed; but it was notable that the desire/interest subscore improved and separated from placebo in this small sample, p=0.049 (12/14 placebo and 7/7 active patients completed the survey.)

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TNX-102 SL: Phase 3 RESILIENT Demographics and Baseline Characteristics

	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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F307 Prior Medication Use

RESILIENT Study

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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F307 Washout Medications

RESILIENT Study

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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F307 Characteristics of Study Population

RESILIENT Study

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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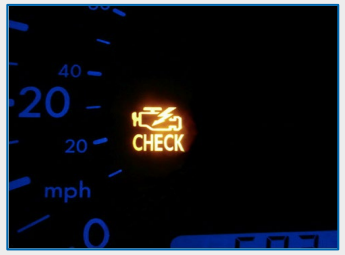
TNX-102 SL*: Fibromyalgia
Cyclobenzaprine Protectic® Sublingual Tablets

PROFILE

Fibromyalgia (FM) is a chronic pain disorder resulting from amplified sensory and pain signaling within the CNS

- Afflicts an estimated 6-12 million adults in the U.S., the majority of whom are women[1]
- Symptoms include chronic widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction
- Patients struggle with daily activities, have impaired quality of life, and frequently are disabled
- Physicians and patients report common dissatisfaction with currently marketed products



When the check engine light malfunctions, the light is on even though the car is not malfunctioning

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Fibromyalgia

Additional Indications: Long COVID, Acute Stress Disorder (ASD), PTSD, Agitation in Alzheimer's, Alcohol Use Disorder

Status: One Positive Phase 3 study RELIEF completed[2]

Second Phase 3 study RALLY missed primary endpoint

Confirmatory Phase 3 study RESILIENT positive, *p*-value = 0.00005

Next Steps: Pre-NDA meeting with FDA

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

[1]American Chronic Pain Association (www.theacpa.org, 2019)
[2]Lederman et al., (2023) *Arthritis Care & Research* "Efficacy and Safety of TNX-102 SL (Sublingual Cyclobenzaprine) for the Treatment of Fibromyalgia: Results From the RELIEF Trial", doi: 10.1002/acr.25142. Epub ahead of print. PMID: 37165930.

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THANK YOU

Overview of TNX-102 SL

RESILIENT Study

Protectic® proprietary formulation of cyclobenzaprine that supports sublingual administration

Scientific Rationale for Protectic® Formulation

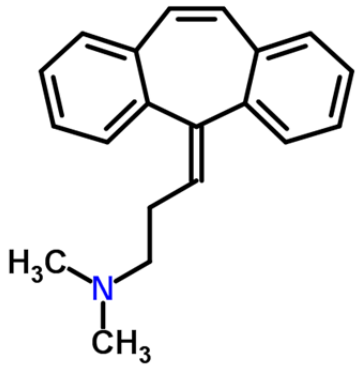
- Engenders unique pharmacokinetic and pharmacodynamic properties that emphasize sleep properties of cyclobenzaprine while minimizing undesirable properties
- Potential therapeutic value in a constellation of disorders where sleep disturbances are:
  - Co-morbid
  - Involved in the onset, progression and severity of the disease

TNX-102 SL - Differentiation from Oral Forms of Cyclobenzaprine

FEATURE	BENEFIT	ADVANTAGE
Cyclobenzaprine	40+ years as oral medication	Established safety record
Formulation: Protectic®	Allows submucosal absorption	Not achievable with oral formulation
Administration: sublingual	Bypasses gut	Avoids first-pass metabolism; reduced formation of "activating" metabolite
Pharmacokinetic profile	Rapid absorption (peak at ~4 hours, low trough levels 8-24 hours)	Desired profile for nighttime action
Dose: low (2.8 to 5.6 mg)	Recruitment of high affinity receptors (5-HT_{2A}, α_1, H_1)	Complimentary trimodal mechanism of action with less risk of off-target interference

