TONIX PHARMACEUTICALS

TNX-102 SL

Lead Indication: Fibromyalgia
Additional Indication: Acute Stress Disorder

NASDAQ: TNXP

June 2025

PO6084 March 2025 (Doc 1601)

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, 2024, as filed with the Securities and Exchange Commission (the “SEC”) on March 18, 2025, 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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Key Clinical Programs

Molecule*	Indication	Phase 1	Phase 2	Phase 3	NDA Submission
TNX-102 SL Cyclobenzaprine HCl Sublingual Tablets	**Fibromyalgia** *Granted FDA Fast Track Designation*	*PDUFA** goal date of August 15, 2025*			
	Acute Stress Disorder	*Phase 2 Study*** Start Expected 1H'25*			
TNX-1300 Cocaine Esterase *NIDA Funded*	**Cocaine Intoxication** *Granted FDA Breakthrough Therapy Designation*	*Phase 2 Study Ongoing*			
TNX-1500 Anti-CD40L mAb	**Organ Transplant Rejection/ Autoimmune Conditions**	*Phase 1 Study Completed*	*Topline Reported 1st Quarter 2025*		

**All of Tonix's product candidates are investigational new drugs or biologics; their safety and efficacy have not been established, and none has been approved for any indication.*
***PDUFA=Prescription Drug User Fee Act*
****Investigator-initiated study*

TNX-102 SL*

(Cyclobenzaprine HCl Sublingual Tablets) 5.6 mg

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

- Non-opioid analgesic – Tertiary Amine Tricyclic (TAT)
- Rapid drug exposure following once-nightly sublingual administration
- Reduction in persistent active metabolite norCBP with chronic dosing
- Durable (14 week) reduction in fibromyalgia pain in two pivotal studies
- Generally well tolerated
- PDUFA goal date August 15, 2025

*5.6 mg once-daily at bedtime, TNX-102 SL is an investigational new drug, its efficacy and safety have not been established and it has not been approved for any indication
norCBP = norCyclobenzaprine

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TNX-102 SL: Sublingual Formulation is Designed for Long-Term Daily Administration at Bedtime and Transmucosal Absorption

- **TNX-102 SL: Proprietary sublingual formulation of cyclobenzaprine (CBP) with transmucosal absorption**
  - Innovation by design with patent-protected eutectic formulation
  - Rapid systemic exposure of CBP – Tertiary Amine Tricyclic (TAT)
  - Increases CBP bioavailability during sleep
  - Avoids first-pass metabolism
  - Lowers exposure to long-lived active major metabolite, norCyclobenzaprine (norCBP)

- **norCBP is a persistent active metabolite generated in the liver by de-methylation**
  - Reduced levels after TNX-102 SL administration relative oral CBP
  - Long half-life (~72 hours) – Secondary Amine Tricyclic (SAT)
  - Less selective for target receptors (5-HT2A, α1-adrenergic, histamine H1)
  - More selective for norepinephrine transporter

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TNX-102 SL (5.6 mg) Fibromyalgia Pivotal Clinical Trial Results

- **Activity**
  - First pivotal Phase 3 study (*RELIEF*) reported – December 2020[1]
    - Statistically significant reduction in daily pain compared to placebo (p = 0.010)
  - Second Phase 3 study (*RALLY*) missed primary endpoint – July 2021
  - Confirmatory pivotal Phase 3 study (*RESILIENT*) reported – December 2023
    - Statistically significant reduction in daily pain compared to placebo (p = 0.00005)

- **Tolerability in two pivotal trials**
  - Generally well tolerated with an adverse event profile comparable to prior studies and with no new safety signals observed
  - The most common treatment-emergent adverse event was tongue or mouth numbness at the administration site, which was temporally related to dosing, self-limited, never rated as severe, and rarely led to study discontinuation (one participant in each study)
  - Excluding COVID-19, rates of systemic adverse events in each of the two studies were all below 4.0%

[1]Lederman S, et al. *Arthritis Care Res (Hoboken)*. 2023 Nov;75(11):2359-2368. doi: 10.1002.

TNX-102 SL (5.6 mg) Fibromyalgia Regulatory Status

- **NDA can be filed without abuse potential assessment studies**
  - April 2017
- **Granted FDA Fast Track Designation**
  - July 2024
- **Submitted NDA to FDA**
  - October 2024
- **NDA assigned a PDUFA goal date of August 15, 2025**[1]
  - December 2024
- **FDA guided that no Advisory Committee Meeting will be required for this NDA**
  - March 2025

Next Milestone:

FDA decision on marketing authorization expected August 15, 2025

[1]PDUFA = Prescription Drug User Fee Act

About Fibromyalgia

*Fibromyalgia is a **chronic pain disorder** resulting from amplified sensory and pain signaling within the CNS – now recognized as **nociplastic pain**[1-4]*

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

Fibromyalgia is considered a **chronic overlapping pain condition (COPC)**[5]
*- the **only COPC** with any **FDA-approved drugs**[6]*

Fibromyalgia is the prototypic nociplastic syndrome

[1]Trouvin AP, et al. *Best Pract Res Clin Rheumatol*. 2019;33(3):101415.
[2]Fitzcharles MA, et al. *Lancet* 2021;397:2098-110
[3]Kaplan CM, et al. *Nat Rev Neurol*. 2024 20(6):347-363..
[4]Clauw DJ. *Ann Rheum Dis*. 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.
[5]Maixner W, et al. *J Pain*. 2016;17(9 Suppl):T93-T107.
[6]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)

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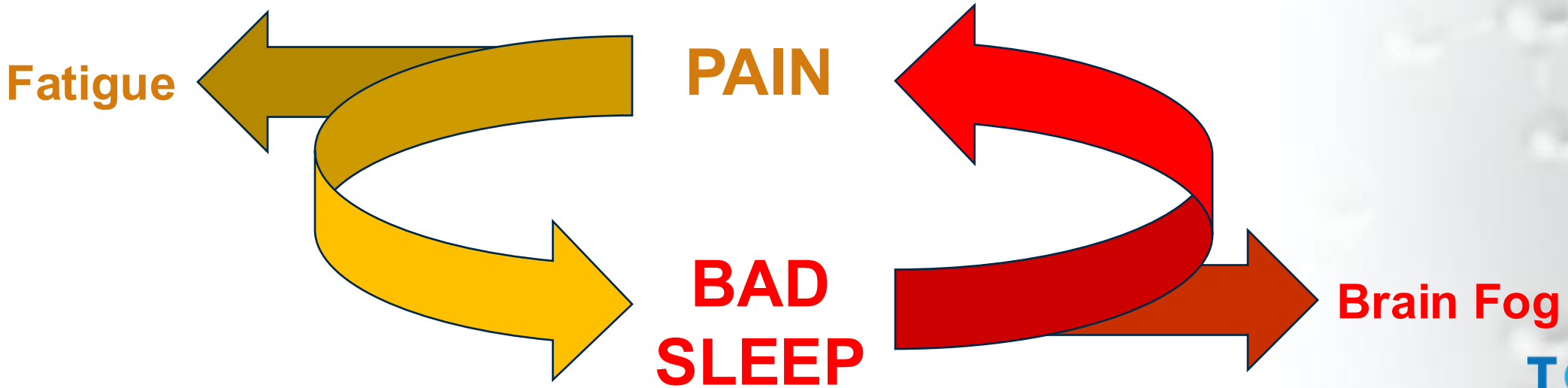
Fibromyalgia is a Large, Underserved and Dissatisfied Population

