UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): June 10, 2024

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

Tonix Pharmaceuticals Holding Corp. (the "Company") updated its investor presentation, which is used to conduct meetings with investors, stockholders and analysts and at investor conferences, and which the Company intends to place on its website, which may contain nonpublic information. A copy of the presentation is filed as Exhibit 99.01 hereto and incorporated herein by reference. The Company updated its TNX-102 SL product candidate presentation, which it intends to place on its website and which may contain nonpublic information. A copy of the product presentation is filed as Exhibit 99.02 and hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01 and 99.02 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On June 10, 2024, the Company announced that it had its Type B CMC (Chemistry, Manufacturing, and Controls) and clinical pre-NDA (New Drug Application) meeting with the U.S. Food and Drug Administration for Tonmya™ (TNX-102 SL), and that it is awaiting formal minutes of the meeting.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	**Description.**

99.01	Corporate Presentation by the Company for June 2024
99.02	TNX-102 SL Product Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: June 10, 2024

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

EXHIBIT 99.01

TONIX PHARMACEUTICALS

Corporate Presentation

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

June 2024

NASDAQ: TNXP

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

Version P0574 June 10, 2024 (Doc 1455)

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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, 2023, as filed with the Securities and Exchange Commission (the "SEC") on April 1, 2024, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

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Who We Are

Tonix is committed to developing and marketing therapeutics to treat pain, neurologic, psychiatric and addiction conditions through our ***central nervous system portfolio*** and within other areas of ***high unmet need***, including immunology, infectious disease, and rare disease

With a Focus on:

Filing a New Drug Application (NDA) with the US Food and Drug Administration (FDA) for Tonmya™ (TNX-102 SL) for the management of Fibromyalgia

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CNS-Focused Biopharma with Preclinical, Clinical and Commercial Stage Products

Tonmya™ for Fibromyalgia: Preparing New Drug Application (NDA)

- Two Phase 3 trials completed with statistical significance on primary endpoint
- NDA filing expected 2H'24
- FDA decision on NDA approval expected 2H'25

Marketed Products

- Zembrace® and Tosymra® indicated for the treatment of acute migraine

Strategic Partnerships

- With government institutions, world-class academic & research organizations

Pipeline

- Phase 2 biologic cocaine antidote, FDA "Breakthrough Therapy Designation"
- Phase 1 anti-CD40L monoclonal antibody to prevent organ transplant rejection

Internal Capabilities

- Commercial prescription drug sales
- R&D and clinical-trial scale manufacturing

*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

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Key Clinical Programs

Molecule*	Indication	Phase 1	Phase 2	Phase 3	NDA Submission
Tonmya™ TNX-102 SL Cyclobenzaprine HCl Protectic® Sublingual Tablets	Fibromyalgia	*Statistically Significant Phase 3 Topline Results Reported 4Q'23*			*Submission expected 2H'24*
	Long COVID	*Phase 2 Topline Results Reported 3Q'23*			
	Acute Stress Disorder	*Phase 2 Study** Start Expected 2Q'24*			
TNX-1300 Cocaine Esterase *NIDA Funded*	Cocaine Intoxication	*Phase 2 Study Start Expected 2Q'24*			
TNX-2900 Intranasal Potentiated Oxytocin *FDA Orphan Drug and Rare Pediatric Disease Designation*	Prader-Willi Syndrome	*Phase 2 Ready*			
TNX-1500 Anti-CD40L mAb	Organ Transplant Rejection/ Autoimmune Conditions	*Phase 1 Study Ongoing*	*Clinical Stage Completed*		

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

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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®)

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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

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

A unique, sublingual formulation of cyclobenzaprine designed to optimize delivery and absorption

*"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.

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

- **Non-opioid analgesic designed for long-term daily bedtime use in fibromyalgia patients**
  - Targets non-restorative sleep
  - Potent binding and antagonist activities at four post-synaptic receptors
    - serotonin-5-HT2A
    - α1-adrenergic
    - histaminergic-H1
    - muscarinic-M1
  - No recognized risk for abuse

- **Improves sleep quality, does not increase sleep quantity:**
  - Not a traditional hypnotic or sedative

- **Proprietary, sublingual transmucosal formulation of cyclobenzaprine designed to optimize delivery and absorption**
  - Protectic® formulation based on eutectic composition of matter
    - Rapid absorption
    - Decrease in major metabolite by bypassing first-pass hepatic metabolism

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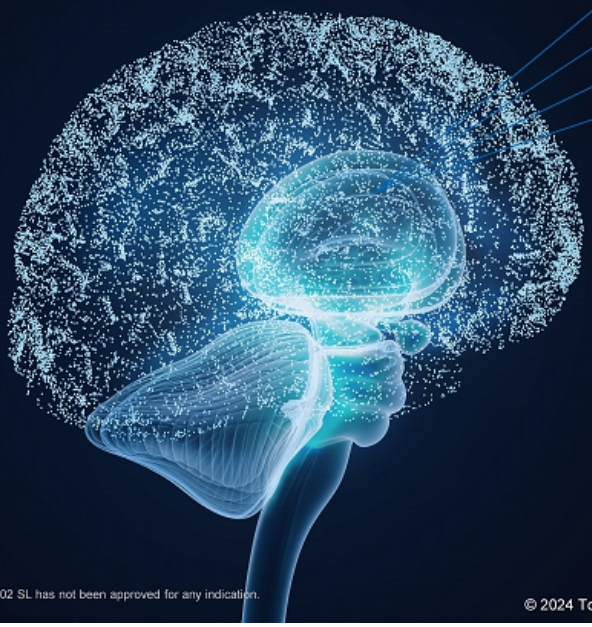
TNX-102 SL: Unique MOA Facilitates Restorative Sleep

Centrally Acting Analgesic

Potent binding and antagonist activities at four key receptors facilitate ***restorative sleep***



- *serotonergic-5-HT2A*
- *adrenergic-α1*
- *histaminergic-H1*
- *muscarinic-M1*

Key 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 nor with recognized abuse potential

Issued patents expected to provide exclusivity to 2034/2035

Protectic® formulation based on eutectic composition of matter

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

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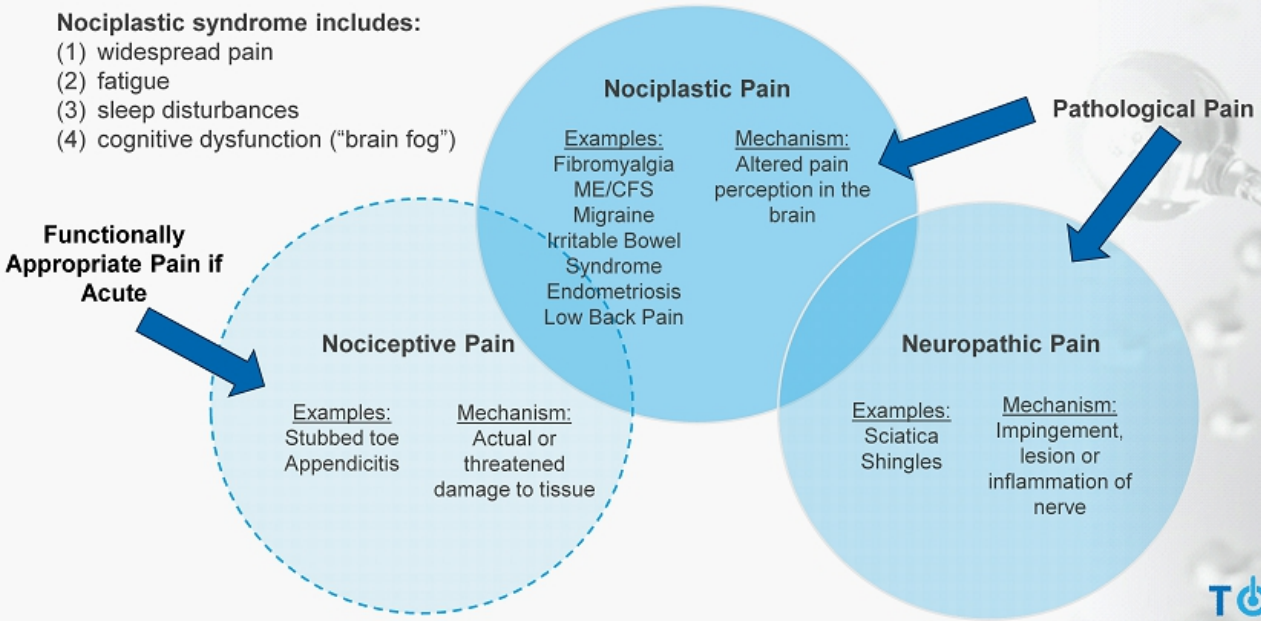
The Third Type of Pain: Nociplastic Pain[1]

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



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

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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

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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)

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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
- Many 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

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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[2,4]

Unmet Need

- Majority of patients do not respond or cannot tolerate therapy[5]

[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

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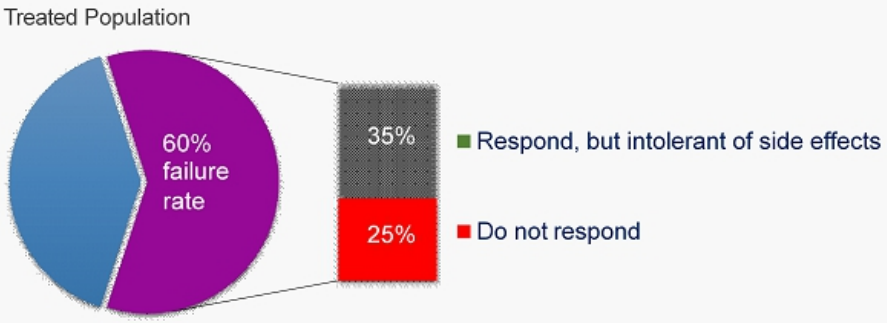
Fewer than Half of Those Treated for Fibromyalgia Receive Sustained Benefit from the Three FDA-Approved Drugs[1]

- 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)

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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)

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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.

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Fibromyalgia Program Status

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

Fibromyalgia

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

- **First pivotal Phase 3 study (*RELIEF*) reported – December 2020[1]**
- **Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021**
- **Confirmatory pivotal Phase 3 study (*RESILIENT*) reported – December 2023**

Next Steps:

- **Type B CMC and clinical pre-NDA meetings with FDA completed; awaiting formal meeting minutes**
- **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

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

RESILIENT Study

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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

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

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RESILIENT Primary Outcome Measure

Reduction in Widespread Pain

RESILIENT Study

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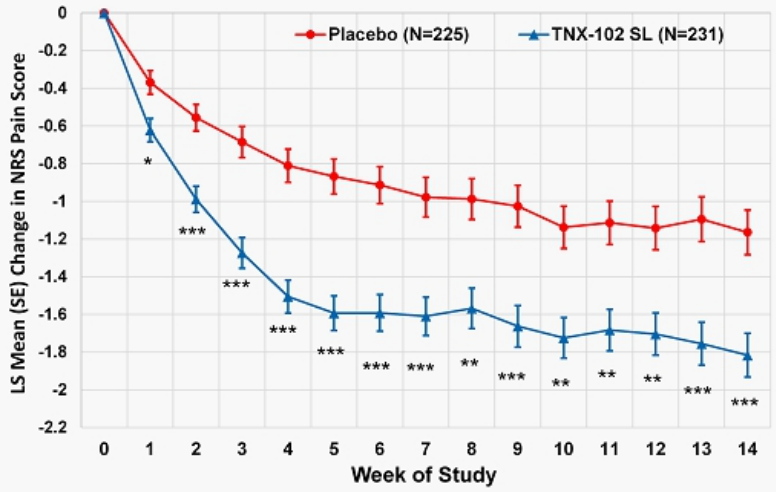
Weekly Average of Daily Diary NRS Ratings of Average Pain Over Prior 24 Hours



*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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Summary of Key Pre-Specified Secondary Outcome Measures

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

RESILIENT Study

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RESILIENT Pre-Specified Primary Endpoint

RESILIENT Study

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Summary[1]

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

Additional Findings

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

[1]The Company plans to present the data at upcoming scientific meetings and publish the results in a journal later this year

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RESILIENT Safety Summary

RESILIENT Study

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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

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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
Systemic Adverse Events			
COVID-19	10 (4.3%)	7 (3.1%)	17 (3.7%)
Somnolence	7 (3.0%)	3 (1.3%)	10 (2.2%)
Headache	7 (3.0%)	4 (1.8%)	11 (2.4%)
Oral Cavity Adverse Events			
Hypoaesthesia oral	55 (23.8%)	1 (0.4%)	56 (12.3%)
Product taste abnormal	27 (11.7%)	2 (0.9%)	29 (6.3%)
Paraesthesia oral	16 (6.9%)	2 (0.9%)	18 (3.9%)
Tongue discomfort	16 (6.9%)	0 (0.0%)	16 (3.5%)

*Safety Population

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

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

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Tonmya™ Showed Broad-Spectrum Activity and was Well Tolerated

		Lyrica®	Cymbalta® Savella®	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

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~50% of U.S. Fibromyalgia Patients are on Medicare: Prescription Coverage in Medicare Stands to Benefit from Changes in IRA

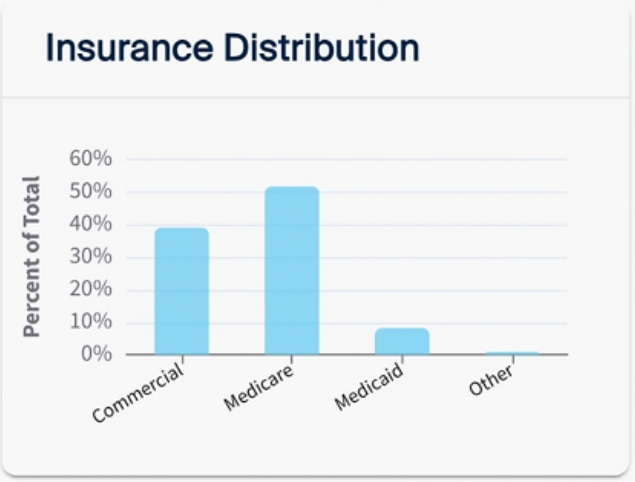
Approximately 50% of fibromyalgia patients are on Medicare

- EVERSANA analysis of claims database consisting of 2.2M patients, for which 1.2M claims were submitted throughout March 2002-March 2023[1]

Beneficial Changes in 2025 to Medicare Part D through Inflation Reduction Act (IRA)[2]

- Medicare prescription payment plan to offer enrollees the option to pay out-of-pocket prescription drug costs in the form of capped monthly installment payments instead of all at once at the pharmacy
- Annual out-of-pocket costs will be capped at $2,000 in year 2025
- Will replace the existing Coverage Gap Discount Program, which sunsets as of January 1, 2025

Fibromyalgia Patients by Coverage[1]



[1] EVERSANA analysis of claims database, May 2024; commissioned by Tonix
[2] Source: Final CY 2025 Part D Redesign Program Instructions Fact Sheet | CMS

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Prescribers Interviewed are Broadly Dissatisfied with Available Fibromyalgia Medications: Results of Primary Research[1]