TNX-102 SL – Experience in Muscle Spasm

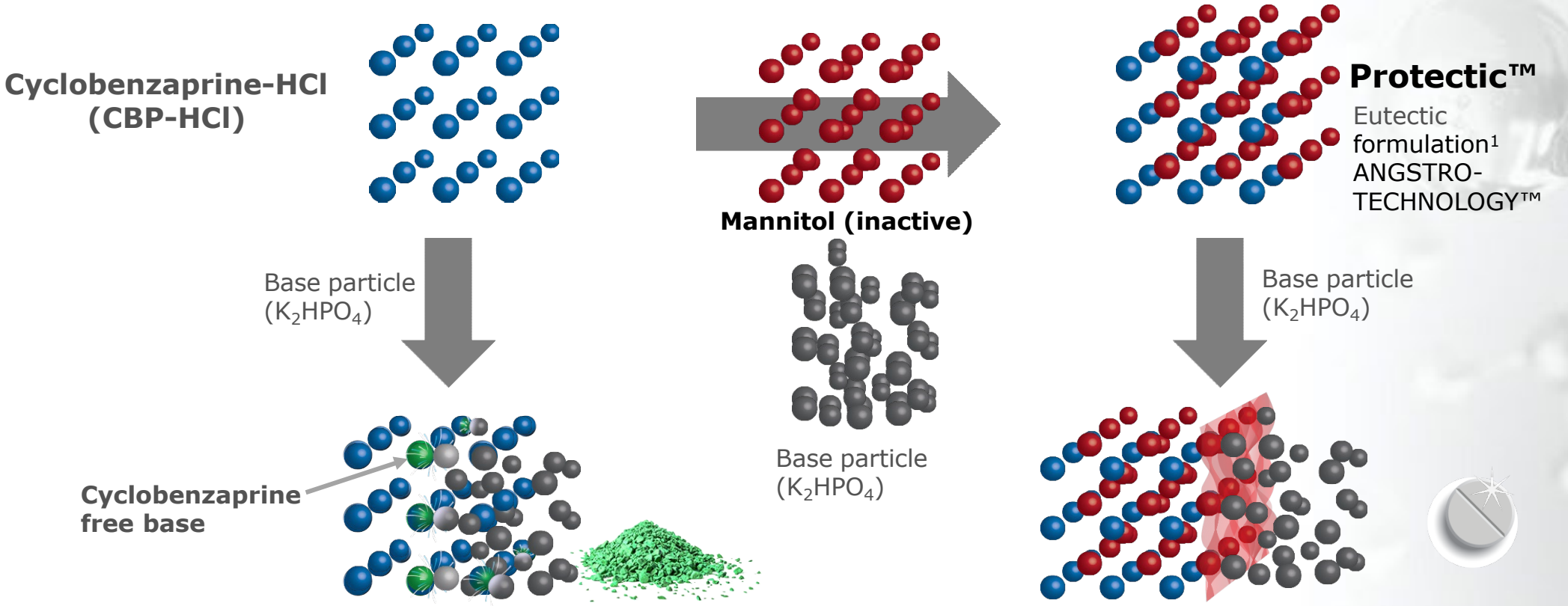
- Extensive Post-Marketing Experience Including Long-Term Utilization



- **Flexeril® approval in 1977 received by Merck for the treatment of muscle spasm**
  - 10 mg T.I.D. for acute use (2-3 weeks)
  - 1999 OTC AdCom Briefing Package noted 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 prior to Tonix program**
  - N=246, placebo controlled, 4-24 week treatment periods
  - Generally well tolerated, although equivocal efficacy across trials
  - Relatively high doses of the immediate-release (IR) oral formulation may have clouded clear efficacy signal with typical adverse effects of IR such as high rates of drowsiness and dry mouth
- **Over 45 years of post-marketing safety data**
  - 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 following 7,607 patients (including 297 treated with 10 mg for ≥ 30 days) found incidence of most common AEs much lower than in controlled studies

TNX-102 SL – Proprietary Eutectic Formulation

- Proprietary Cyclobenzaprine HCL Eutectic Mixture Stabilizes Sublingual Tablet Formulation