- **More than 10 million U.S. adults are affected – predominantly women[1,2]**
  - Debilitating and life altering condition
  - Significant economic impact
- **Patients have expressed dissatisfaction, despite three FDA approved drugs[3,4]**
  - 85% of patients fail first-line therapy[5]: efficacy variability, tolerability issues especially when used long-term and lack of broad-spectrum activity
  - Typical for patients to rotate between drugs and be on multiple drugs at the same time; 79% of FM patients are on multiple therapies[5]
- **~2.7 million FM patients diagnosed and treated[6]**
  - >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[7,8]
- **No new R*x* product since 2009**
- *The treatment objective is to **restore functionality** and **quality of life** while avoiding intolerable side effect burden*

[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]EVERSANA primary physician research, May 2024; commissioned by Tonix
[6]EVERSANA analysis of claims database, May 2024; commissioned by Tonix
[7]Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.
[8]Market research by Frost & Sullivan, commissioned by Tonix, 2011

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

- **Harvey Moldofsky – recognition of unrefreshing/non-restorative sleep in fibromyalgia**
- **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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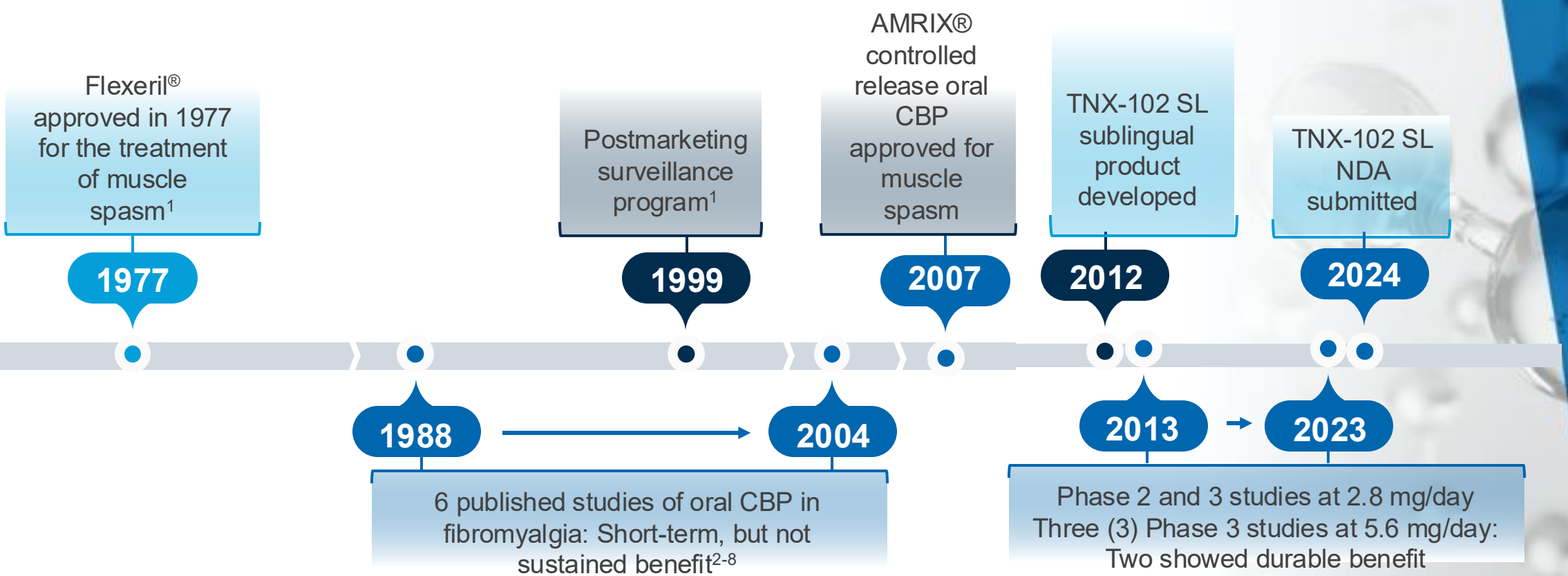
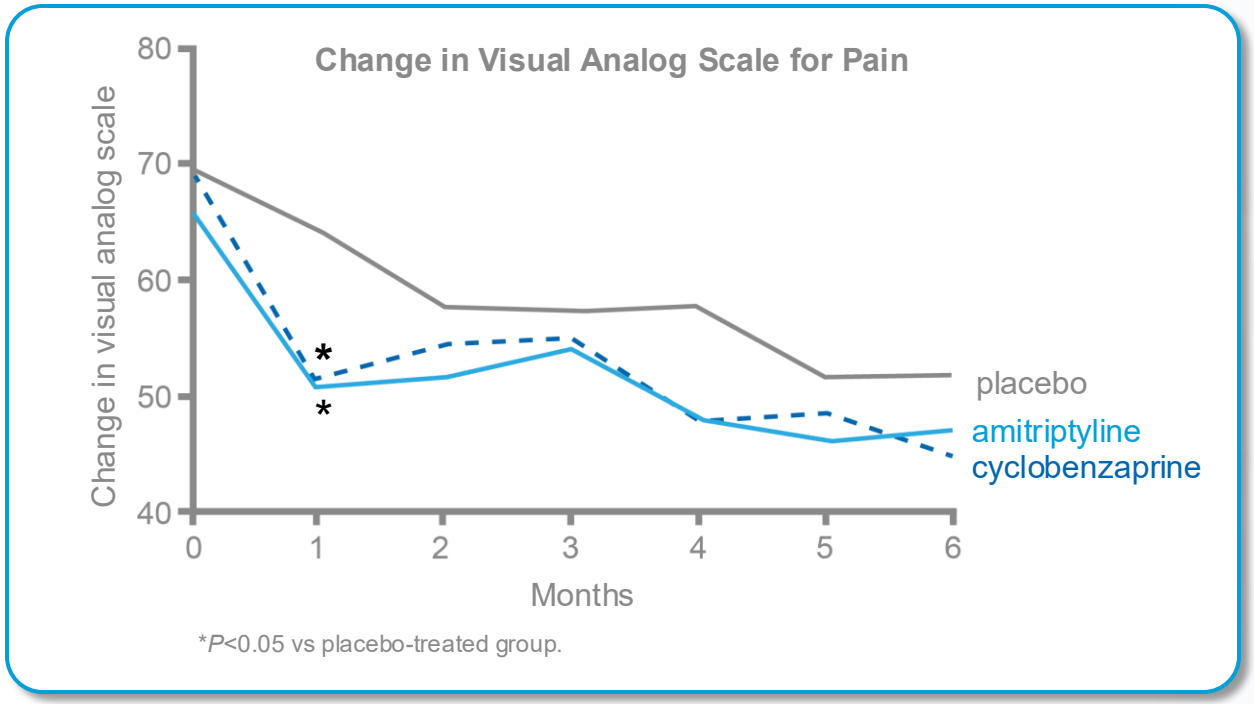
Cyclobenzaprine (CBP) as an Oral Product for Muscle Spasm and Investigational Sublingual Product for Fibromyalgia



Oral CBP has an **extensive safety record** in humans for **over 45 years**[9]

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. 9. IMS report 2011 of cyclobenzaprine use in 2009 – Data on File.

Neither Cyclobenzaprine nor Amitriptyline Has Durable (>1 Month) Activity on Pain in Fibromyalgia[1]



*P<0.05 vs placebo-treated group.

Study

- Double-blind, randomized
- 3 arms
- n=208
- 6 months

Bedtime dosing*

- First 3 months:
  - Cyclobenzaprine 20 mg
  - Amitriptyline 25 mg
- Last 3 months
  - Cyclobenzaprine 20 mg + 10 mg in the morning
- Amitriptyline 50 mg

Dosage note

- Cyclobenzaprine dosage is near maximum for muscle spasm
- Amitriptyline dosage is “low dose” (not depression dosing)

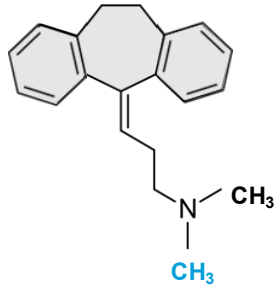
[1]Redrawn from Carette S, et al. *Arthritis Rheum*. 1994;37(1):32-40.