Perspectives on FM Therapies from Prescribers Interviewed		
Drug	**Positives**	**Negatives**
Duloxetine *(Cymbalta, generic)*	• Relatively high efficacy (compared to alternatives) • Can be titrated slowly from 20mg to 120mg	• Tolerability issues: worsening depression, insomnia • Seldom used as a monotherapy; often requires adjunct
Pregabalin *(Lyrica, generic)*	• Relatively high efficacy (compared to alternatives) • Can often be safely combined with other medications	• Suboptimal for long-term use (e.g., weight gain) • Schedule V status makes some HCPs more cautious to Rx
Savella *(milnacipran)*	• Offers another option if patient fails Cymbalta or Lyrica	• Subpar efficacy does not counterbalance tolerability issues • High cost and access constraints (~$50/month)
Cyclobenzaprine *(Flexeril, generic; oral formulation, off-label)*	• Active for initiating and sustaining sleep; can be titrated up • Active for pain driven by stiffness and muscle spasms	• Mixed perspectives on pain benefit independent of sleep • Suboptimal long-term results as efficacy wanes

85% of patients (avg) fail first line therapy

79% of FM patients (avg) are on multiple therapies

[1]EVERSANA primary physician research, May 2024; commissioned by Tonix

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Opportunity for a New, Unique Fibromyalgia Treatment Option: Results of Primary Research from EVERSANA[1,2]

FM Landscape	• Prescribers indicate a **very high unmet need** in FM (ranked ≥4.0 on a 5-point scale) • Prescribers report there is **no standard of care in FM**, employ an **individualized approach** based on symptomology • No new treatments approved since 2009 • Prescribers report minimal promotional activities by any pharmaceutical company • Highly concentrated prescriber base with 50% of patients treated by ~16k physicians
Physician Primary Market Research	• **Physicians reacted positively to Tonmya's efficacy and safety profile (based on Phase 3 Study results)** • Median interest = 4.0 on a 5-point scale • Driving attributes included **strong efficacy, safety and tolerability** • Unique & differentiating efficacy features included improvements in **sleep and fatigue**
Anticipated Use	• **Physicians indicated intended use in 40% of their FM patients** • Majority of respondents indicated Tonmya would be their first choice, if accessible • Physicians surveyed indicated they are well-equipped to deal with access restrictions including prior authorizations and step-edits

[1] EVERSANA primary physician research, May 2024; commissioned by Tonix
[2] EVERSANA analysis of claims database, May 2024; commissioned by Tonix

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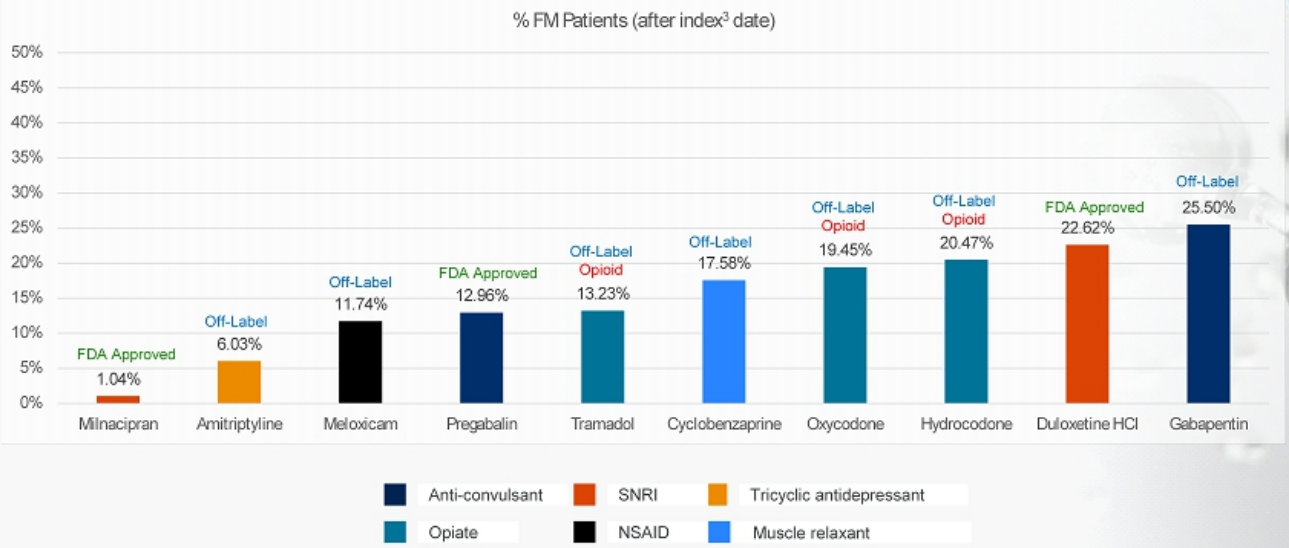
Many Fibromyalgia Patients are Prescribed Off-Label Drugs; ~53% FM Patients Prescribed Opioids Off-Label[1,2]



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

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CNS PORTFOLIO

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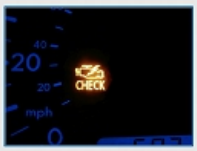
Tonmya™ (TNX-102 SL): Fibromyalgia Cyclobenzaprine Protectic® Sublingual Tablets

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

Status: One statistically significant Phase 3 study RELIEF completed, *p*-value = 0.01[2]

Second Phase 3 study RALLY missed primary endpoint

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

Next Steps: Type B CMC and clinical pre-NDA meetings with FDA completed; awaiting formal meeting minutes

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

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

[1] American Chronic Pain Association (www.theacpa.org, 2019)
[2] Lederman S, et al. *Arthritis Care Res (Hoboken)*. 2023 Nov;75(11):2359-2368. doi: 10.1002.

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CNS PORTFOLIO

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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	$3.5 B	Auvelity®	Depression	8/2022	
Biohaven	BHVN	$3.0 B	Nurtec®	Migraine	2/2020	Sold to PFE for $12 B in Oct 2022
IntraCellular	ITCI	$7.2 B	Caplyta®	Schizophrenia	12/2019	
Supernus	SUPN	$1.4 B	Oxtella-XR®	Seizures	1/2019	
Neurocrine	NBIX	$13.6 B	Ingrezza®	Tardive Dyskinesia	4/2017	
Acadia	ACAD	$2.5 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]Accessed June 7, 2024

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

Fibromyalgia-Type Long COVID

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

Next Steps: Meet with FDA

Acute Stress Reaction/ Acute Stress Disorder

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

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

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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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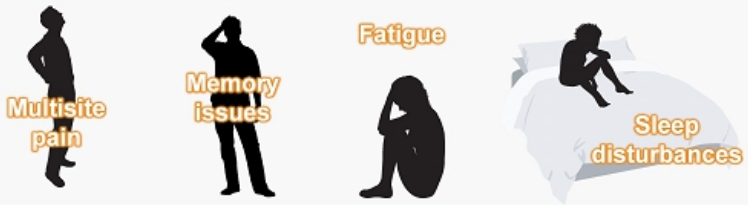
About Fibromyalgia-Type Long COVID

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

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

PREVAIL Study

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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)*

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

Placebo once-daily at bedtime

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)"

14 weeks

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

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

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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.

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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

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TNX-102 SL for ASR/ASD: Program Status

Status: Expect to start Phase 2 in 2Q 2024; received IND clearance from FDA

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

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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

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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.

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Tonix Medicines: Commercial-Stage Specialty Pharma Subsidiary

- **Tonix Medicines is a wholly-owned subsidiary of Tonix (NASDAQ: TNXP)**
  - Currently marketing two products indicated for the treatment of acute migraine: Zembrace® SymTouch ® and Tosymra®
  - ~16 M in net sales[1]
  - Nascent commercial organization
- **Tonix Medicines is preparing to launch Tonmya™ (TNX-102 SL) for fibromyalgia**
  - Fibromyalgia care is relatively concentrated to specialized providers
  - We believe prescribing physicians can be targeted effectively by a specialty sales force
  - Evolving landscape in commercial markets favors distribution channels such as specialty pharmacies

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[1]Tonix 10-Q for 3Q23

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Two Marketed Proprietary Migraine Drugs
Non-oral Formulations of Sumatriptan

Zembrace® SymTouch®
(sumatriptan injection) 3 mg[1]

- Each indicated for the ***treatment of acute migraine with or without aura in adults***
- Sumatriptan remains the acute migraine 'gold standard' treatment for many patients and continues to represent the largest segment of the market in terms of unit sales[3]
- Each may provide migraine ***pain relief in as few as 10 minutes*** for some patients[1,2,4,5]
- Patents to 2036 (Zembrace) and 2031 (Tosymra)

Tosymra®
(sumatriptan nasal spray) 10 mg[2]

Acquired from Upsher-Smith Laboratories which has managed care contracts covering ~200 M lives
- Contract includes a transition period during which Tonix expects to secure its own contracts

Tonix Medicines Commercial Subsidiary
- Complete commercialization capability
  - Manage supply chain and contract manufacturer
  - Distribution
  - Trade, Managed Care & Government contracting
- Team of professionals including Sales & Marketing personnel

[1]Zembrace SymTouch [package insert]. Maple Grove, MN: Upsher-Smith Laboratories, LLC: February 2021 - For more information, talk to your provider and read the Patient Information and Instructions for Use. – Important Safety Information is provided in the appendix
[2]Tosymra [package insert]. Maple Grove, MN: Upsher-Smith Laboratories, LLC: Feb 2021. For more information, talk to your provider and read the Patient Information and Instructions for Use. – Important Safety Information is provided in the appendix
[3]Tonix Medicines, Inc.; Data On File, 2023
[4]Mathew NT, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49(12):1271-1276.
[5]Wendt J, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. Clinical Therapeutics. 2006;28(4):517-526.

Zembrace SymTouch and Tosymra are registered trademarks of Tonix Medicines, Inc. Intravail is a registered trademark of Aegis Therapeutics, LLC, a wholly owned subsidiary of Neurelis, Inc.

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Zembrace and Tosymra Bypass the GI Tract

Bypassing gastrointestinal (GI) tract is *potential advantage for treating acute migraine*
- GI absorption may be inconsistent in migraineurs due to gastric stasis (also called "gastroparesis")[1-4]
- Nausea and vomiting are symptoms of migraine[5] which can complicate oral treatment

Existing Subcutaneous injectable products
- Imitrex® SQ Injection (sumatriptan succinate)-6mg and 4mg preparations
- DHE 45 (dihydroergotamine mesylate) SQ Injection

Existing intranasal products
- Imitrex® nasal spray (sumatriptan)
- Migranal® (dihydroergotamine) nasal spray – developed by Novartis, sold by Bausch Health
- Zavzpret® (zavegepant) nasal spray, FDA approved in March, 2023[5] is the first intranasal gepant-marketed by Pfizer
- Zomig® nasal spray (zolmitriptan)
- Onzetra® Xsail® (sumatriptan nasal powder) marketed by Currax
- Trudhesa® (dihydroergotamine) nasal spray

[1]Zembrace SymTouch [package insert]. Maple Grove, MN: Upsher-Smith Laboratories, LLC: February 2021.
[2]Mathew NT, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49(12):1271-1276.
[3]Landy, S. et al. Efficacy and safety of DFN-11 (sumatriptan injection, 3 mg) in adults with episodic migraine: a multicenter, randomized, double-blind, placebo-controlled study. *J Headache Pain*. 19, 69 (2018).
[4]Brand-Schieber E, Munjal S, Kumar R, et al. Human factors validation study of 3 mg sumatriptan autoinjector, for migraine patients. Med Devices (Auckl). 2016;9:131-137.
[5]Pfizer Press Release March 10, 2023. – https://www.pfizer.com/news/press-release/press-release-detail/pfizers-zavzprettm-zavegepant-migraine-nasal-spray

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Pipeline

Programs and Strategy for Partnerships

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Pipeline Development Strategy

Focusing on government and academic collaborations

- Validates Tonix's scientific expertise and technology
- Reduces internal spend
- Increases number of trials
- Potentially speeds time to market
- Grants, contracts, cost-sharing or "in-kind" arrangements

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External Partnerships

Government partners providing direct funding, cost sharing or in-kind support include:

- National Institutes of Health (NIH)
- National Institute of Allergy and Infectious Disease (NIAID)
  - TNX-1800 selected for Project NextGen
- National Institute on Drug Abuse (NIDA)
  - TNX-1300 for cocaine intoxication; Phase 2 study funding
- Department of Defense (DoD)
  - TNX-102 SL for ASD; Phase 2 study funding

Academic partners sponsoring clinical trials of Tonix's investigational drug products include:

- Massachusetts General Hospital (MGH)
- University of Washington
- University of North Carolina

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Key Partnerships

TNX-1500: ALLOGRAFT REJECTION

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

TNX-1300: COCAINE INTOXICATION

NIH National Institute on Drug Abuse

COLUMBIA UNIVERSITY

TNX-102 SL: ACUTE STRESS DISORDER

U.S. Department of Defense

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

TNX-1800: COVID-19 VACCINE

NIH National Institutes of Health

NIH National Institute of Allergy and Infectious Diseases

TNX-2900: PRADER-WILLI SYNDROME

InsermTransfert

CHU de Toulouse

Aix*Marseille université

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TNX-2900

Intranasal Potentiated Oxytocin with Magnesium

A novel, non-CGRP antagonist approach to treatment

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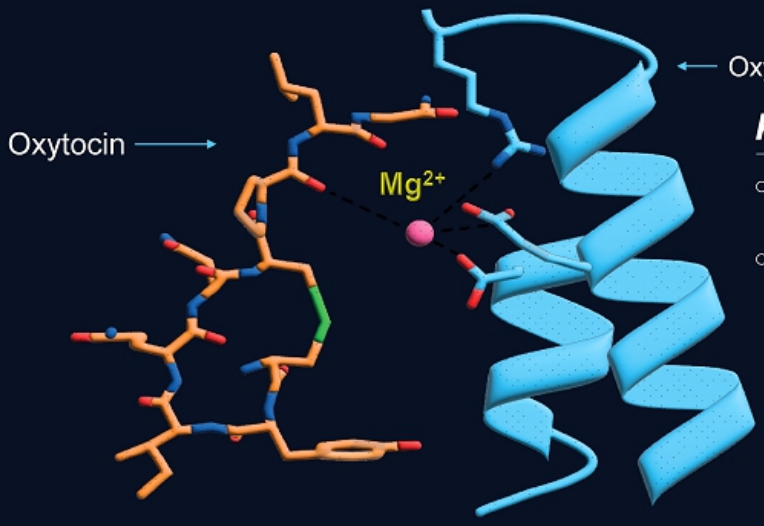
TNX-2900: Novel Formulation of Intranasal Oxytocin (OT) Potentiated with Magnesium

*Magnesium is known to **potentiate the binding of OT** to its receptor*[1,2]



Key Differentiators

- Targeted intranasal delivery
  - Low systemic exposure
- When delivered via the nasal route, concentrates in trigeminal system
  - Binding of OT to receptors on neurons in trigeminal system inhibits release of CGRP and transmission of pain signals
  - Blocking CGRP release is a distinct mechanism compared with CGRP antagonist and anti-CGRP antibody drugs, which block the binding of CGRP to its receptor

[1]Antoni et al., 1989. *Biochem J.* 257(2):611-4
[2]Meyerowitz et al., 2022. *Nat Struct Mol Biol.* (3):274-281
*TNX-1900 and TNX-2900 have not been approved for any indication.