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

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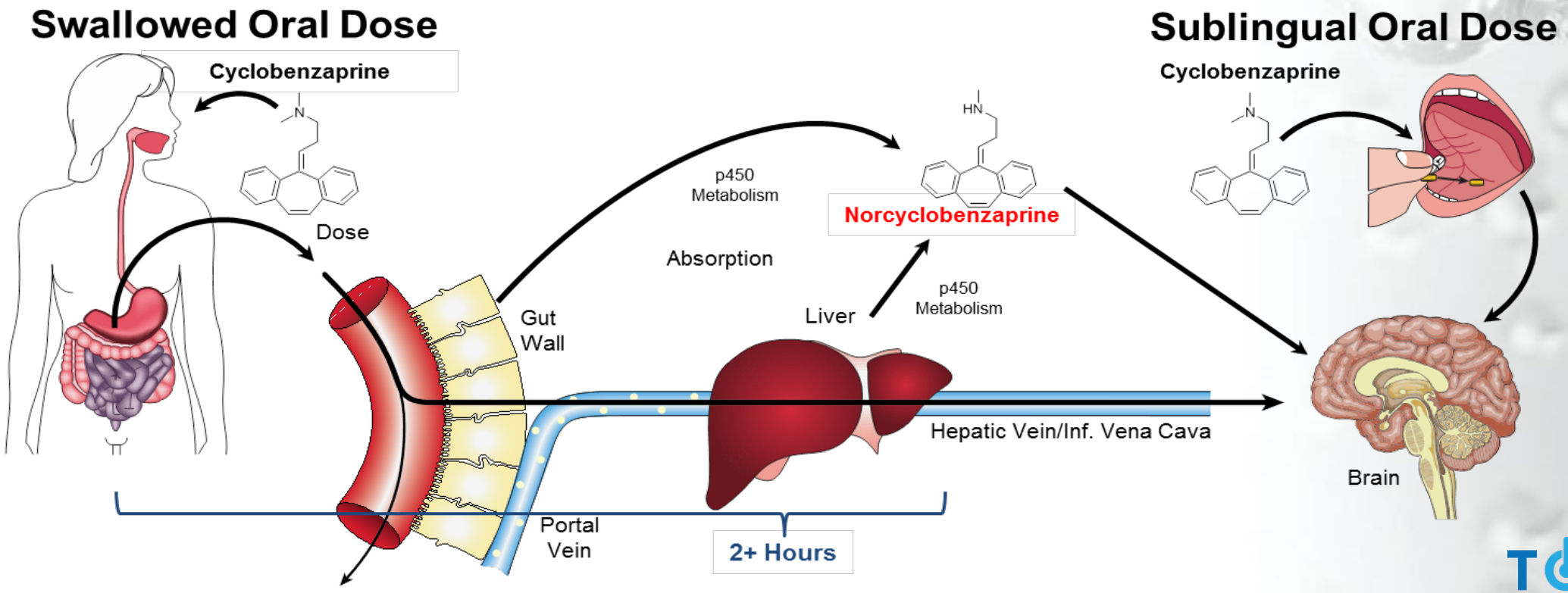
TNX-102 SL – Sublingual Administration and Transmucosal Delivery

- 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)



TNX-102 SL 5.6 mg: Fibromyalgia
Three Phase 3 Trials Completed

Phase 3 Study, RESILIENT, compared TNX-102 SL 5.6 mg and placebo

- First patient enrolled in April 2022, completed *p*-value = 0.00005
- Parallel design, double-blind, randomized placebo-controlled study, all US sites
- Primary endpoint is pain at Week 14 analyzed by MMRM with MI
- All continuous key secondaries by MMRM with MI
- Same key secondary efficacy endpoints as F304 RELIEF and F306 RALLY studies