*Amitriptyline group: 10 mg daily at bedtime for the first week, 25 mg daily at bedtime for the second through twelfth weeks, and 50 mg daily at bedtime for the last 12 weeks. Cyclobenzaprine group: 10 mg daily at bedtime for the first week, 20 mg daily at bedtime for the second through twelfth weeks and 10 mg in the morning with 20 mg at bedtime for the last 12 weeks.

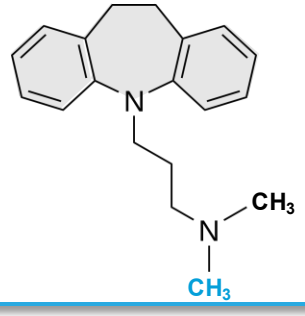
Oral Tertiary Amine Tricyclics (TATs) Are Prodrugs for Active Secondary Amine Tricyclics (SATs) in Depression

Tertiary Amine Tricyclics

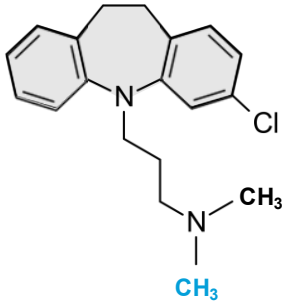
Amitriptyline



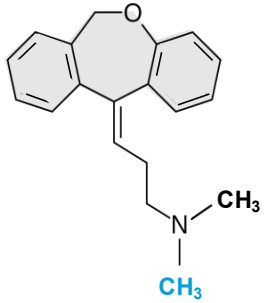
Imipramine



Clomipramine



Doxepin

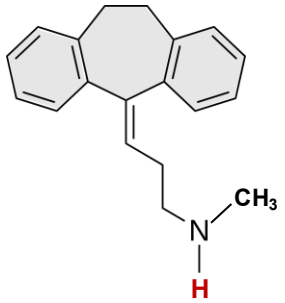


- Dynamic PK profiles with shorter half-lives[1]
  - **Short-term** utility for bedtime dosing to target nonrestorative sleep at very low dose
- Higher SERT inhibition than NET inhibition[2,3]

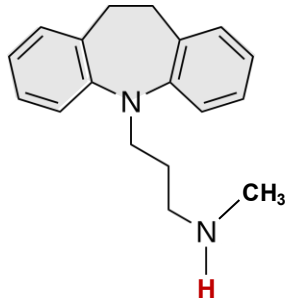
First-pass hepatic metabolism → CH_3 Demethylation

Secondary Amine Tricyclics

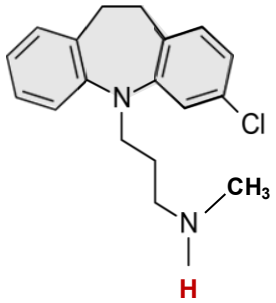
Nortriptyline



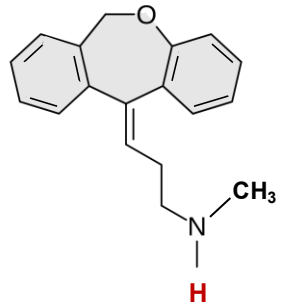
Desipramine



Norclomipramine



Nordoxepin

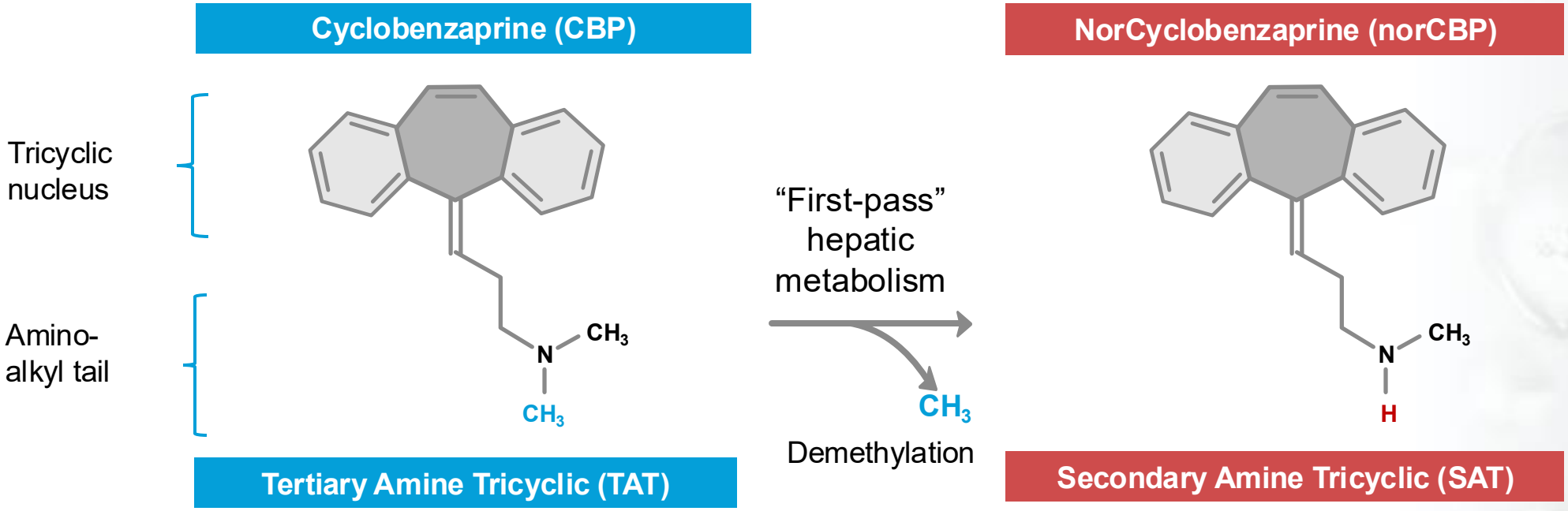


- Flat PK profiles and accumulation with daily dosing (longer half-lives)[1]
  - **Long-term** utility for treating major depressive disorder at high doses
- Relatively potent NET inhibition[2,3]

NET=norepinephrine transporter; PK=pharmacokinetic; SERT=serotonin transporter.

[1]Stahl SM. 7th ed. Cambridge University Press; 2020.
[2]Moraczewski J, et al. StatPearls Publishing; 2025. Updated August 17, 2023. Accessed February 24, 2025. https://www.ncbi.nlm.nih.gov/books/NBK557791
[3]Mitchell HA, et al. *Biochem Pharmacol*. 2010;79(6):801-809.