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About Prader-Willi Syndrome

*Prader-Willi Syndrome (PWS) is the most common genetic cause of life-threatening childhood obesity. PWS causes unhealthy behaviors around food[1-4], consequences such as **obesity, type 2 diabetes, and cardiovascular disease**[1-5], and creates significant caretaker burden[1-4]*

10-20 *thousand individuals* **Rare genetic disease that afflicts 10-20 thousand individuals in the US**

Current standard of care:

- Human growth hormone treatment is FDA-approved for growth failure in PWS children

Large unmet need:

- Currently no cure, and no treatment for PWS-related hyperphagia
- Consequences can be life threatening - obesity and cardiovascular disease are leading cause of death

TNX-2900 has been granted FDA Orphan Drug and Rare Pediatric Disease Designations, and received IND clearance by FDA for Phase 2 Trial

RARE DISEASE PORTFOLIO

[1]Miller et al., 2011. *Am J Med Genet A.* 155A(5):1040-1049
[2]Butler et al., 2017. *Genet Med.* 19(6):635-642
[3]Butler MG. NORD. Updated 2018. Accessed May 25, 2022. https://rarediseases.org/rare-diseases/prader-willi-syndrome/
[4]Prader-Willi Syndrome Association USA. Accessed May 25, 2022. https://www.pwsausa.org/what-is-prader-willi-syndrome/
[5]Muscogiuri et al., 2021. *J Endocrinol Invest.* 44(10):2057-2070

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TNX-1300

Cocaine Esterase

Fast acting antidote for life threatening cocaine intoxication

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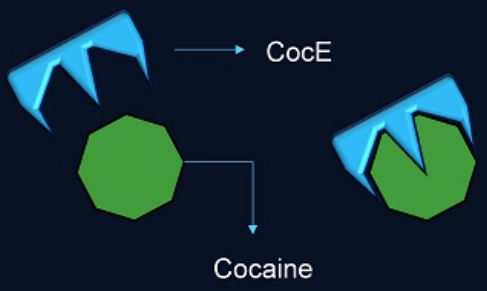
TNX-1300: Recombinant Protein Rapidly Degrades Cocaine in the Bloodstream

Drops plasma exposure by 90% in 2 minutes



FDA Breakthrough Therapy Designation

Awarded Cooperative Agreement Grant from ***National Institute on Drug Abuse (NIDA)***

Key Differentiators

- Rapidly metabolizes cocaine within matter of minutes
- No other product currently on the market for this indication

*TNX-1300 has not been approved for any indication.

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About Cocaine Intoxication

Over 5 million Americans reported current cocaine use in 2020, which is almost 2% of the population[1]. In 2021, more than 24,900 individuals in the US died from drug overdose deaths involving cocaine[2]

500k **Over 500,000 emergency department visits for cocaine, annually[3,4]**

Current standard of care:

- Patients are currently managed only by supportive care for the adverse effects of cocaine intoxication on the cardiovascular and central nervous systems

Large unmet need:

- No other product currently on the market for this indication
- TNX-1300 could significantly reduce the time and resources required for other detox services
- Potentially reduces the risk of morbidity and mortality

CNS PORTFOLIO

[1]Substance Abuse and Mental Health Services Administration. (2021). Results from the 2020 National Survey on Drug Use and Health: Detailed Tables: Prevalence Estimates, Standard Errors, and Sample Sizes.
[2] Centers for Disease Control and Prevention (CDC) - https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

[3]Substance Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
[4] Drug Abuse Warning Network, 2011: Selected Tables of National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA, 2013.

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IMMUNOLOGY: KEY CANDIDATES
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TNX-1500
Anti-CD40L Monoclonal Antibody
Next Generation mAb preserves efficacy without risk of thrombosis
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TNX-1500: Next Generation anti-CD40L mAb

Re-engineered to better modulate the binding of FcγR and mitigate risk of thrombosis

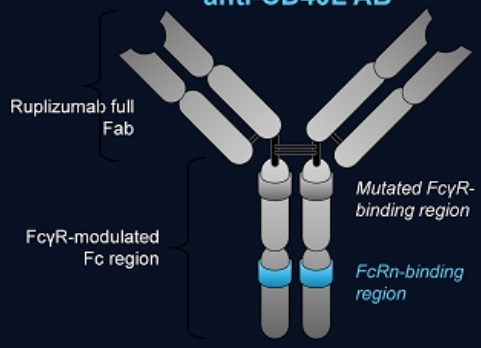
Clinical Stage of Phase 1 study completed

Key Differentiators

Expected to deliver efficacy without compromising safety

- **First Generation:** Development halted due to thromboembolic (TE) complications—blood clots—traced to Fc gamma receptor (FcγR)
- **Second Generation:** Eliminated the FcγR TE complication but potency and half life was reduced, limiting utility
- **Third Generation (TNX-1500):** Re-engineered to better modulate the binding of FcγR.

Selectively Modified anti-CD40L AB



Contains the full ruplizumab Fab and the engineered Fc region that modulates FcγR-binding, while preserving FcRn function

*TNX-1500 has not been approved for any indication.

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TNX-1500 Strategy and Status

IMMUNOLOGY PORTFOLIO

1 Proposed Initial Indication: Prevention of Allograft Rejection

Status: ***Clinical stage Phase 1 complete***

Collaborations ongoing with Mass General Hospital on heart and kidney transplantation in non-human primates

- Collaboration with Boston Children's on bone marrow transplantation in non-human primates

Next Steps: Initiate Phase 2 study in Kidney Transplant Recipients

2 Second Indication: Hematopoietic Cell Transplant (Bone Marrow Transplant)

- Potential to reduce GvHD

3 Third Indication (and beyond): Autoimmune Diseases (e.g., Multiple Sclerosis, Sjögen's Syndrome, Systemic Lupus Erythematosus)

- These indications require large studies, but represent large target markets

Currently exploring strategic partnerships and out-licensing opportunities

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TNX-1500 Preclinical Data and Publications

Non-human Primate Kidney Allo-Transplantation

- TNX-1500 monotherapy consistently prevents kidney transplant rejection with no thrombosis observed
- April 2023 Publication: Lassiter, G., et al. (2023). TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Renal Allograft Survival. *American Journal of Transplantation*. www.sciencedirect.com/science/article/pii/S1600613523003714

Non-human Primate Heart Heterotopic Allo-Transplantation

- TNX-1500 monotherapy consistently prevents heart transplant rejection. Similar activity to chimeric hu5c8[2] during treatment phase in prior studies
- April 2023 Publication: Miura, S., et al. (2023) TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Cardiac Allograft Survival. *American Journal of Transplantation*. www.sciencedirect.com/science/article/pii/S1600613523003969

Non-Human Primate Kidney Xenograft Transplantation

- TNX-1500 therapy is part of a regiment to prevent rejection in kidney xenograft transplants
  - Anand, R.P., Layer, J.V., Heja, D. et al. (2023). Design and testing of a humanized porcine donor for xenotransplantation. *Nature*. https://www.nature.com/articles/s41586-023-06594-4
  - Kozlov, M. (2023). Monkey survives two years after gene-edited pig-kidney transplant. *Nature*. https://www.nature.com/articles/d41586-023-03176-2
  - Mohiuddin, M. (2023). Pig-to-primate organ transplants require genetic modifications of donor. *Nature*. https://www.nature.com/articles/d41586-023-02817-w

IMMUNOLOGY PORTFOLIO

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α-CD40L Headlines

- Mass General Hospital just transplanted a genetically engineered pig kidney into a living human[1]
  - Boston Globe, March 21, 2024
  - Patient's death announced May 11, 2024[2]
- The patient was being treated with anti-CD40L mAb tegoprubart from Eledon[1]
- ***The preclinical work was performed with TNX-1500[3]***

The Boston Globe

In a first, Mass. General surgeons transplant a pig kidney into a man

The patient is doing well, but many unknowns remain

By Felice J. Freyer Globe Staff, Updated March 21, 2024, 7:40 p.m.

Dr. Leonardo V. Riella, medical director of kidney transplantation, center, broke down as he thanked his colleagues. Dr. Tatsuo Kawai, director of the Legorreta Center for Clinical Transplant Tolerance, left, and Dr. Winfred Williams, associate chief of the Division of Nephrology, also spoke at a news conference on Thursday. DAVID L. RYAN/GLOBE STAFF

Seventy years after surgeons at Brigham & Women's Hospital performed the world's first kidney transplant, doctors at its sister hospital, Massachusetts General, announced an

[1] Massachusetts General Hospital press release. March 21, 2024. "World's First Genetically Edited Pig Kidney Transplant into Living Recipient Performed at Massachusetts General Hospital." www.massgeneral.org/news/press-release/worlds-first-genetically-edited-pig-kidney-transplant-into-living-recipient (accessed March 29, 2024)

[2] Stoico, N. *Boston Globe*. May 11, 2023. "Mass Man who received first kidney transplant from genetically engineered pig has died, family says".

[3] Anand, R.P., et al *Nature*. 622, 393–401 (2023). https://doi.org/10.1038/s41586-023-06594-4

CNS PORTFOLIO

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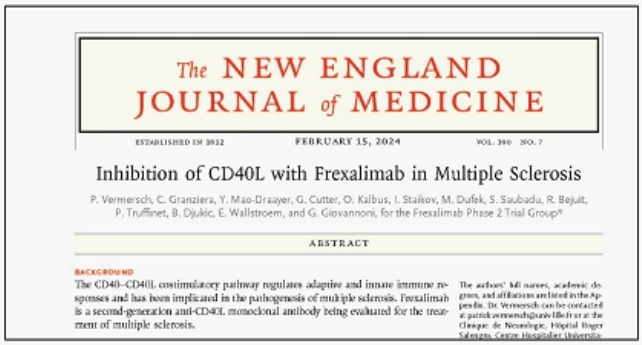
Anti-CD40L Headlines

- Sanofi recently published their Phase 2 data on their frexalimab in multiple sclerosis in the the *New England Journal of Medicine*[1]
  - Sanofi projects its Fc-modified humanized anti-CD40L mAb frexalimab will exceed €5 B per year in peak sales[2]

- Like frexalimab, TNX-1500 is Fc-modified to reduce/eliminate the risk of thrombosis seen with "first generation" anti-CD40L mAbs.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 15, 2024 VOL. 390 NO. 7

Inhibition of CD40L with Frexalimab in Multiple Sclerosis

P. Vermersch, C. Granziera, Y. Mao-Draayer, G. Cutter, O. Kalbus, I. Staikov, M. Dufek, S. Saubadu, R. Bejuit, P. Truffinet, B. Dijukic, E. Wallstroem, and G. Giovannoni, for the Frexalimab Phase 2 Trial Group*

ABSTRACT

BACKGROUND

The CD40–CD40L costimulatory pathway regulates adaptive and innate immune responses and has been implicated in the pathogenesis of multiple sclerosis. Frexalimab is a second-generation anti-CD40L monoclonal antibody being evaluated for the treatment of multiple sclerosis.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Vermersch can be contacted at patrick.vermersch@univ-lille.fr or at the Clinique de Neurologie, Hôpital Roger Salengro, Centre Hospitalier Universitaire

[1] Vermersch P, et al. N Engl J Med. 2024 Feb 15;390(7):589-600. doi: 10.1056/NEJMoa2309439. PMID: 38354138.
[2] Dunn, A. Endpoints. December 7, 2023. "Sanofi CEO Paul Hudson pitches 12 blockbusters in a bid to convince investors on boosting R&D spend".https://endpts.com/sanofi-rd-day-ceo-paul-hudson-touts-12-blockbusters-ups-rdspend/

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TNX-1700

Recombinant Trefoil Factor Family Member 2 (rTFF2-HSA) Fusion Protein

Targeting the toxic tumor micro-environment

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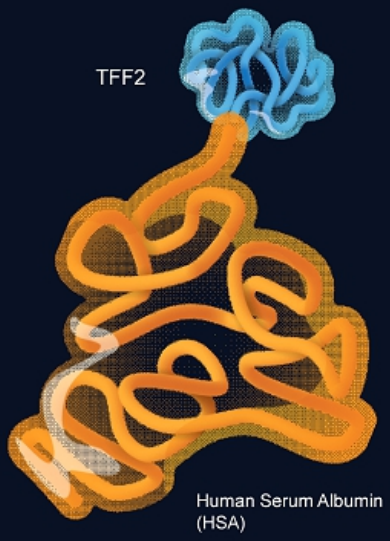
TNX-1700: Fighting Cancer by Targeting the Tumor Micro-Environment

Suppresses myeloid-derived suppressor cells (MDSCs) and activates anti-cancer CD8+ T cells



Key Differentiators

- Different MOA than checkpoint inhibitors
- ***Potential synergy with anti-PD-1 or anti-PD-L1 monoclonal antibodies***

Preclinical Evidence

- mTNX-1700 (mTFF2-MSA fusion protein) and anti-PD-1 monotherapy each was able to evoke anti-tumor immunity in the MC38 model of colorectal cancer[1]
- mTNX-1700 augmented the anti-tumor efficacy of anti-PD-1 therapy in both the MC38 and the CT26.wt models[1]

*TNX-1700 is in the pre-IND stage of development and has not been approved for any indication.
[1]Daugherty, B. et al. March 6, 2023 Keystone Poster. https://bit.ly/48nIRHM

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About Gastric and Colorectal Cancer

Gastric and colorectal cancer are both leading cancers in the US. Colorectal cancer is the 3rd leading cause of cancer-related deaths in both men and women.[1]

>1.3M **People living with colorectal cancer in the US[2]**

>125k **People living with gastric cancer in the US[3]**

Current standard of care:

- PD-1 blockade
  - However, gastric and colorectal cancer are relatively unresponsive

Large unmet need:

- Gastric and colorectal cancer have a relative 5-year survival rate of 35.7% and 65%, respectively
  - Despite advances in the field, patients are still in need of life saving treatment

[1]American Cancer Society, accessed September 2023 - https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html
[2]NIH, accessed September 2023 - https://seer.cancer.gov/statfacts/html/colorect.html
[3]NIH, accessed September 2023 - https://seer.cancer.gov/statfacts/html/stomach.html

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IMMUNOLOGY PORTFOLIO

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Broad-Spectrum Antiviral Discovery Programs

Host-directed antiviral discovery programs

- **CD45 targeted therapeutics**
  - Small molecule therapeutics that reduce endogenous levels of CD45, a protein tyrosine phosphatase
  - Reduction in CD45 protects against many viruses including the Ebola virus
- **Cathepsin inhibitors**
  - Small molecule therapeutics that inhibit ***essential cathepsins*** which are required by viruses such as coronaviruses and filoviruses to infect cells
  - Activity as monotherapy and in combination with other antivirals