Phase 3 Study, RALLY, comparison of TNX-102 SL 5.6 mg and placebo

- As expected from interim analysis results published in July 2021, RALLY Study missed primary endpoint
- Unexpected ~80% increase in adverse event-related discontinuations in both drug and placebo arms
- Multiple imputation approach on 'Missing Data' attenuated statistical significance of efficacy endpoints’
- TNX-102 SL was generally well tolerated with overall adverse event profile comparable to prior studies; no new safety signals observed

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TNX-102 SL: Fibromyalgia
Program Update

Phase 3 Study, RELIEF, compared TNX-102 SL 5.6 mg and placebo

- First patient enrolled in December 2019, completed *p*-value = 0.010
- Parallel design, double-blind, randomized placebo-controlled study, all US sites
- Primary endpoint is pain at Week 14 analyzed by MMRM with MI

TNX-102 SL 5.6 mg Phase 3 Study Comparisons on Primary Pain Endpoint

Study	LSMD (SE)*	p-value**	Significance Met?
F304	-0.4 (0.16)	p = 0.010	Yes
F306	-0.2 (0.16)	p = 0.115	No
F307	-0.7 (0.16)	p = 0.0005	Yes

**LSMD (SE) – Least Squared Means Difference (Standard Error)*

TNX-102 SL 5.6 mg Key Secondaries – Study Comparison

Rating Scale	F304	F307
Patient Global Impression of Change (PGIC)	*p = 0.058*	*p < 0.001*
Fibromyalgia Impact Questionnaire - Symptoms	*p = 0.007*	*p < 0.001*
Fibromyalgia Impact Questionnaire - Function	*p = 0.009*	*p = 0.001*
PROMIS Sleep Disturbance	*p < 0.001*	*p < 0.001*
PROMIS Fatigue	*p = 0.018*	*p < 0.001*
Weekly average of daily Sleep Quality scores	*p < 0.001*	*p < 0.001*

F304 – RELIEF
F307 – RESILIENT

Abbreviations: PROMIS, Patient-Rated Outcome Measurement Information System

TNX-102 SL 2.8 mg Studies in Fibromyalgia

RESILIENT Study

Completed Trials in FM:

- Phase 2 (F202 BESTFIT) – 205 patients randomized
- Phase 3 (F301 AFFIRM) – 519 patients randomized

Topline Efficacy Results:

- Studies did not achieve statistical significance in the primary efficacy endpoint

More In-Depth Results:

- Both studies showed efficacy signals justifying continued development in FM

Safety:

- Well tolerated; side effects consistent with known side effects of cyclobenzaprine

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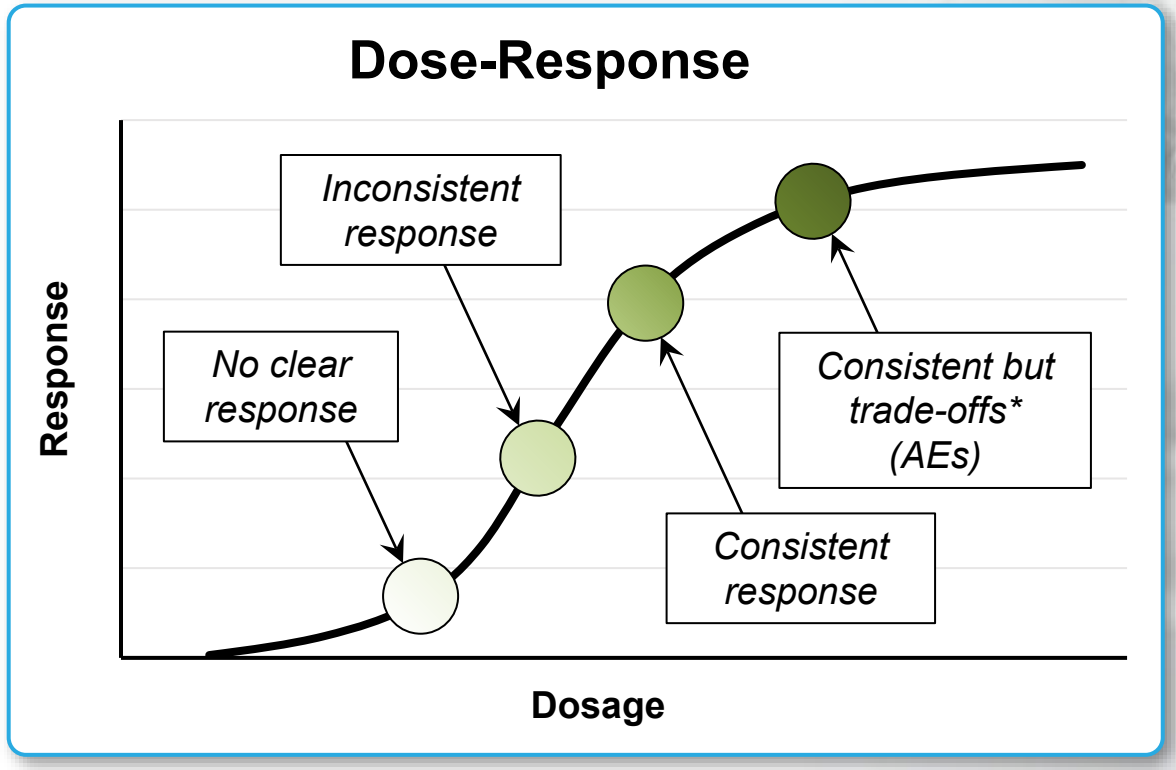
Summary of TNX-102 SL 2.8 mg Trials