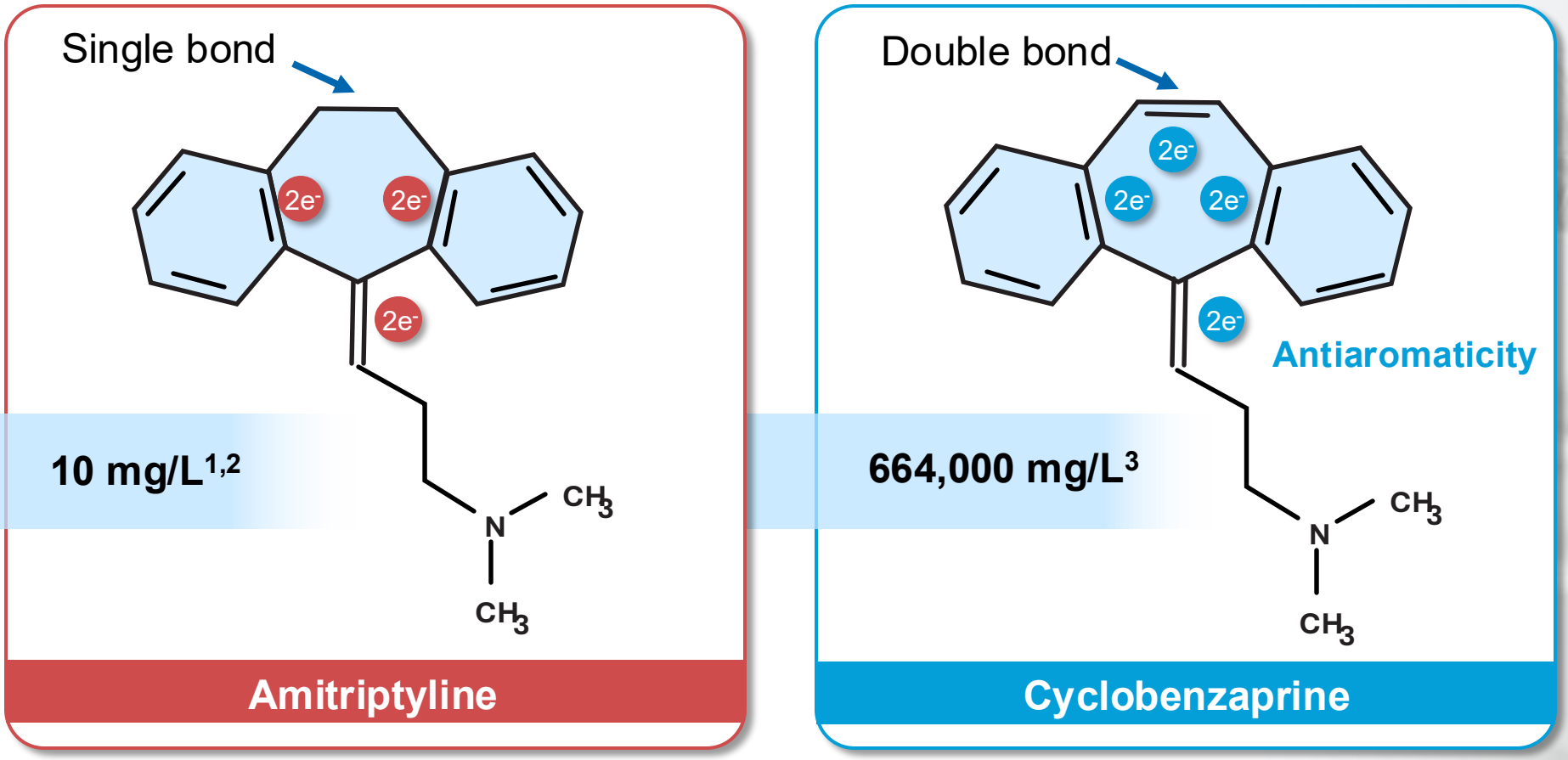
Cyclobenzaprine Is a Tertiary Amine Tricyclic That Was Not Developed as an Antidepressant



- **Cyclobenzaprine was developed as a short-term (2-3) week treatment for acute muscle spasm**
  - Flexeril® is an immediate-release cyclobenzaprine HCl tablet (15 or 30 mg/day)
  - Cyclobenzaprine, like other TATs, has tolerability issues related to dynamic changes in blood levels
  - Amrix® was developed as a controlled-release cyclobenzaprine HCl capsule (15 or 30 mg/day)
  - Similar to tricyclic antidepressants, cyclobenzaprine is demethylated in the liver

Cyclobenzaprine HCl Is 66,000 Times More Water Soluble Than Amitriptyline HCl

- A subtle change in cyclobenzaprine's structure (2 fewer hydrogen atoms than amitriptyline) causes a surprising increase in the drug-like character for cyclobenzaprine



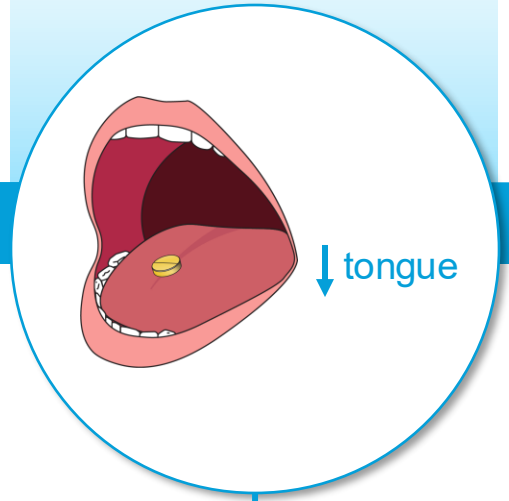
	Amitriptyline	Cyclobenzaprine
Solubility in water:	**10 mg/L[1,2]**	**664,000 mg/L[3]**

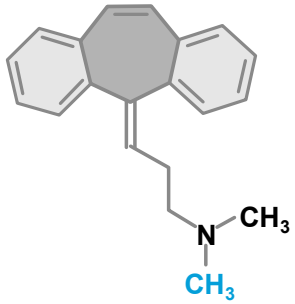
- Exocyclic double bond in central 7-member ring leads to antiaromaticity in cyclobenzaprine: 4n electron (e^-) rule

[1]Abdollahi M, et al. 3rd ed. Academic Press; 2014:838-845.
[2]Ledeti A, et al. *J Therm Anal Calorim*. 2018;131:155-165.
[3]Brioschi TM, et al. *Biomed Res Int*. 2013;2013:281392.

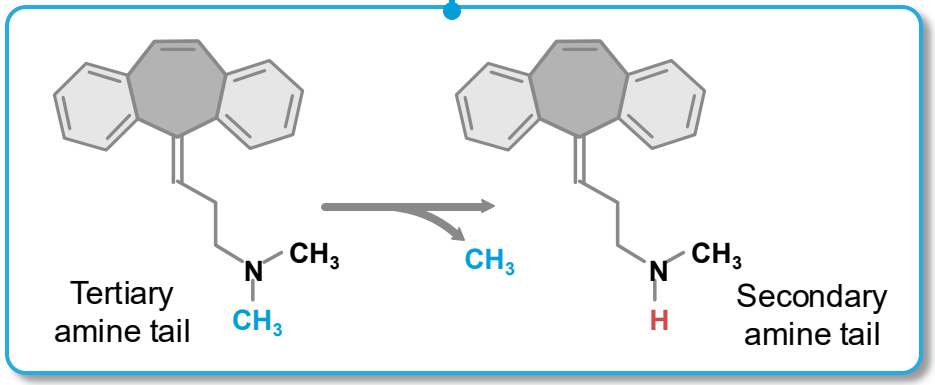
Oral Cyclobenzaprine Undergoes First-Pass Metabolism

CBP administered as a swallowed oral dose

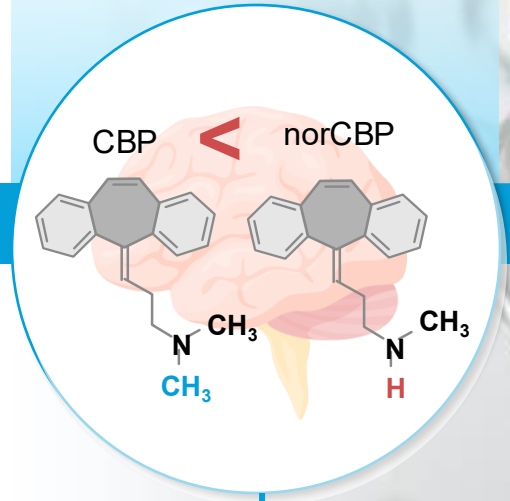




CBP undergoes “first-pass” hepatic metabolism and is ~50% converted to the persistent active metabolite norCyclobenzaprine (norCBP)



CBP and norCBP enter the brain

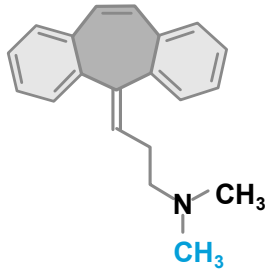


A swallowed oral dose leads to increased concentrations of norCBP relative to CBP over time