Virus-directed antivirals discovery program

- **Viral glycan-targeted engineered biologics**
  - Bind to viral densely branched high-mannose (DBH) glycans
  - ***Neutralize circulating virus*** and stop the entry of the progeny virus into cells
  - Antiviral activity against a broad range of RNA viruses
  - Activity as monotherapy and in combination with other antivirals

R&D Center (RDC): Frederick, MD

- Accelerated development of vaccines and antiviral drugs against infectious diseases
- ~48,000 square feet, BSL-2 with some areas designated BSL-3

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TNX-801

Live Virus Vaccine

Live virus vaccine platform with multitude of potential applications

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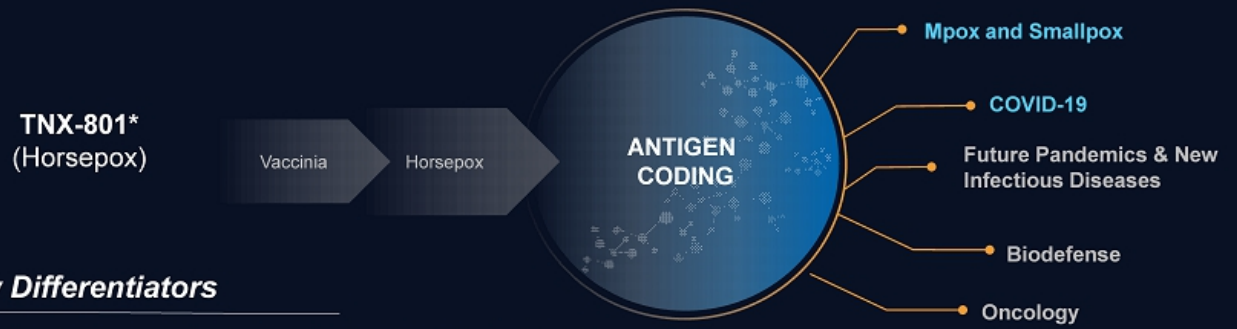
TNX-801: Recombinant Pox Vaccine (RPV) Platform Using Live Virus Technology

Cloned version of horsepox[1] purified from cell culture



Key Differentiators

Live virus vaccines are the most established vaccine technology

- Prevents forward transmission
- Effective in eliciting durable or long-term immunity

Economical to manufacture at scale

- Low dose because replication amplifies dose *in vivo*
- Single administration

Standard refrigeration for shipping and storage

*TNX-801 is in the pre-IND stage of development and has not been approved for any indication.
[1]Noyce et al., 2018. *PLoS One*. 13(1):e0188453.

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Smallpox and Monkeypox

- Smallpox has been eradicated, but fears of malicious reintroduction persist[1-2]
  - Russia and North Korea have capabilities to weaponize smallpox
  - The U.S. population is largely vaccine-naïve (under ~60 years old almost 100% naïve except for immigrants from Russia, China, etc.)
- Monkeypox in Africa was suppressed by vaccination with live virus vaccines to protect against smallpox
  - The cessation of vaccination against smallpox has resulted in outbreaks of monkeypox in Africa
- Monkeypox (Clade 2) spread rapidly around the world in MSM[3] population since May 2022[1-2]
  - >30,000 cases in the U.S. – now endemic in the U.S.
  - >90,000 cases worldwide in countries who did not previously have monkeypox
  - Clade 2 has <1% fatality rate
- Monkeypox (Clade 1) is experiencing an outbreak in Democratic Republic of the Congo and Nigeria[4]
  - Clade 1 has ~11% fatality rate, is more infectious and kills mostly children

[1] U.S. National Academy of Sciences. March 28, 2024. "Consensus Study Report: Future State of Smallpox Medical Countermeasures." https://nap.nationalacademies.org/catalog/27652/future-state-of-smallpox-medical-countermeasures
[2] Bipartisan Commission on Biodefense. (2024). *Box the Pox: Reducing the Risk of Smallpox and Other Orthopoxviruses*. Bipartisan Commission on Biodefense: Washington, DC. https://biodefensecommission.org/reports/box-the-pox-reducing-the-risk-of-smallpox-and-other-orthopoxviruses/
[3] Men who have sex with men
[4] Emanuel, G. *NPR*. March 27, 2024. "Why the mpox outbreak in the Democratic Republic of Congo is worrying disease docs." URL: www.npr.org/sections/goatsandsoda/2024/03/27/1239276957/mpox-outbreak-democratic-republic-of-congo-deadlier-strain

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Monkeypox Outbreak Recent Headlines

- Outbreak in the Congo
  - NPR, April 2, 2024[1]

npr

Goats and Soda

GOATS AND SODA

Major mpox outbreak in the Democratic Republic of Congo is a worry to disease docs

UPDATED APRIL 2, 2024 · 6:54 AM ET

HEARD ON MORNING EDITION

By Gabrielle Emanuel

- U.S. Bipartisan Commission on Biodefense (2024)[2]:
  - "The shift of Mpox in Africa to the more lethal and sexually transmitted Clade I dictates that further clade shifts could create a more serious global health challenge even without nefarious actions by state/non-state actors). This, in turn, would create further potential risk of depletion of the SNS [U.S. Strategic National Stockpile] if the United States deployed vaccine globally. Though 42 USC 247d-6b(a)(2) requires annual threat-based reviews of the contents of the SNS, the statute does not currently require this review to consider the threat of all orthopoxviruses that smallpox vaccines, antivirals, and therapeutics could treat."

[1] Emanuel, G. *NPR*. March 27, 2024. "Why the mpox outbreak in the Democratic Republic of Congo is worrying disease docs." URL: www.npr.org/sections/goatsandsoda/2024/03/27/1239276957/mpox-outbreak-democratic-republic-of-congo-deadlier-strain
[2] Bipartisan Commission on Biodefense. (2024). *Box the Pox: Reducing the Risk of Smallpox and Other Orthopoxviruses*. Bipartisan Commission on Biodefense: Washington, DC. https://biodefensecommission.org/reports/box-the-pox-reducing-the-risk-of-smallpox-and-other-orthopoxviruses/

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Monkeypox Headlines

- Multiple recent statements by U.S. Agencies warning about smallpox and monkeypox[1-6]
- U.S. National Academy of Sciences Consensus Report (March, 2024)[6]
  - *"Additionally, safer, single-dose vaccines and a diverse set of therapeutic options against smallpox would improve the U.S. readiness and response posture for immediate containment and long-term protection in a smallpox emergency.*
  - *"Smallpox vaccines that have improved safety across different population subgroups and are available as a single dose would support faster and more effective response to contain smallpox and other orthopoxvirus outbreaks. The development of novel smallpox vaccines using multi-vaccine platforms (i.e., use common vaccine vectors, manufacturing ingredients, and processes) would improve the capacity for rapid vaccine production in response to a smallpox event and reduce the need for stockpiling in the SNS at current levels.*
  - *"Given the lack of commercially available orthopoxvirus diagnostics, vaccines, and therapeutics, planning for logistics and supply chain management considerations is critical. Efforts could give consideration to developing plans to increase the number of smallpox vaccine and therapeutics manufacturers as well as optimizing current manufacturing capacities should they be needed in the shorter term."*

[1] Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021
[2] National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023
[3] Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021
[4] National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023
[5] BARDA Strategic Plan 2022-2026.
[6] U.S. National Academy of Sciences. March 28, 2024. "Consensus Study Report: Future State of Smallpox Medical Countermeasures." https://nap.nationalacademies.org/catalog/27652/future-state-of-smallpox-medical-countermeasures

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TNX-1800: Designed to Express the SARs-CoV-2 Spike Protein

TNX-1800 (recombinant horsepox virus) is a live virus vaccine based on Tonix's TNX-801 that is designed to express the spike protein of the SARS-CoV-2 virus and to elicit a predominant T cell response

- Immunogenic and well tolerated[1]
- Showed promise in protecting animals from challenge with SARS-CoV-2 delivered directly into the lungs[1]

Status: ***National Institute of Allergy and Infectious Diseases (NIAID) will conduct a Phase 1 clinical trial with TNX-1800***

- First vaccine candidate using Tonix's live virus recombinant pox virus (RPV) platform technology to enter clinical trials
- "Project NextGen" is an initiative by the U.S. Department of Health and Human Services (HHS) to advance a pipeline of new, innovative vaccines and therapeutics for COVID-19. NIAID will be conducting clinical trials to evaluate several early-stage vaccine candidates, including TNX-1800
- Phase 1 study is designed to assess safety and immunogenicity in approximately 60 healthy adult volunteers
- Upon completion of the trial, NIAID and Tonix will assess the results and determine the next steps for the development of TNX-1800

[1]Awasthi, M. et al. *Viruses*. 2023. 15(10):2131.
[2]Awasthi, M. et al. *Vaccines (Basel)*. 2023. 11(11):1682.

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Management Team

Seth Lederman, MD
Co-Founder, CEO & Chairman

TARGENT Rx · Fusilev (levoleucovorin) for injection · vela

Gregory Sullivan, MD
Chief Medical Officer

Bradley Saenger, CPA
Chief Financial Officer

Shire · VERTEX · Steward · pwc

Jessica Morris
Chief Operating Officer

Deutsche Bank · svb Silicon Valley Bank · American Capital

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Milestones: Recently Completed and Upcoming

Tonmya™ Milestones

☑ 4th Quarter 2023	Statistically significant topline results of Phase 3 RESILIENT study for Tonmya™ for the management of fibromyalgia
☑ 2nd Quarter 2024	Type B CMC and clinical pre-NDA meetings with FDA for Tonmya™ for fibromyalgia
❑ 2nd Half 2024	Submit NDA to FDA for Tonmya™ for fibromyalgia

Other Key Program Milestones

❑ 2nd Quarter 2024	Initiate Phase 2 study of TNX-102 SL for acute stress disorder
❑ 2nd Quarter 2024	Initiate Phase 2 study of TNX-1300 for the treatment of cocaine intoxication

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THANK YOU

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Zembrace® Important Safety Information (1 of 2)

Zembrace SymTouch (Zembrace) can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop use and get emergency help if you have any signs of a heart attack:

- Discomfort in the center of your chest that lasts for more than a few minutes or goes away and comes back; severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw; pain or discomfort in your arms, back, neck, jaw or stomach; shortness of breath with or without chest discomfort; breaking out in a cold sweat; nausea or vomiting; feeling lightheaded

Zembrace is not for people with risk factors for heart disease (high blood pressure or cholesterol, smoking, overweight, diabetes, family history of heart disease) unless a heart exam shows no problem.

Do not use Zembrace if you have:

- History of heart problems; narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease); uncontrolled high blood pressure; hemiplegic or basilar migraines. If you are not sure if you have these, ask your provider.
- Had a stroke, transient ischemic attacks (TIAs), or problems with blood circulation; severe liver problems; taken any of the following medicines in the last 24 hours: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, ergotamines, dihydroergotamine; are taking certain antidepressants, known as monoamine oxidase (MAO)-A inhibitors or it has been 2 weeks or less since you stopped taking a MAO-A inhibitor. Ask your provider for a list of these medicines if you are not sure.
- An allergy to sumatriptan or any of the components of Zembrace

Tell your provider about all of your medical conditions and medicines you take, including vitamins and supplements.

Zembrace can cause dizziness, weakness, or drowsiness. If so, do not drive a car, use machinery, or do anything where you need to be alert.

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Zembrace® Important Safety Information (2 of 2)

Zembrace may cause serious side effects including:

- Changes in color or sensation in your fingers and toes; sudden or severe stomach pain, stomach pain after meals, weight loss, nausea or vomiting, constipation or diarrhea, bloody diarrhea, fever; cramping and pain in your legs or hips; feeling of heaviness or tightness in your leg muscles; burning or aching pain in your feet or toes while resting; numbness, tingling, or weakness in your legs; cold feeling or color changes in one or both legs or feet; increased blood pressure including a sudden severe increase even if you have no history of high blood pressure; medication overuse headaches from using migraine medicine for 10 or more days each month. If your headaches get worse, call your provider.
- Serotonin syndrome, a rare but serious problem that can happen in people using Zembrace, especially when used with anti-depressant medicines called SSRIs or SNRIs. Call your provider right away if you have: mental changes such as seeing things that are not there (hallucinations), agitation, or coma; fast heartbeat; changes in blood pressure; high body temperature; tight muscles; or trouble walking.
- Hives (itchy bumps); swelling of your tongue, mouth, or throat
- Seizures even in people who have never had seizures before

The most common side effects of Zembrace include: pain and redness at injection site; tingling or numbness in your fingers or toes; dizziness; warm, hot, burning feeling to your face (flushing); discomfort or stiffness in your neck; feeling weak, drowsy, or tired.

Tell your provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of Zembrace. For more information, ask your provider.

This is the most important information to know about Zembrace but is not comprehensive. For more information, talk to your provider and read the Patient Information and Instructions for Use. You can also visit www.upsher-smith.com or call 1-888-650-3789. For full Prescribing Information, visit: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6e5b104f-2b9e-416e-92fb-ef1bdaea867d

You are encouraged to report adverse effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Zembrace is a prescription medicine used to treat acute migraine headaches with or without aura in adults who have been diagnosed with migraine.

Zembrace is not used to prevent migraines. It is not known if it is safe and effective in children under 18 years of age.

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Tosymra® Important Safety Information (1 of 2)

Tosymra® can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop Tosymra and get emergency medical help if you have any signs of heart attack:

- Discomfort in the center of your chest that lasts for more than a few minutes or goes away and comes back; severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw; pain or discomfort in your arms, back, neck, jaw, or stomach; shortness of breath with or without chest discomfort; breaking out in a cold sweat; nausea or vomiting; feeling lightheaded

Tosymra is not for people with risk factors for heart disease (high blood pressure or cholesterol, smoking, overweight, diabetes, family history of heart disease) unless a heart exam is done and shows no problem.

Do not use Tosymra if you have:

- History of heart problems; narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease); uncontrolled high blood pressure; severe liver problems; hemiplegic or basilar migraines. If you are not sure if you have these, ask your healthcare provider.
- Had a stroke, transient ischemic attacks (TIAs), or problems with blood circulation; taken any of the following medicines in the last 24 hours: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, ergotamines, or dihydroergotamine. Ask your provider if you are not sure if your medicine is listed above
- are taking certain antidepressants, known as monoamine oxidase (MAO)-A inhibitors or it has been 2 weeks or less since you stopped taking a MAO-A inhibitor. Ask your provider for a list of these medicines if you are not sure
- An allergy to sumatriptan or any ingredient in Tosymra

Tell your provider about all of your medical conditions and medicines you take, including vitamins and supplements. Tosymra can cause dizziness, weakness, or drowsiness. If so, do not drive a car, use machinery, or do anything where you need to be alert.