		Phase 2b F202 (BESTFIT) *Dose: 2.8 mg*	Phase 3 F301 (AFFIRM) *Dose: 2.8 mg*
Primary Endpoint: Pain Relief at Week 12	Pre-specified pain endpoint	Change in daily pain score (ANCOVA with JTC/MI*) **Trend: p=0.172**	Responder analysis ≥30% pain reduction (Logistic regression) **Trend: p=0.095**
	Post hoc analysis	Responder analysis ≥30% pain reduction (Logistic Regression) **p=0.033**	• Imbalance in missing data and individuals with missing data treated as 'non-responder' • Current FDA statistical guidance on handling missing data: analysis with MMRM with MI* **p=0.002**
Key Secondary Endpoints: Global improvement or improvement in symptoms and function	Patient Global Impression of Change (PGIC)	**p=0.025**	**p=0.038**
	Fibromyalgia Impact Questionnaire-Revised (FIQ-R) total score	**p=0.015 (ANCOVA)**	**P<0.001**
	PROMIS Sleep Disturbance instrument	**p=0.004 (ANCOVA)**	**P<0.001**
	FIQ-R Pain Item	**p=0.004**	**P<0.001**

TNX-102 SL Dose Response

Basic Pharmacology

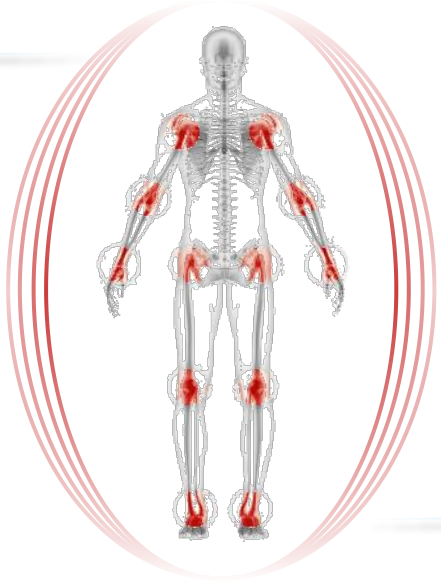
- Dose can make the difference in the strength of the response