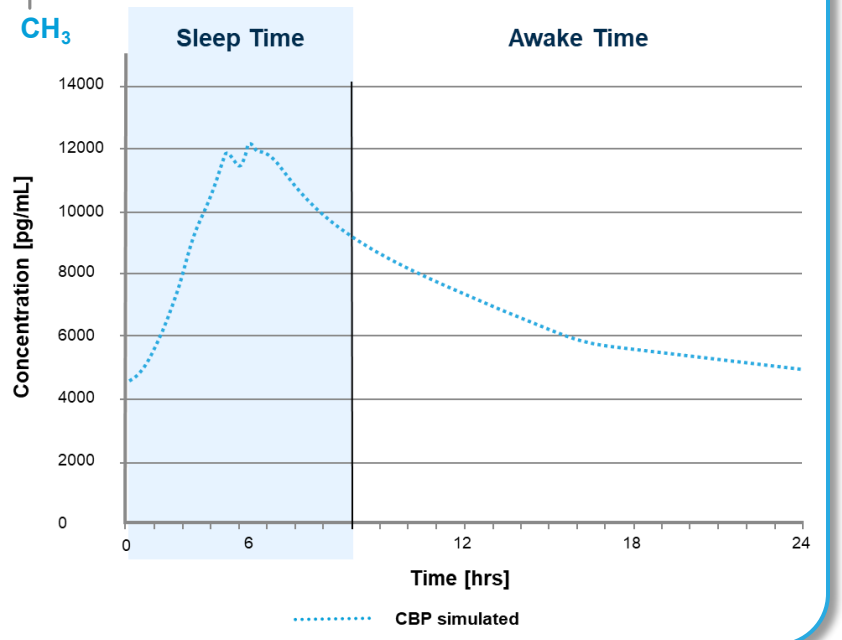
CNS PORTFOLIO

Oral Cyclobenzaprine: Simulated Day 20 Steady-State Blood Levels: Secondary Amine Tricyclic norCBP Accumulates

Cyclobenzaprine (CBP)



Bedtime dosing – blood levels peak ~5 hours after dosing and then rapidly fall to waking

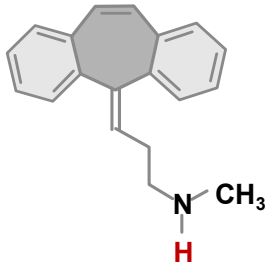


"First-pass" hepatic metabolism

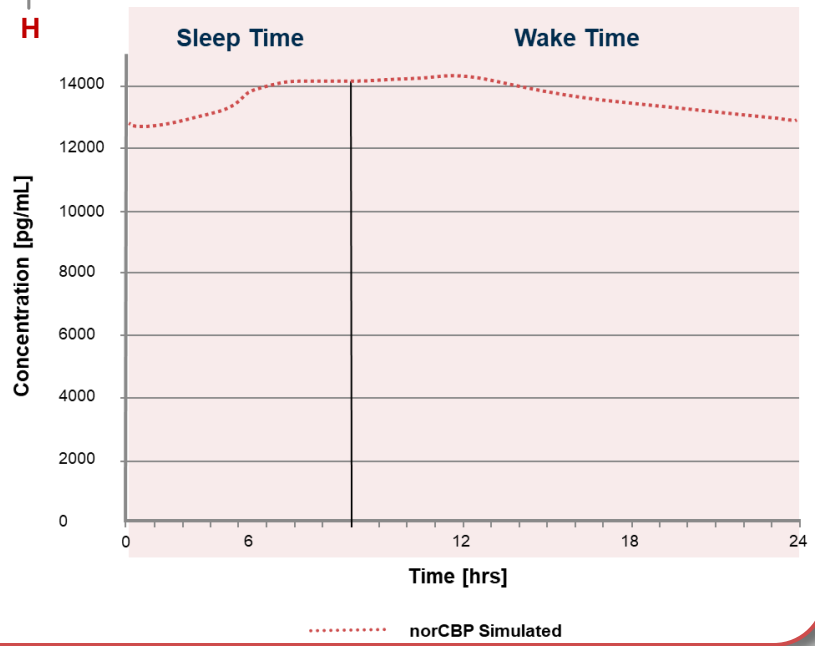
CH_3

Demethylation

NorCyclobenzaprine (norCBP)



Accumulates with oral dosing – little diurnal variation in blood levels



Many CNS drugs have pharmacodynamic effects from rising and falling drug blood levels

Cyclobenzaprine Binding Affinities* for Receptors and Transporters

	H_1	5-HT_{2A}	α_{1A}	α_{1B}	M_1	SERT	NET
Cyclobenzaprine (CBP)	1.3	5.2	5.6	9.1	7.9	29	35
norCyclobenzaprine (norCBP)	5.6	13	34	11	30	91	2.6

CBP/norCBP Activity: Antagonist | Inhibitor

CBP: more active (lower K_i) at the key receptors involved in sleep quality

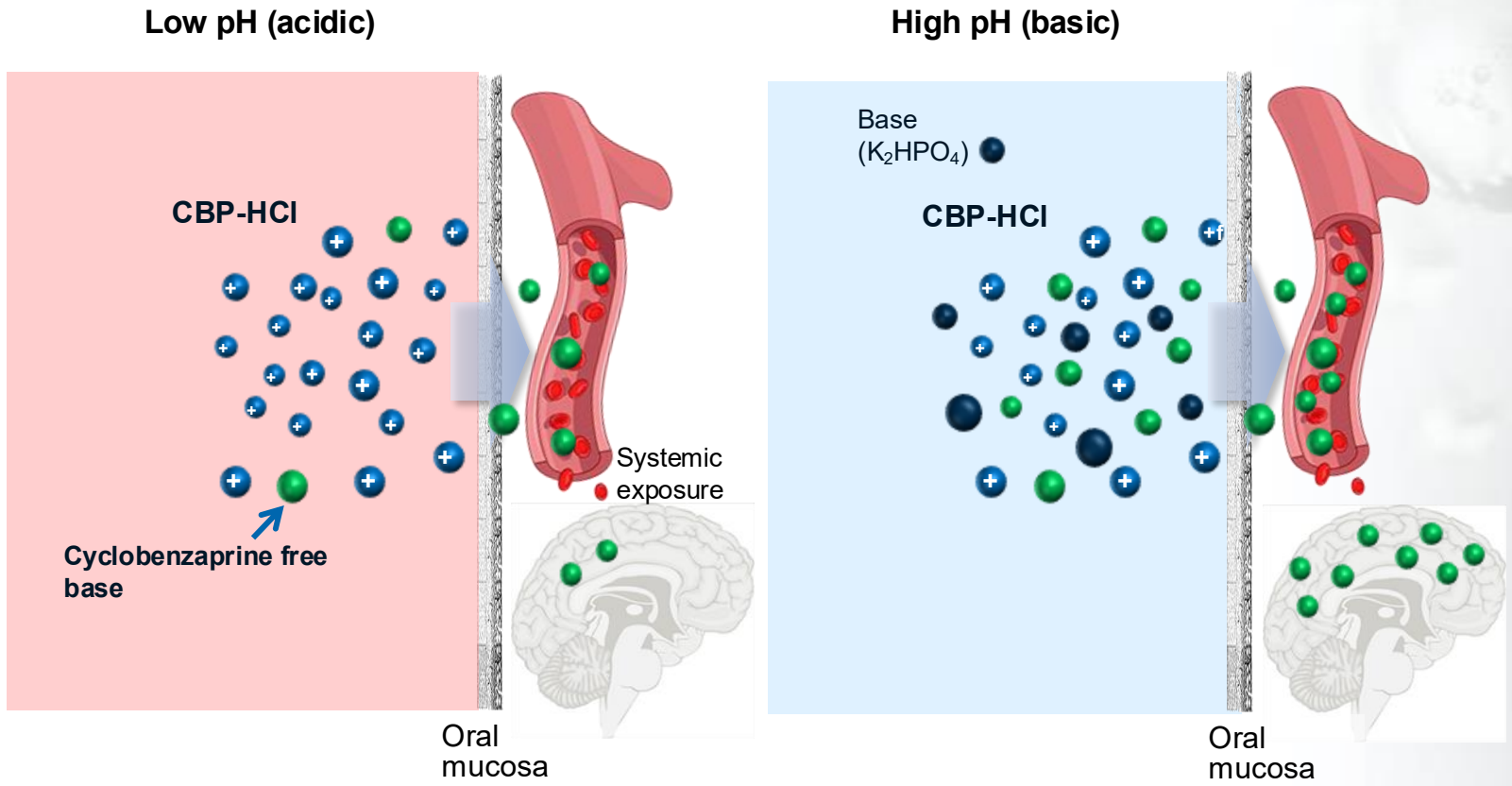
norCBP: more active on the norepinephrine transporter (NET)