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Tosymra® Important Safety Information (2 of 2)

Tosymra may cause serious side effects including:

- Changes in color or sensation in your fingers and toes; sudden or severe stomach pain, stomach pain after meals, weight loss, nausea or vomiting, constipation or diarrhea, bloody diarrhea, fever; cramping and pain in your legs or hips, feeling of heaviness or tightness in your leg muscles, burning or aching pain in your feet or toes while resting, numbness, tingling, or weakness in your legs, cold feeling or color changes in one or both legs or feet; increased blood pressure including a sudden severe increase even if you have no history of high blood pressure; medication overuse headaches from using migraine medicine for 10 or more days each month. **If your headaches get worse, call your provider**.
- Serotonin syndrome, a rare but serious problem that can happen in people using Tosymra, especially when used with anti-depressant medicines called SSRIs or SNRIs. **Call your provider right away if you have**: mental changes such as seeing things that are not there (hallucinations), agitation, or coma; fast heartbeat; changes in blood pressure; high body temperature; tight muscles; or trouble walking.
- Seizures even in people who have never had seizures before

The most common side effects of Tosymra include: tingling, dizziness, feeling warm or hot, burning feeling, feeling of heaviness, feeling of pressure, flushing, feeling of tightness, numbness, application site (nasal) reactions, abnormal taste, and throat irritation.

Tell your provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of Tosymra. For more information, ask your provider.

This is the most important information to know about Tosymra but is not comprehensive. For more information, talk to your provider and read the Patient Information and Instructions for Use. You can also visit www.upsher-smith.com or call 1-888-650-3789. For full Prescribing Information, visit: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=015a5cf9-f246-48bc-b91e-cd730a53d8aa

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Tosymra is a prescription medicine used to treat acute migraine headaches with or without aura in adults.

Tosymra is not used to treat other types of headaches such as hemiplegic or basilar migraines or cluster headaches.

Tosymra is not used to prevent migraines. It is not known if Tosymra is safe and effective in children under 18 years of age.

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EXHIBIT 99.02

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.

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Indications Most Recently Pursued

Fibromyalgia

Status: Two statistically significant Phase 3 studies completed
- First pivotal Phase 3 study (RELIEF) completed
- Second Phase 3 study (RALLY) missed primary endpoint
- Confirmatory pivotal Phase 3 study (RESILIENT) completed

Next Steps: Type B CMC and clinical pre-NDA meetings with FDA complete; awaiting formal meeting minutes

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 2Q 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®)

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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

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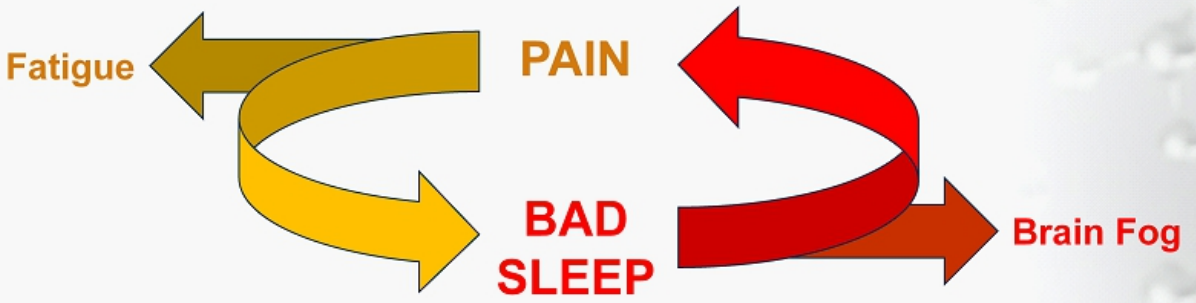
Poor Sleep and Pain have Bi-directional Reinforcing Effects[1]

- **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: Unrefreshing Sleep and Cyclobenzaprine Treatment

- **Non-restorative sleep[1,2]**
  - Harvey Moldofsky – recognition of unrefreshing/non-restorative sleep:
    - Symptom
    - Potential causative or potentiating factor
- **Cyclobenzaprine[3,9]**
  - Potentially the earliest drug studied in fibromyalgia as an oral swallowed agent
  - Studies showed equivocal effects and tolerability issues at "muscle spasm" doses
- **Bedtime, *low-dose* cyclobenzaprine targeting non-restorative sleep[10-11]**
  - Recognition of unrefreshing sleep as a target of therapy
  - Primitive oral, swallowed formulation – "flat" pharmacokinetics
- **Bedtime, *sublingual transmucosal* cyclobenzaprine targeting non-restorative sleep[12]**
  - Dynamic pharmacokinetic profile, rapid absorption, decrease in major metabolite
  - Two studies (Phase 2 and Phase 3) at 2.8 mg; three Phase 3 studies at 5.6 mg.

[1]Moldofsky H et al. *Psychosom Med*. 1975. 37:341-51.
[2]Moldofsky H and Scarisbrick P. *Psychosom Med*. 1976. 38:35-44.
[3]Bennett RM, et al. *Arthritis Rheum* 1988. 31:1535–42.
[4]Quimby LG, et al. *J Rheumatol Suppl*. 1989 Nov;19:140–3.
[5]Reynolds WJ, et al. *J Rheumatol*. 1991.18:452–4.
[6]Santandrea S, et al. *J Int Med Res*. 1993.21:74–80.
[7]Cantini F, et al. *Minerva Med*. 1994. 85:97–100.
[8]Carette S, et al. *Arthritis Rheum*. 1994. 37:32–40.
[9]Tofferi JK, et al. *Arthritis Rheum*. 2004. 51:9–13.1
[10]Iglehart IW. 2003; US Patent 6,541,523.
[11]Moldofsky et al. *J Rheumatol*. 2011. 38:2653-2663
[12]Lederman S et al. *Arthritis Care Res*. 2023. 75:2359-2368.

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Fibromyalgia Program Status

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

Fibromyalgia

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

- **First pivotal Phase 3 study (*RELIEF*) reported – December 2020[1]**
- **Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021**
- **Confirmatory pivotal Phase 3 study (*RESILIENT*) reported – December 2023**

Next Steps:

- **Type B CMC and clinical pre-NDA meetings with FDA completed; awaiting formal meeting minutes**
- **NDA filing expected 2H'24**
- **FDA decision on NDA approval expected 2H'25**

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*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.

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Phase 3 RESILIENT Study Population

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

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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 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 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 Study Efficacy Findings

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RESILIENT Summary of Primary and Key Secondary Endpoints

Endpoint	P-value	Effect Size (ES)
Primary Endpoint		
Daily Diary Pain ratings	***p* = 0.00005**	ES = 0.38
Key Secondary Endpoints		
Patient Global Impression of Change (PGIC), responders	*p* = 0.00013	--
Fibromyalgia Impact Questionnaire – Symptoms domain	*p* = 0.000002	ES = 0.44
Fibromyalgia Impact Questionnaire – Function domain	*p* = 0.001	ES = 0.30
PROMIS Sleep Disturbance instrument	*p* = 0.0000001	ES = 0.50
PROMIS Fatigue instrument	*p* = 0.00009	ES = 0.37
Diary Sleep Quality ratings	*p* = 0.0007	ES = 0.32

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

RESILIENT Study

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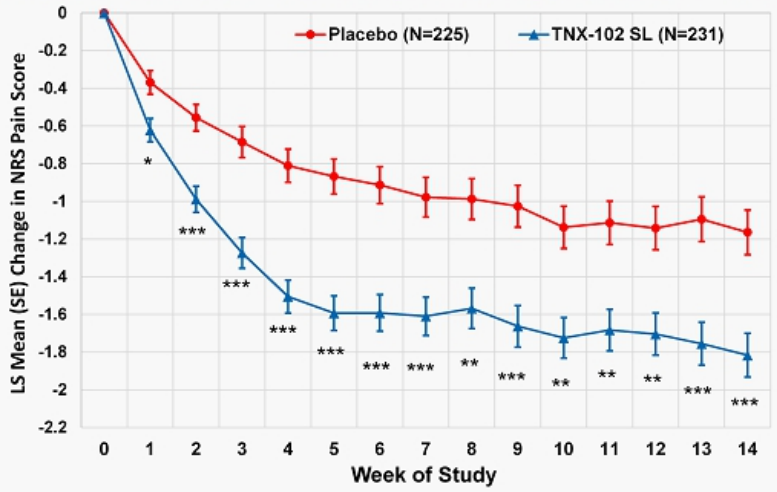
RESILIENT Primary Outcome Measure
Reduction in Widespread Pain

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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RESILIENT Continuous Pain Responder Graph

RESILIENT Study

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30% Responders# (45.9% vs 27.1%) p < 0.001

50% Responders# (22.5% vs. 13.3%) p = 0.011

*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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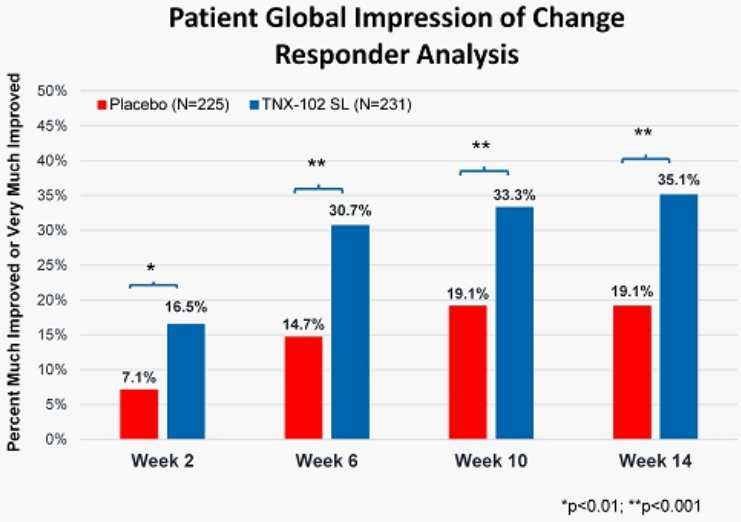

*p<0.01; **p<0.001

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

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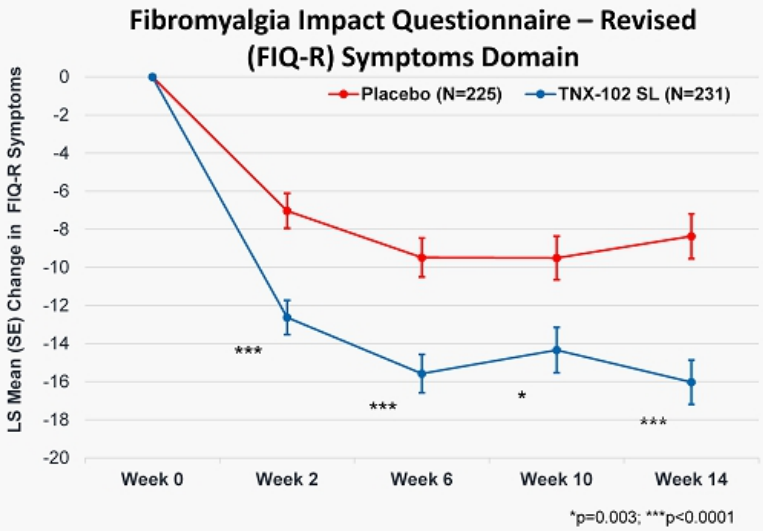

Week 14 LS mean (SE) change from baseline for TNX-102 SL -16.0 (1.17) and for placebo -8.4 (1.17); LSMD from placebo -7.7 (1.62); **p=0.000002#**

#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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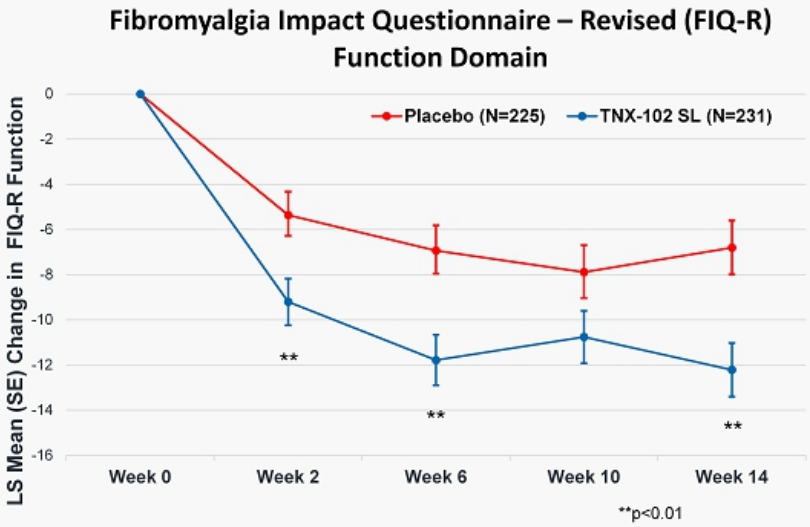

Week 14 LS mean (SE) change from baseline for TNX-102 SL -12.2 (1.19) and for placebo -6.8 (1.21); LSMD from placebo -5.4 (1.66); **p=0.001#**

#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

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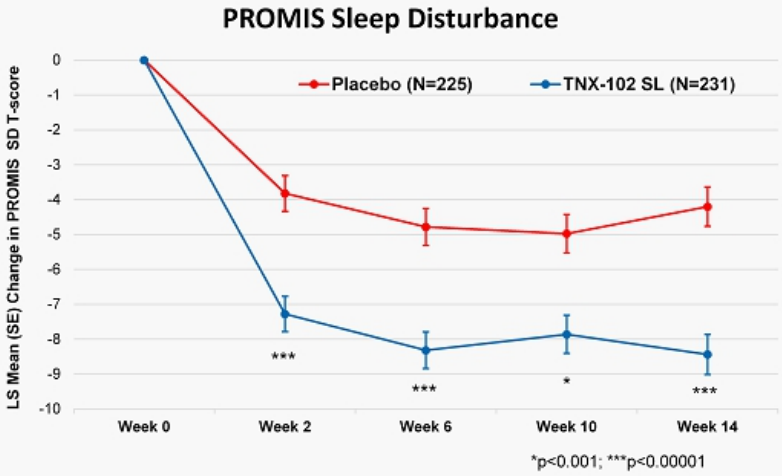

Week 14 LS mean (SE) change from baseline for TNX-102 SL -8.4 (0.57) and for placebo -4.2 (0.56); LSMD from placebo -4.2 (0.79); **p=0.0000001[#]**

[#]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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RESILIENT PROMIS Fatigue Inventory
Key Secondary Outcome Measure

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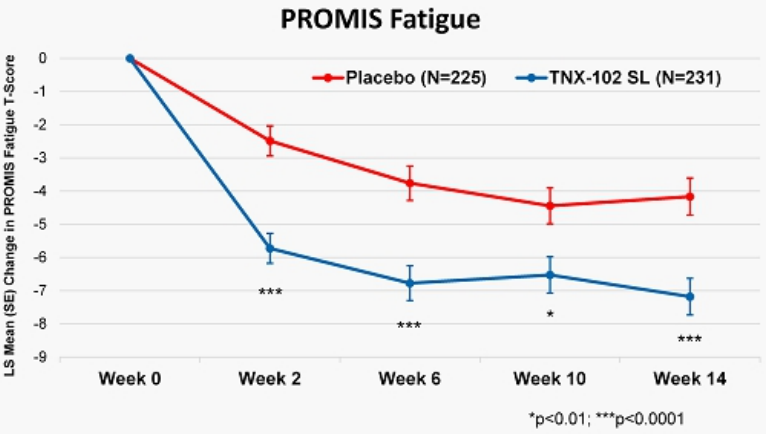