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

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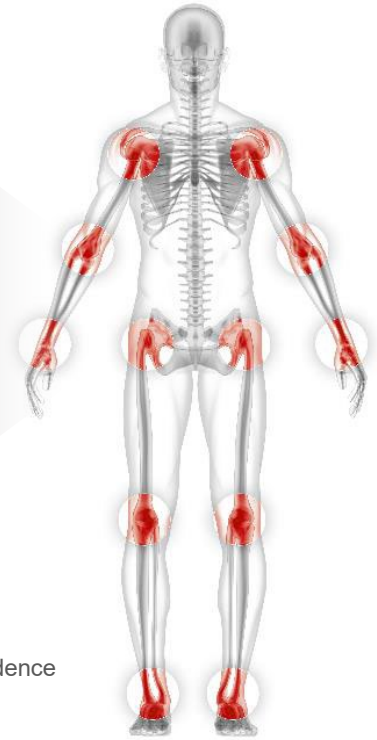
Role of Infections in Triggering Fibromyalgia or Chronic fatigue (CFS)-Like Illnesses

- 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.

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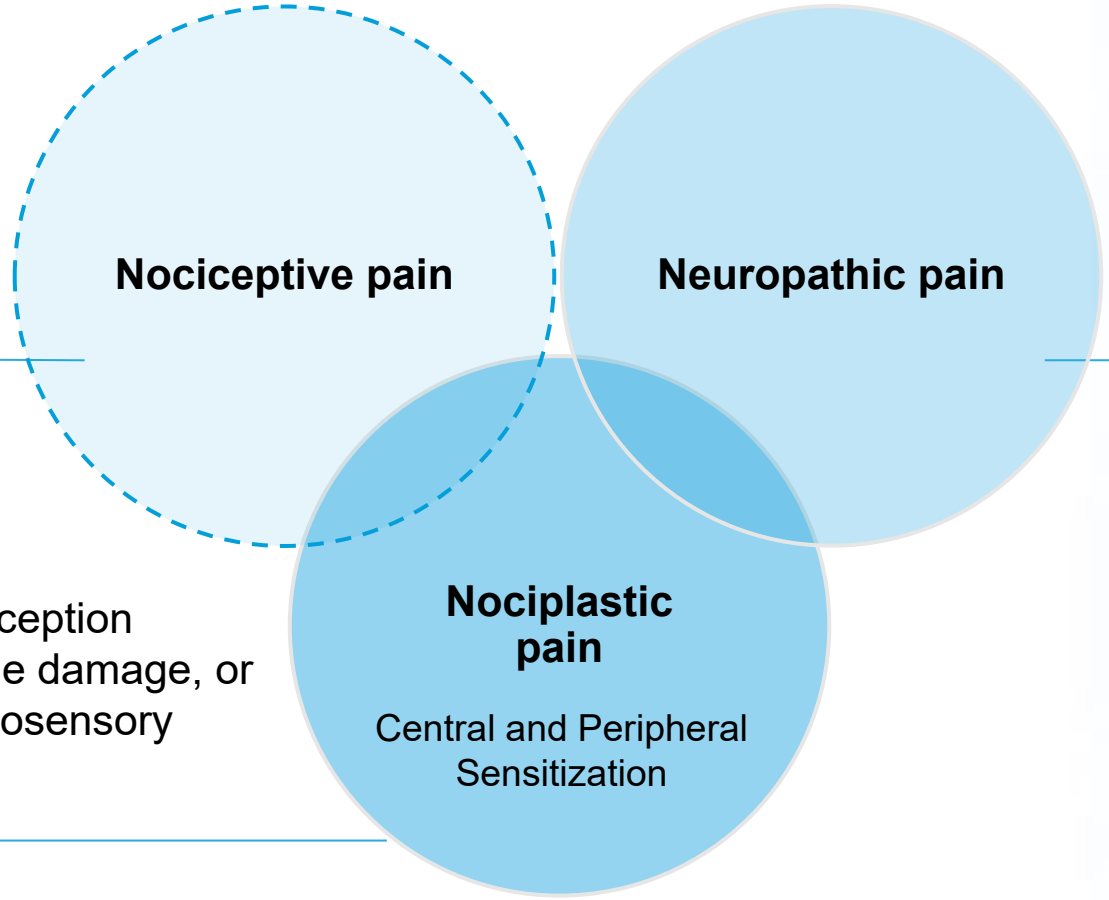
New Classification for Central Pain: Nociplastic Pain[1]