Note: inhibitors of NET are generally “activating”

*K_i binding in nM

Formulation with Basic Excipient Increases Transmucosal Absorption of Sublingual Cyclobenzaprine[1]

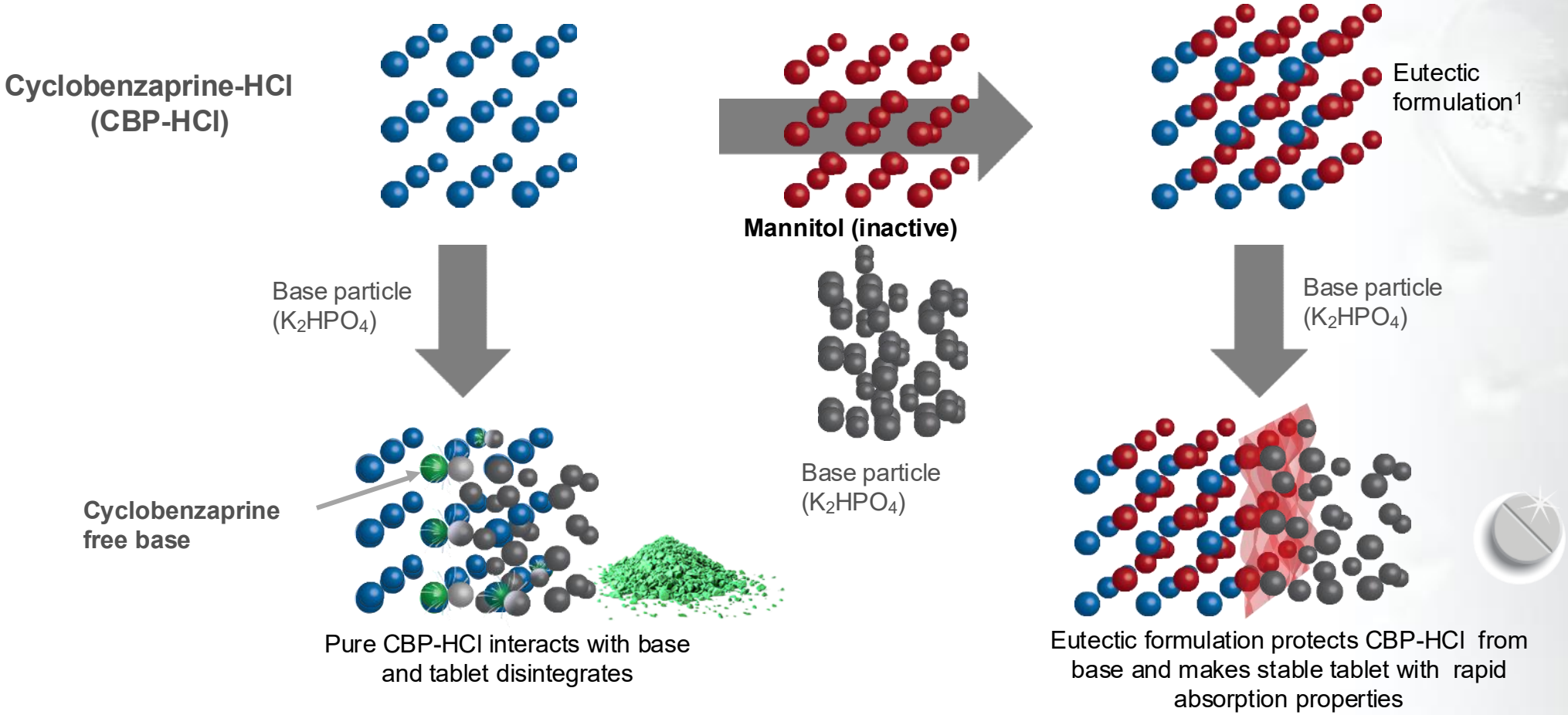
Concentration gradient increases diffusion of free base across oral mucosa (Le Chatelier's Principle)



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

TNX-102 SL: Proprietary Eutectic Formulation

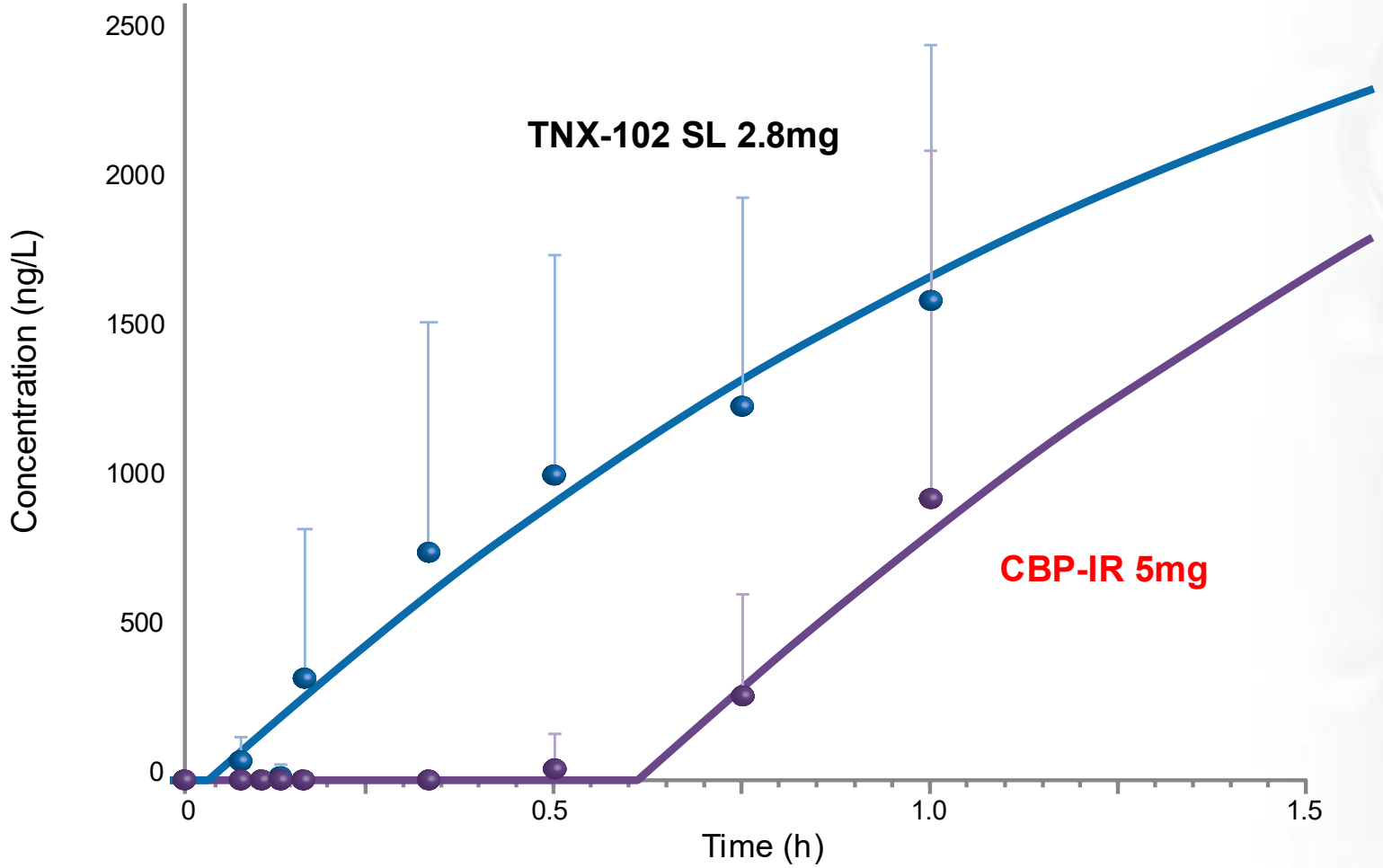
Proprietary cyclobenzaprine HCl eutectic composition stabilizes sublingual tablet formulation