Week 14 LS mean (SE) change from baseline for TNX-102 SL -7.2 (0.55) and for placebo -4.2 (0.56); LSMD from placebo -3.0 (0.77); **p=0.00009[#]**

[#]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

RESILIENT Study

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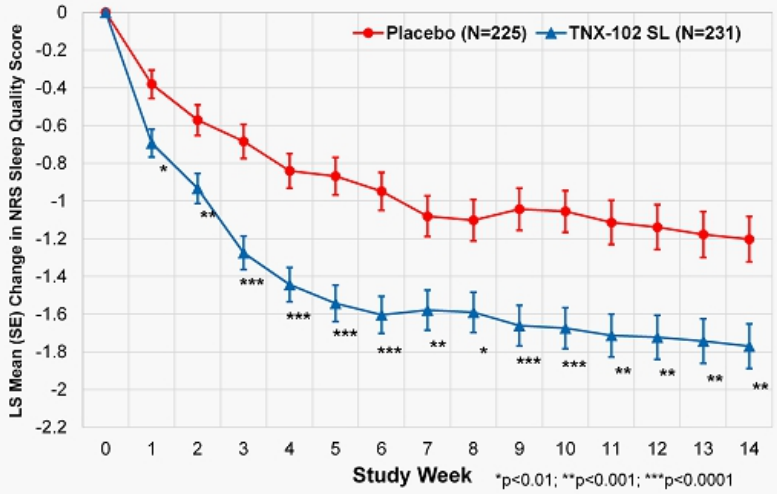
Weekly Average of Daily Diary NRS Ratings of Prior Night Sleep Quality



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 Summary of Primary Endpoint and Key Secondary Efficacy Endpoints

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RESILIENT Study

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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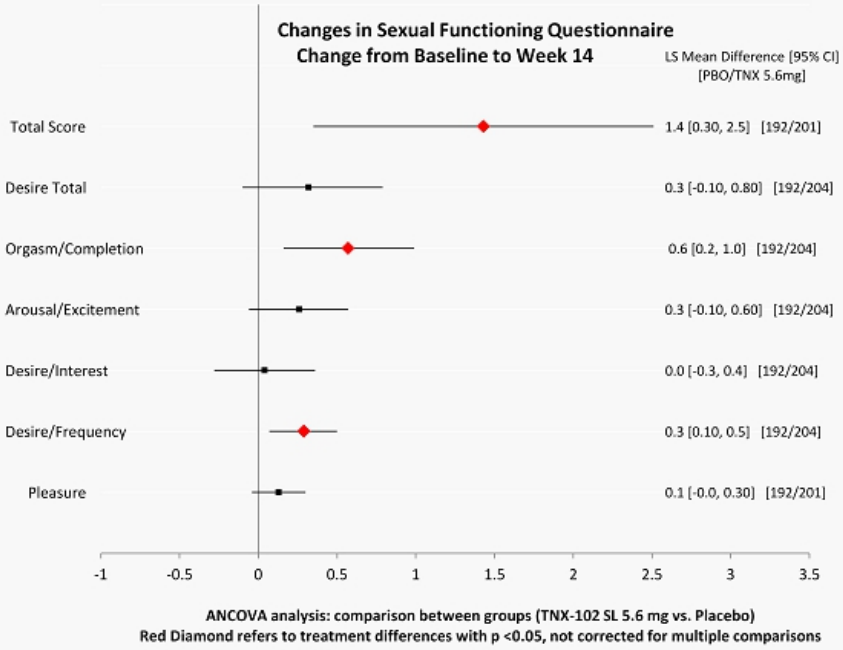
RESILIENT: CSFQ-14 Females

Pre-specified exploratory endpoint

RESILIENT Study



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

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RESILIENT: FIQR Individual Items[1]

Affective Symptoms, Sensory Sensitivity, Cognition, and Energy

Pre-specified exploratory endpoint

Selected Fibromyalgia Impact Questionnaire-Revised Symptoms Domain Item Scores

Pre-specified exploratory endpoints

FIQ-R Item Please rate your level of... (past 7 days)	Week 14 LS Mean (SE) Difference from Placebo#	95% Confidence Interval#	P-value^	Effect Size
Depression	-0.8 (0.21)	-1.2, -0.6	<0.001	0.35
Anxiety	-0.8 (0.24)	-1.2, -0.3	0.001	0.30
Sensitivity to…*	-0.6 (0.24)	-1.0, -0.1	0.020	0.22
Memory problems	-0.8 (0.23)	-1.2, -0.3	0.001	0.31
Energy	-0.8 (0.23)	-1.2, -0.3	<0.001	0.31

*…loud noises, bright lights, odors, and cold

[1]FIQR=Fibromyalgia Impact Questionnaire- Revised
#Mixed model repeated measures analysis (no imputation); fixed categorical effects of treatment, site, study week, and treatment x study week interaction; fixed covariates of baseline value and baseline value x study week interaction
^Uncorrected for multiple comparisons

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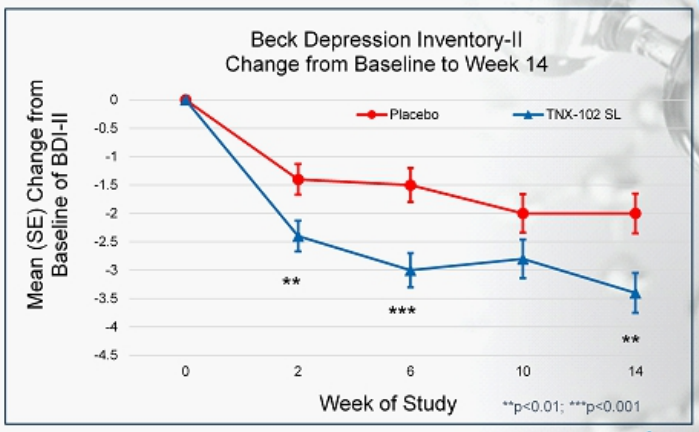
RESILIENT: Beck Depression Inventory-II
Pre-specified Exploratory Endpoint

	Placebo Mean (SD)	Placebo LS MCFB (SE)	TNX Mean (SD)	TNX LS MCFB (SE)	Difference in LS Means (SE)	95% CI for Difference	P-value	Effect Size
Baseline	10.0 (6.72)		9.6 (6.32)					
Week 14		-2.0 (0.35)		-3.4 (0.35)	-1.4 (0.49)	-2.3, -0.4	0.005#	0.27

- Greater reduction in total BDI-II score in TNX-102 SL group over placebo at Week 14 with p=0.005#, effect size of 0.27
  - Also separated, with p<0.01#, at Week 2 when on TNX-102 SL 2.8 mg first two weeks
  - And separated, with p<0.001#, at Week 6



#Uncorrected for multiple comparisons
SE=standard error; SD=standard deviation

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RESILIENT: Summary of Baseline Depression BDI-II and FIQR Item

- While the rate of current MDE diagnosis was ~2% of the ITT, ~25% ITT had experienced a lifetime MDE, and ~47% reported past 6 month depression on FM Dx*
- Also, about 25% of the ITT enrolled on concomitant antidepressant or buspirone
- By end of treatment (Week 14), there was a greater reduction in depression severity by total BDI-II score in TNX-102 SL group compared with placebo (p=0.005)
  - And greater reduction in FIQR items for depression (p<0.001), anxiety (p=0.001), and sensory sensitivity (p=0.020) in the TNX-102 SL group compared with placebo
  - The FIQR memory item, a measure of cognitive impairment in FM, was more improved in the TNX-102 SL group than placebo (p=0.001)
  - The FIQR energy item, another indicator of less fatigue in FM, was also more improved in the TNX-102 SL group than placebo (p<0.001)
- Cohen's *d* effect sizes were between 0.27 and 0.35 for all Week 14 outcomes above except sensory sensitivity

Abbreviations: BDI-II, Beck Depression Inventory-II; Dx, diagnosis; FIQR, Fibromyalgia Impact Questionnaire-Revised; FM, fibromyalgia; ITT, Intention-to-Treat

*Wolfe F, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016; 46(3):319-329.

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RESILIENT Summary of Efficacy

RESILIENT Study

CNS PORTFOLIO

Primary Pain, and Key Secondaries

- Pain (primary endpoint, daily pain diary): *p*-value = 0.00005
- Fatigue (PROMIS fatigue): *p*-value = 0.00009
- Sleep (PROMIS sleep disturbance): *p*-value = 0.0000001
- Global (PGIC) *p*-value = 0.00013
- Symptoms (FIQR Symptoms *p*-value = 0.000002
- Function (FIQR Function) *p*-value = 0.001

Exploratory endpoints

- Female Sexual Function (CSFQ) *p*-value = 0.010
- Depression (BDI-II) *p*-value < 0.001
- Depression (FIQR): *p*-value < 0.001
- Anxiety (FIQR): *p*-value = 0.001
- Sensitivity to environment* (FIQR): *p*-value = 0.020
- Memory (FIQR) : *p*-value = 0.001
- Energy (FIQR): *p*-value < 0.001

*loud noises, bright lights, odors, and cold

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RESILIENT Summary of Efficacy

RESILIENT Study

CNS PORTFOLIO

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 Study Safety Findings

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RESILIENT Subject Disposition

RESILIENT Study

CNS PORTFOLIO

	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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RESILIENT Prior Medication Use

RESILIENT Study

CNS PORTFOLIO

Summary of Lifetime and Prior Fibromyalgia Pharmacotherapy*

	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

RESILIENT Study

CNS PORTFOLIO

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

	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 Safety Summary

RESILIENT Study

CNS PORTFOLIO

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

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RESILIENT Safety

RESILIENT Study

CNS PORTFOLIO

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
Systemic Adverse Events			
COVID-19	10 (4.3%)	7 (3.1%)	17 (3.7%)
Somnolence	7 (3.0%)	3 (1.3%)	10 (2.2%)
Headache	7 (3.0%)	4 (1.8%)	11 (2.4%)
Oral Cavity Adverse Events			
Hypoaesthesia oral	55 (23.8%)	1 (0.4%)	56 (12.3%)
Product taste abnormal	27 (11.7%)	2 (0.9%)	29 (6.3%)
Paraesthesia oral	16 (6.9%)	2 (0.9%)	18 (3.9%)
Tongue discomfort	16 (6.9%)	0 (0.0%)	16 (3.5%)

- Among patients randomized to TNX-102 SL and to placebo, 81.0% and 79.6%, respectively, completed the study
- No new safety signals observed; aside from COVID-19, no systemic AEs greater than 3% in TNX-102 SL group
- 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 cavity AEs were higher in TNX-102 SL than placebo, 42.9% and 10.2%, respectively
  - Most common oral AEs were oral numbness, product taste abnormal, oral tingling, and tongue discomfort (numbness and tingling believed due to weak local anesthetic properties of CBP due to sodium channel inhibition)
  - Nearly all these common oral AEs were temporally related to dosing and generally lasted <60 minutes

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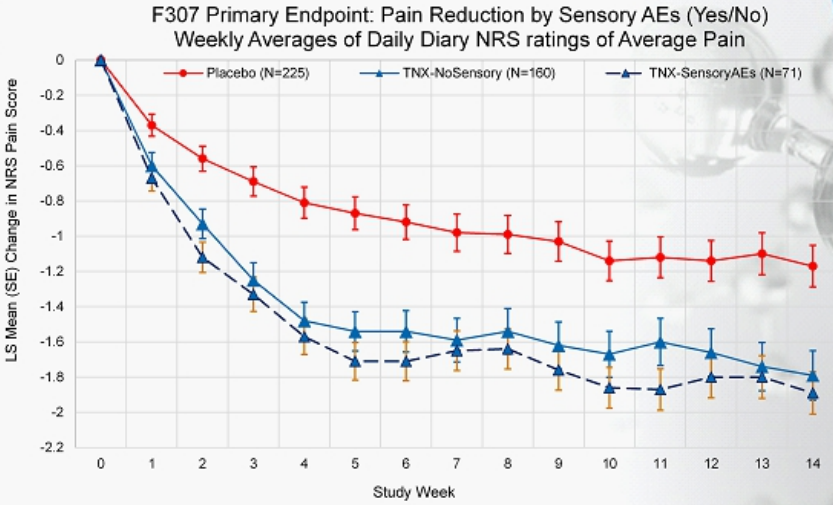
RESILIENT Analysis by Sensory Adverse Events (AEs)

TNX-102 SL group divided for presence/absence of 3 sensory AEs

- AEs of oral numbness, oral tingling, and bitter aftertaste named 'Sensory AEs'*
- Graph shows negligible advantage for presence of sensory AEs
- At Week 14:
  - TNX-NoSensory v Placebo
    - Diff in LS Mean (SE): -0.62 (0.179)
    - p<0.001
  - TNX-SensoryAEs v Placebo
    - Diff in LS Mean (SE): -0.72 (0.239)
    - p<0.003
  - TNX-NoSensory v TNX-SensoryAEs
    - Diff in LS Mean (SE): -0.10 (0.254)
    - p<0.701
  - Both TNX-102 SL subgroups show significantly greater pain reduction than placebo
  - The two TNX-102 SL subgroups do not significantly differ from each other



*Preferred Terms: Hypoaesthesia oral, Paraesthesia oral, Product taste abnormal

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RESILIENT Safety, Continued

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

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

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.7 (12.38) mmHg

Placebo = 0.5 (10.42) mmHg

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

Week 14 mean (SD) change from baseline:

TNX-102 SL = 1.1 (8.60) mmHg

Placebo = 0.2 (8.22) mmHg

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

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.02 (2.940) kg

Placebo = 0.20 (2.932) kg

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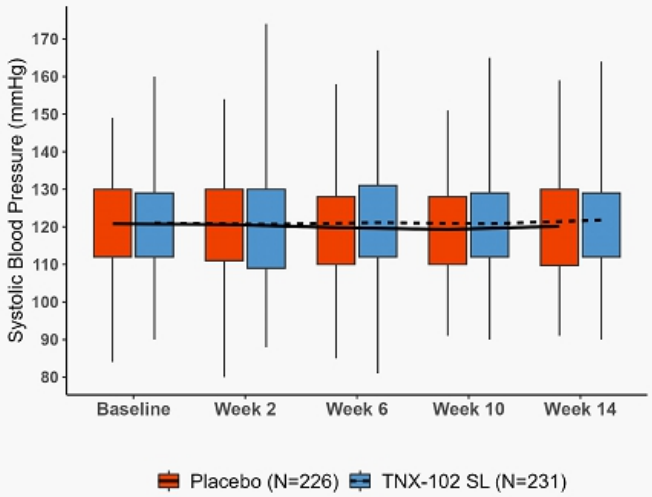
RESILIENT Systolic blood pressure
Safety Measure



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.