Pain due to the activation of nociceptors that arises from actual or threatened damage to non-neural tissue



Pain caused by a lesion or disease of the somatosensory nervous system

Pain that arises from altered nociception despite no clear evidence of tissue damage, or for disease or lesion of the somatosensory system causing the pain

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

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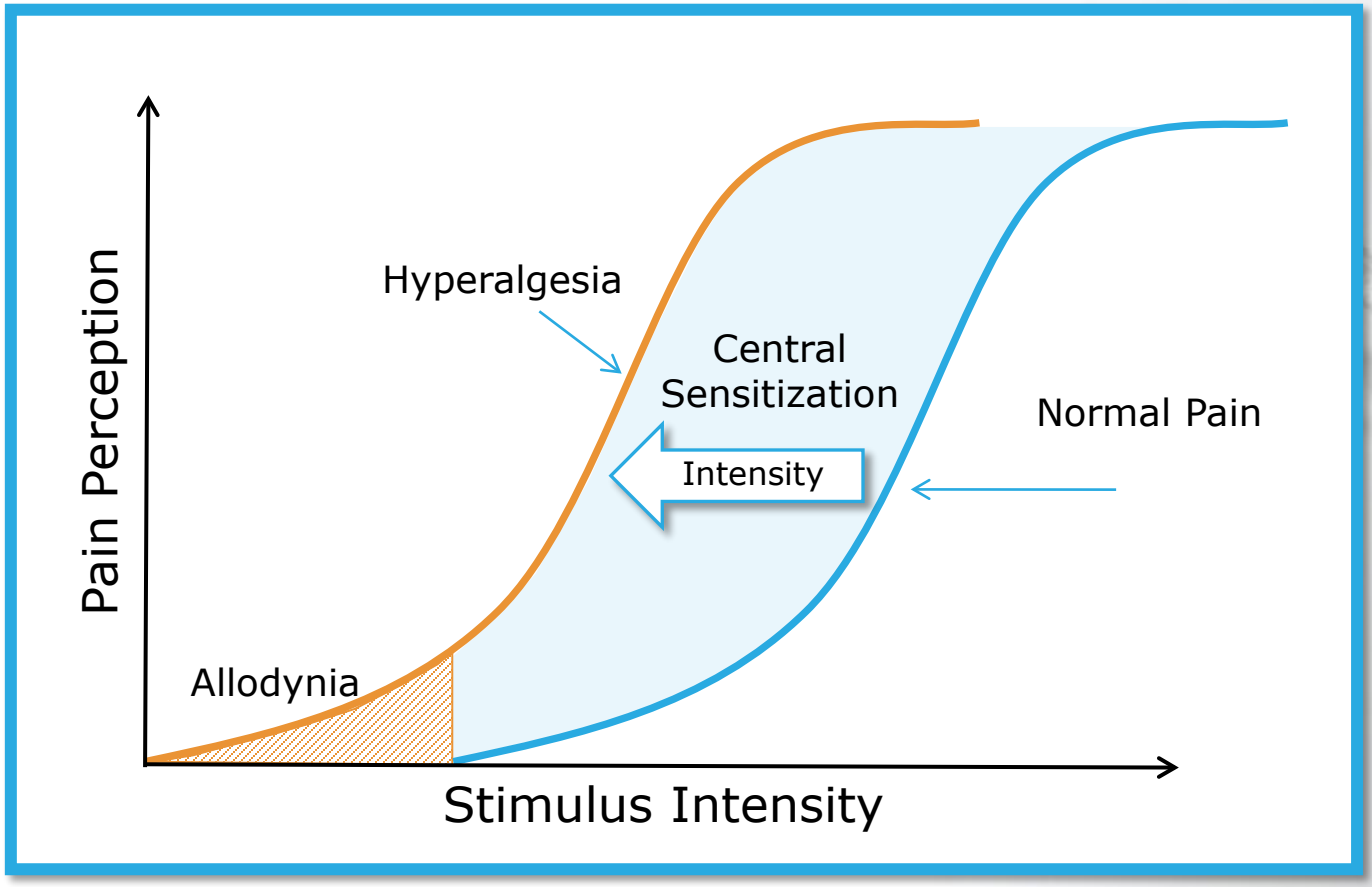
Central Sensitization (CS)
A Feature of Many Nociplastic Pain Syndromes

- 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.