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

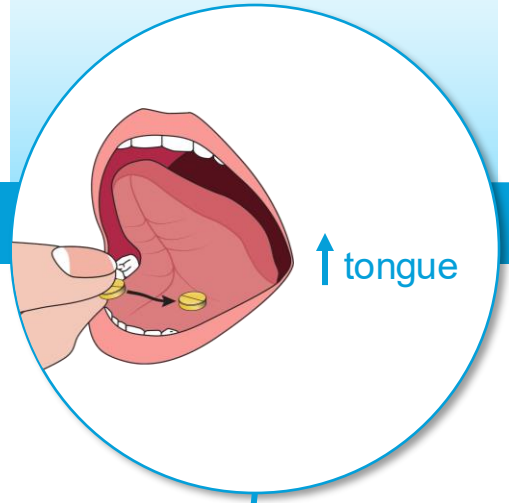
TNX-102 SL: CBP Detected in Plasma Within Minutes Following Sublingual Administration

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



TNX-102 SL: Transmucosal CBP Bypasses First-Pass Metabolism

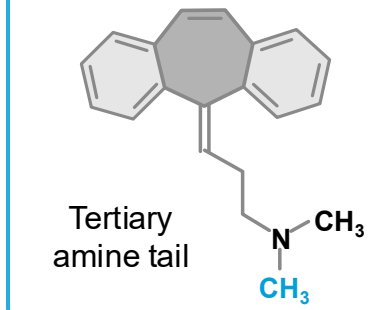
TNX-102 SL is administered sublingually

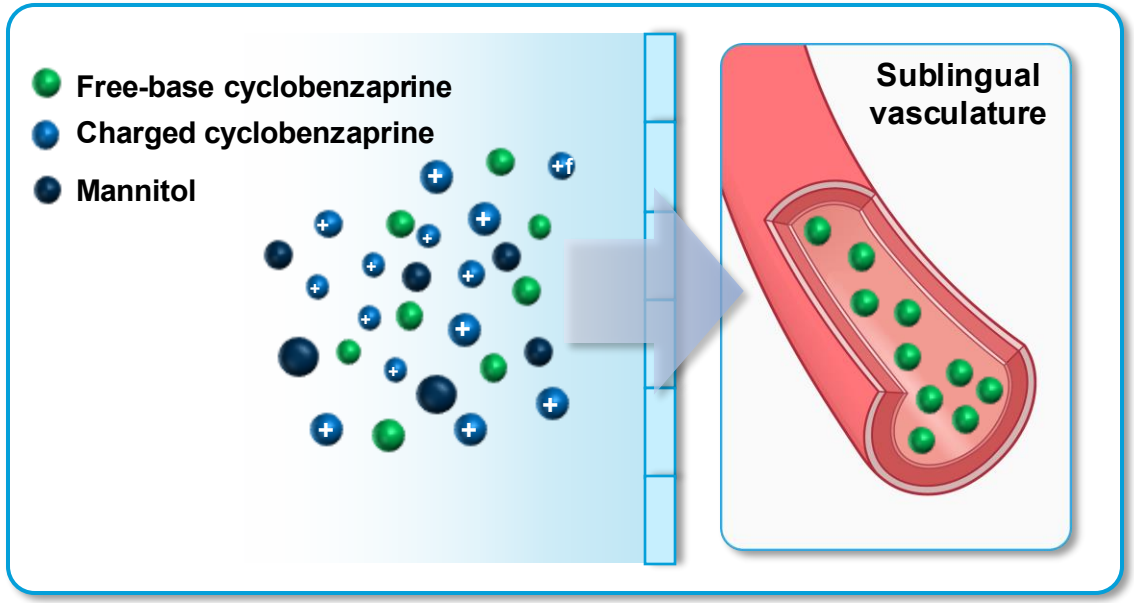


The sublingual tablet rapidly disintegrates, dissolves, and releases solubilized CBP into the saliva adjacent to the mucosal membrane

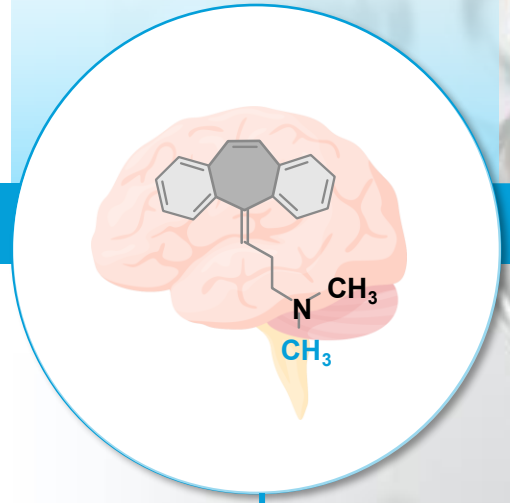
The base drives formation of CBP free-base, which enters the circulatory system across the mucosal membrane (transmucosal absorption)

Tonix's proprietary eutectic formulation contains a basic ingredient that enhances efficient transmucosal absorption and results in a stable tablet with a long shelf-life