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

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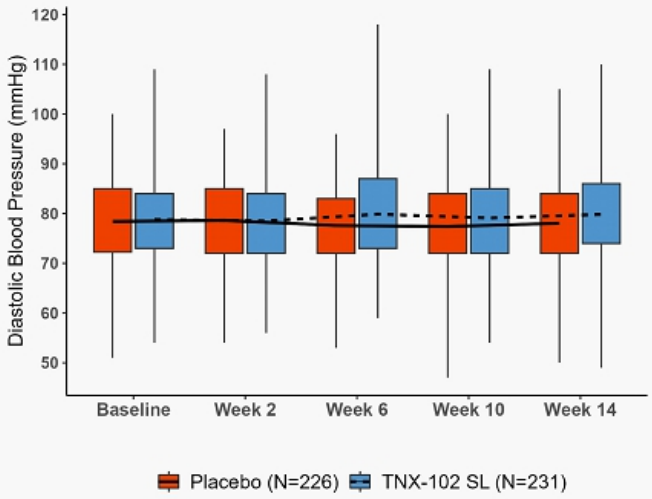
RESILIENT Diastolic blood pressure
Safety Measure



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.

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

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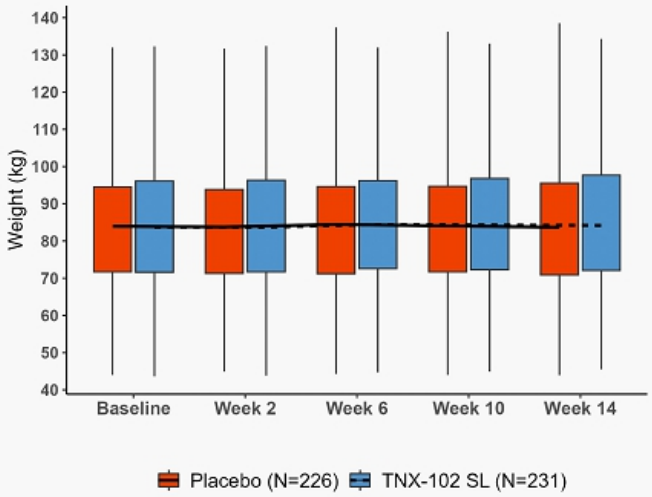
RESILIENT Weight
Safety Measure

RESILIENT Study

CNS PORTFOLIO



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.

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Fibromyalgia Market Characteristics

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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

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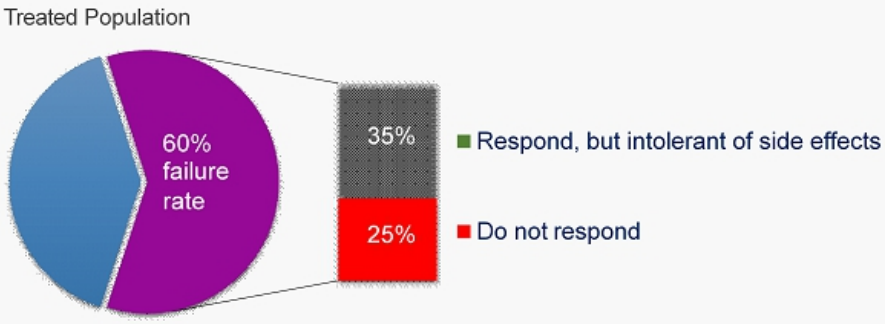
Fewer than Half of Those Treated for Fibromyalgia Receive Sustained Benefit from the Three FDA-Approved Drugs[1]

- 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)

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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)

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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.

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Tonmya™ Showed Broad-Spectrum Activity and was Well Tolerated

		Lyrica®	Cymbalta® Savella®	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

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~50% of U.S. Fibromyalgia Patients are on Medicare: Prescription Coverage in Medicare Stands to Benefit from Changes in IRA

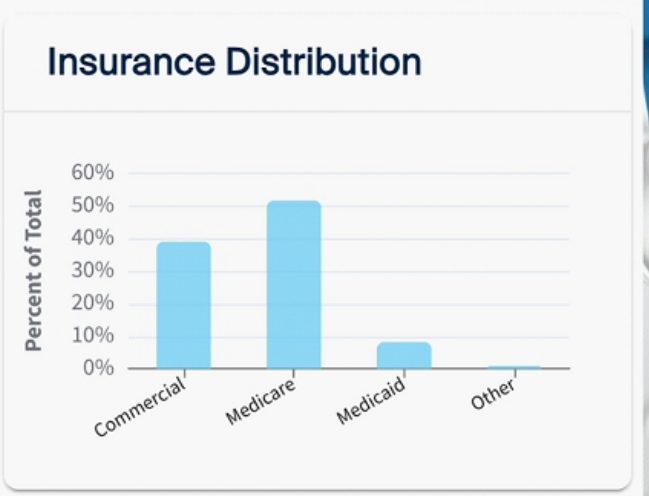
Approximately 50% of fibromyalgia patients are on Medicare

- EVERSANA analysis of claims database consisting of 2.2M patients, for which 1.2M claims were submitted throughout March 2002-March 2023[1]

Beneficial Changes in 2025 to Medicare Part D through Inflation Reduction Act (IRA)[2]

- Medicare prescription payment plan to offer enrollees the option to pay out-of-pocket prescription drug costs in the form of capped monthly installment payments instead of all at once at the pharmacy
- Annual out-of-pocket costs will be capped at $2,000 in year 2025
- Will replace the existing Coverage Gap Discount Program, which sunsets as of January 1, 2025

Fibromyalgia Patients by Coverage[1]



[1]EVERSANA analysis of claims database, May 2024; commissioned by Tonix
[2]Source: Final CY 2025 Part D Redesign Program Instructions Fact Sheet | CMS

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Prescribers Interviewed are Broadly Dissatisfied with Available Fibromyalgia Medications: Results of Primary Research[1]

Perspectives on FM Therapies from Prescribers Interviewed		
Drug	**Positives**	**Negatives**
Duloxetine *(Cymbalta, generic)*	• Relatively high efficacy (compared to alternatives) • Can be titrated slowly from 20mg to 120mg	• Tolerability issues: worsening depression, insomnia • Seldom used as a monotherapy; often requires adjunct
Pregabalin *(Lyrica, generic)*	• Relatively high efficacy (compared to alternatives) • Can often be safely combined with other medications	• Suboptimal for long-term use (e.g., weight gain) • Schedule V status makes some HCPs more cautious to Rx
Savella *(milnacipran)*	• Offers another option if patient fails Cymbalta or Lyrica	• Subpar efficacy does not counterbalance tolerability issues • High cost and access constraints (~$50/month)
Cyclobenzaprine *(Flexeril, generic; oral formulation, off-label)*	• Active for initiating and sustaining sleep; can be titrated up • Active for pain driven by stiffness and muscle spasms	• Mixed perspectives on pain benefit independent of sleep • Suboptimal long-term results as efficacy wanes

85% of patients (avg) fail first line therapy

79% of FM patients (avg) are on multiple therapies

[1] EVERSANA primary physician research, May 2024; commissioned by Tonix

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Opportunity for a New, Unique Fibromyalgia Treatment Option: Results of Primary Research from EVERSANA[1,2]

FM Landscape	• Prescribers indicate a **very high unmet need** in FM (ranked ≥4.0 on a 5-point scale) • Prescribers report there is **no standard of care in FM**, employ an **individualized approach** based on symptomology • No new treatments approved since 2009 • Prescribers report minimal promotional activities by any pharmaceutical company • Highly concentrated prescriber base with 50% of patients treated by ~16k physicians
Physician Primary Market Research	• **Physicians reacted positively to Tonmya's efficacy and safety profile (based on Phase 3 Study results)** • Median interest = 4.0 on a 5-point scale • Driving attributes included **strong efficacy, safety and tolerability** • Unique & differentiating efficacy features included improvements in **sleep and fatigue**
Anticipated Use	• **Physicians indicated intended use in 40% of their FM patients** • Majority of respondents indicated Tonmya would be their first choice, if accessible • Physicians surveyed indicated they are well-equipped to deal with access restrictions including prior authorizations and step-edits

[1] EVERSANA primary physician research, May 2024; commissioned by Tonix
[2] EVERSANA analysis of claims database, May 2024; commissioned by Tonix

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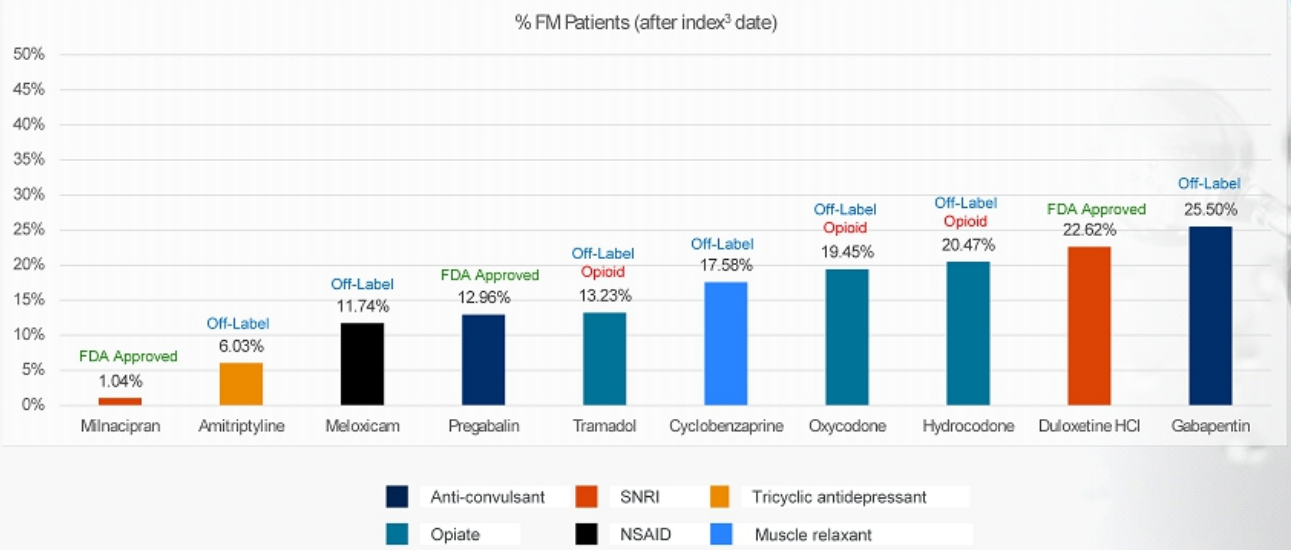
Many Fibromyalgia Patients are Prescribed Off-Label Drugs; ~53% FM Patients Prescribed Opioids Off-Label[1,2]



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

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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

9

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

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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	$3.5 B	Auvelity®	Depression	8/2022	
Biohaven	BHVN	$3.0 B	Nurtec®	Migraine	2/2020	Sold to PFE for $12 B in Oct 2022
IntraCellular	ITCI	$7.2 B	Caplyta®	Schizophrenia	12/2019	
Supernus	SUPN	$1.4 B	Oxtella-XR®	Seizures	1/2019	
Neurocrine	NBIX	$13.6 B	Ingrezza®	Tardive Dyskinesia	4/2017	
Acadia	ACAD	$2.5 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]Accessed June 7, 2024

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About Cyclobenzaprine and Tonmya™

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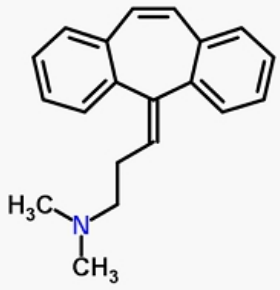
Cyclobenzaprine Long-Term Utilization



- **Flexeril® approved in 1977 by Merck for the treatment of muscle spasm**
  - 10 mg T.I.D. for acute use (2-3 weeks)
  - 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*."[1]
- **6 published studies in fibromyalgia**[2-8]
  - 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**
  - Widely used in the U.S., ~20 million prescriptions and ~ 1 billion tablets dispensed *per year*[9]
  - Chronic cyclobenzaprine use is common *(*~12% of users)[9]
- **Post-marketing surveillance program**[1]
  - 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

[1]1999 Merck OTC AdCom Briefing Package
[2]Bennett RM, et al. *Arthritis Rheum* 1988. 31:1535–42.
[3]Quimby LG, et al. *J Rheumatol Suppl,* 1989 Nov;19:140–3.
[4]Reynolds WJ, et al. *J Rheumatol.* 1991.18:452–4.
[5]Santandrea S, et al. *J Int Med Res.* 1993.21:74–80.
[6]Cantini F, et al. *Minerva Med.* 1994. 85:97–100.
[7]Carette S, et al. *Arthritis Rheum.* 1994. 37:32–40.
[8]Tofferi JK, et al. *Arthritis Rheum.* 2004. 51:9–13.*1*
[9]IMS report 2011 of cyclobenzaprine use in 2009 – Data on File

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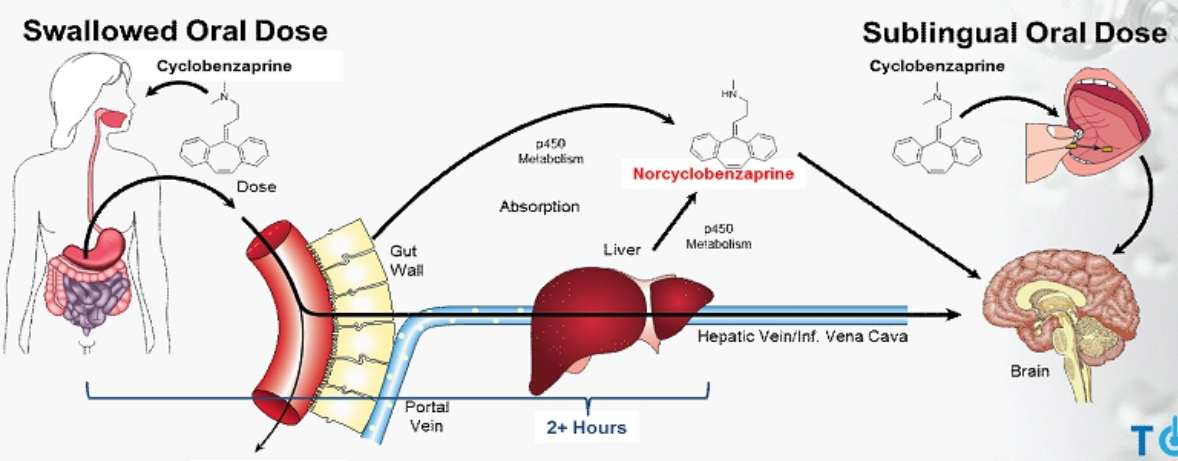
TNX-102 SL: Sublingual Administration and Transmucosal Delivery

- 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)