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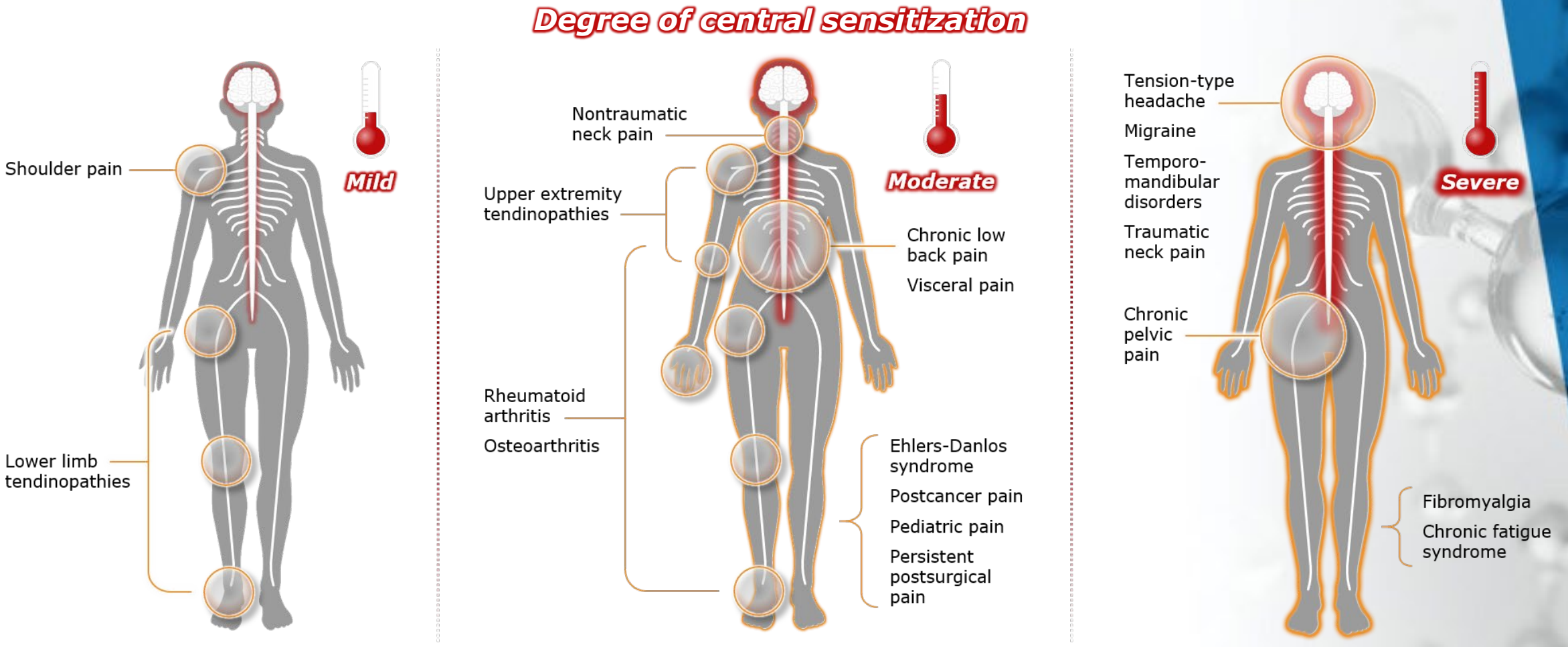
Central Sensitization (CS)
Can Occur in a Range of Diseases and Conditions



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

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THANK YOU