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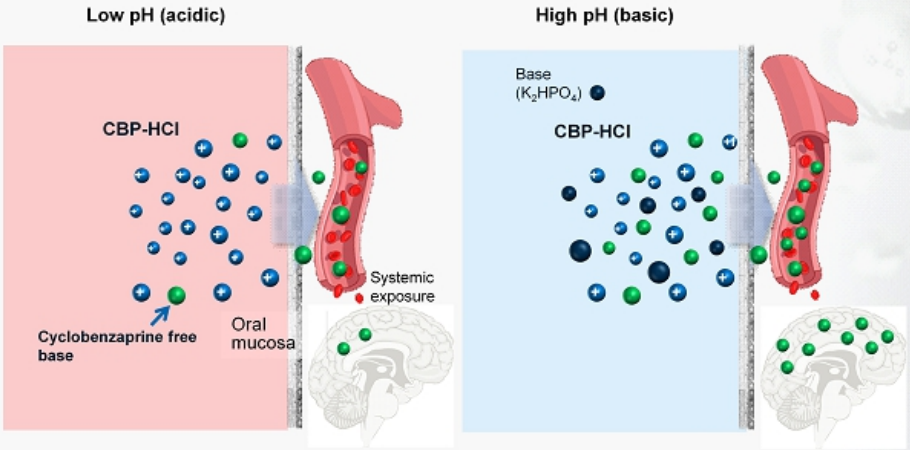
Formulation with Base Increases Systemic Absorption of Sublingual Cyclobenzaprine[1]

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

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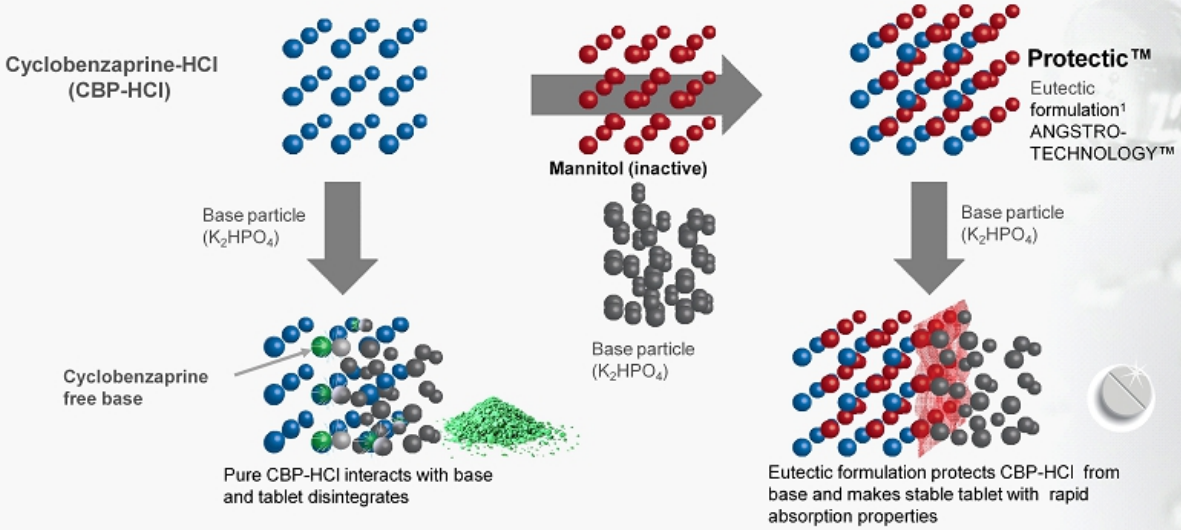
Tonmya™ (TNX-102 SL): Proprietary Eutectic Formulation

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



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

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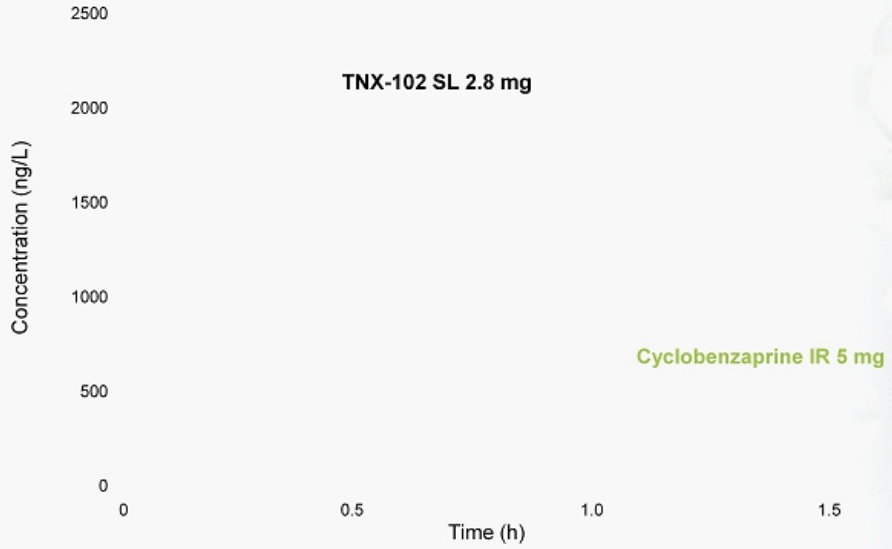
Tonmya™ (TNX-102 SL): Cyclobenzaprine Detected in Plasma Within Minutes Following Sublingual Administration

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



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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

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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)

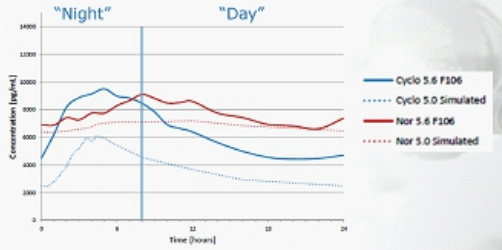
CBP undergoes extensive first-pass hepatic metabolism when orally ingested

- Active major metabolite, norCBP

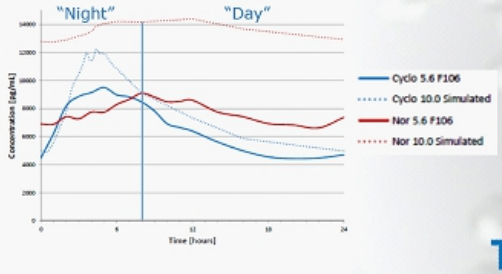
PK = pharmacokinetics
IR = immediate release
CBP = Cyclo = cyclobenzaprine
Nor = norCBP = norcyclobenzaprine

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



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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).

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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

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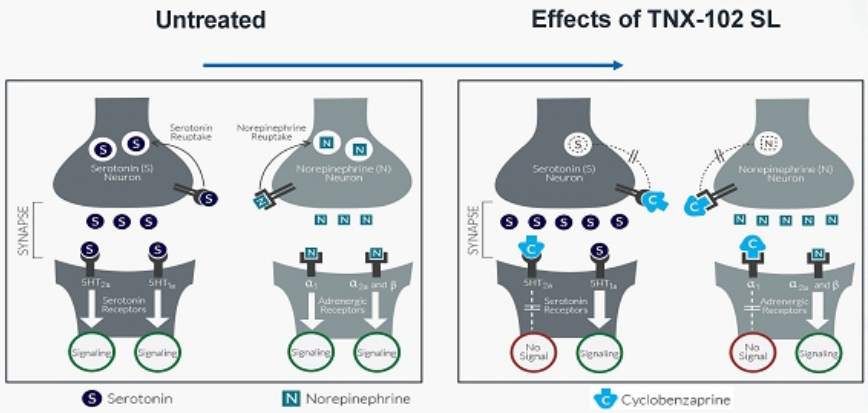
Cyclobenzaprine Effects on Nerve Cell Signaling

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

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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

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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

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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.

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

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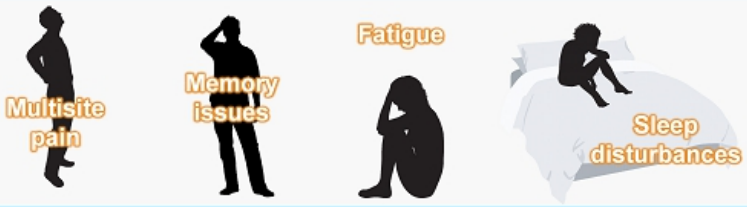
About Fibromyalgia-Type Long COVID

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

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

PREVAIL Study

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)*

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

Placebo once-daily at bedtime

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)"

14 weeks

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

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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.

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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

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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

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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

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THANK YOU

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APPENDIX

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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.

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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 statistically significant 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

	RALLY (F306)			
	MMRM+MI*		MMRM**	
Endpoints	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
	RELIEF (F304)			
	MMRM+MI*		MMRM**	
Endpoints	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

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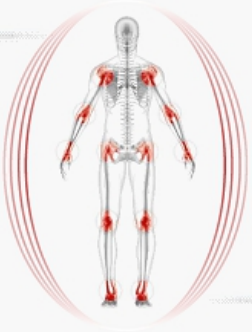
Chronic Overlapping Pain Conditions (COPC) Believed to Result from Shared Brain Processes

- 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.
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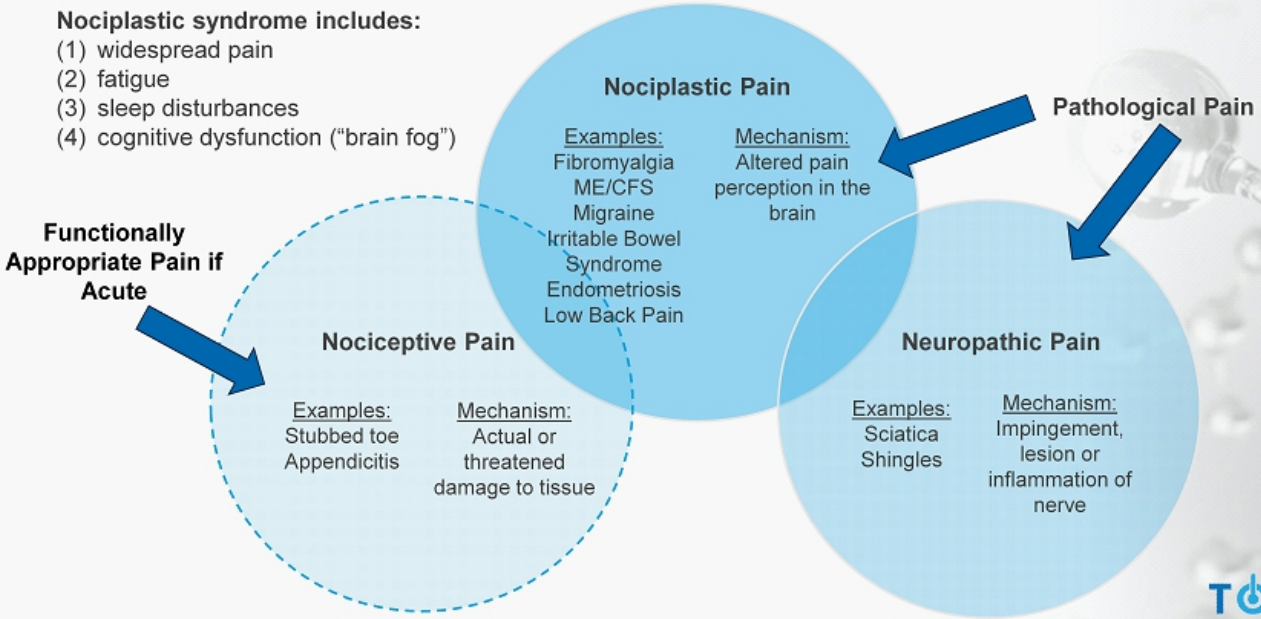
The Third Type of Pain: Nociplastic Pain[1]

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.

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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

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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)

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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

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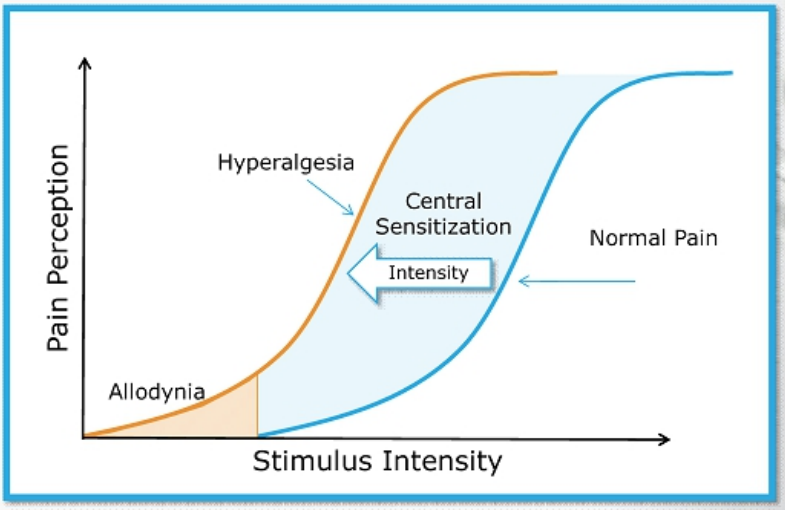
Central Sensitization (CS)
A Feature of Many Nociplastic Pain Syndromes

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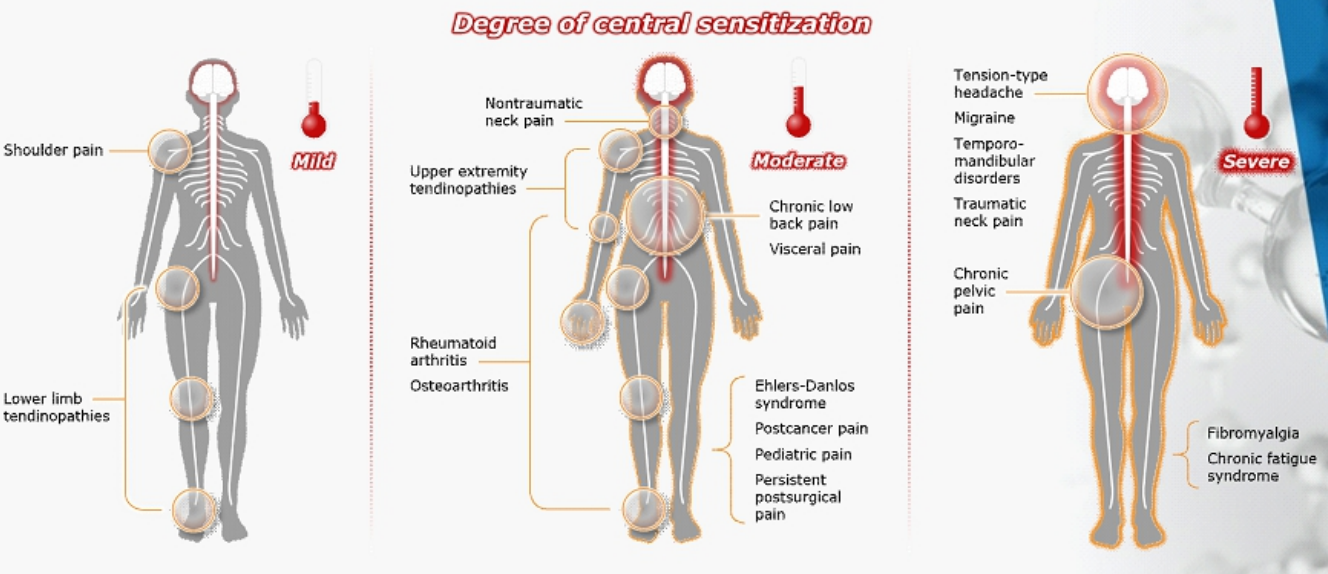
Central Sensitization (CS)
Can Occur in a Range of Diseases and Conditions



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

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