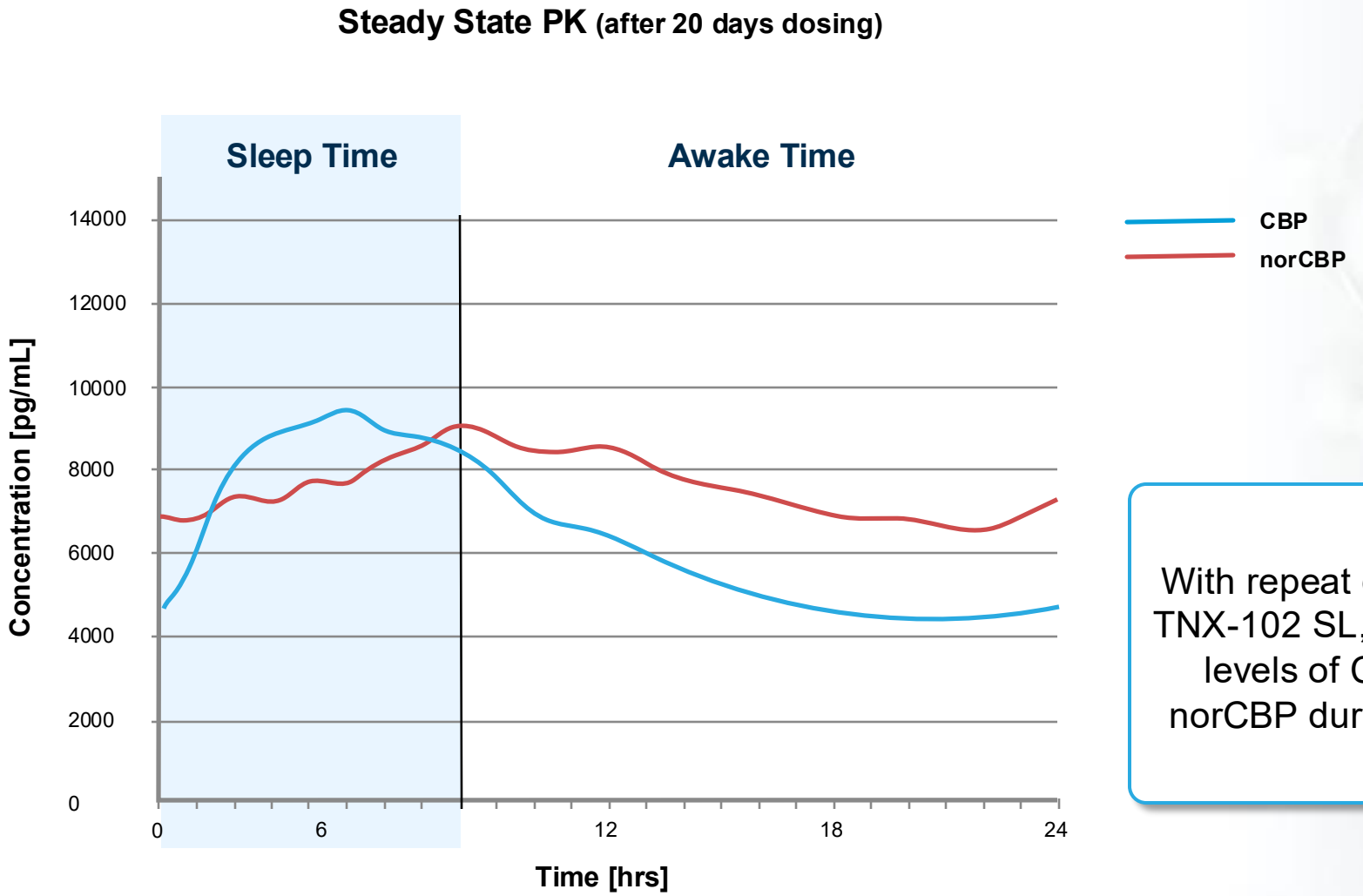


CBP enters the brain directly via the circulatory system



Transmucosal CBP administered sublingually bypasses "first-pass" hepatic metabolism, leading to faster absorption and reduced norCBP

Steady State Pharmacokinetics of Daily Sublingual TNX-102 SL (5.6 mg) at Bedtime



With repeat daily dosing of TNX-102 SL, dynamic peak levels of CBP exceed norCBP during sleep time

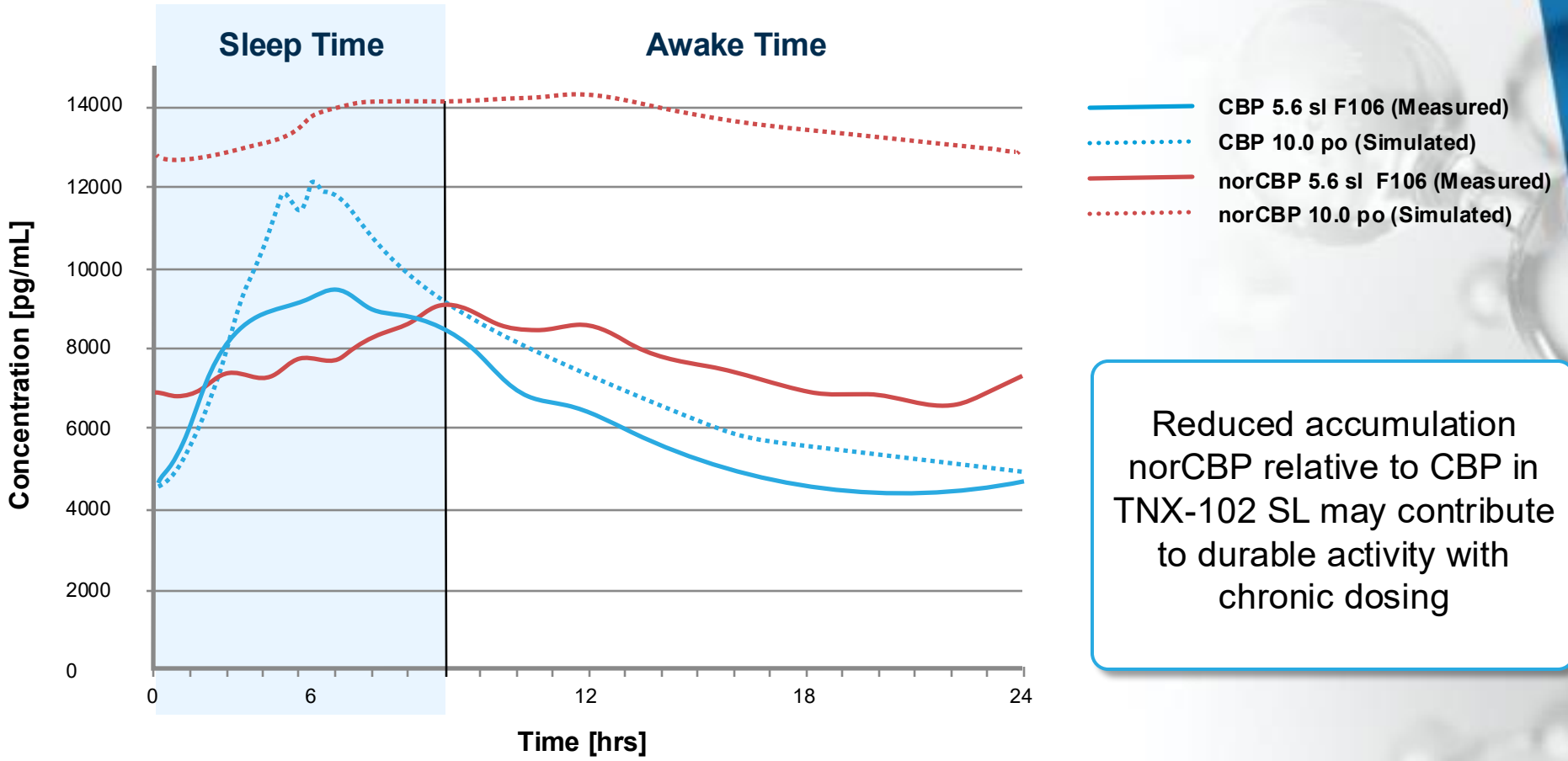
Many CNS drugs have pharmacodynamic effects from rising and falling drug blood levels

CNS PORTFOLIO

TNX-102 SL: Multi-Dose PK Differentiation from Simulated Oral Cyclobenzaprine (CBP)-Immediate Release (IR)

Steady State PK (after 20 days dosing)

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



Reduced accumulation norCBP relative to CBP in TNX-102 SL may contribute to durable activity with chronic dosing

Accumulation of norCBP may blunt dynamic effects of oral CBP after repeated daily dosing

sl = sublingual
po = by mouth

TNX-102 SL: Sublingual Formulation is Designed for Long-Term Daily Administration at Bedtime and Transmucosal Absorption

- **Cyclobenzaprine (CBP) - Tertiary Amine Tricyclic (TAT)**
  - Dynamic pharmacokinetics (PK)
    - Elimination by *N*-glucuronidation
- **Oral administration results in first-pass metabolism**
  - Generation of active metabolite, norCBP
- **NorCyclobenzaprine (norCBP) – Secondary Amine Tricyclic (SAT)**
  - Flat pharmacokinetics (PK)
    - No elimination by *N*-glucuronidation
- **TNX-102 SL delivers CBP by transmucosal absorption and is designed to bypass first-pass hepatic metabolism and lower norCBP accumulation**
  - Provides rapid absorption for bedtime dosing

TNX-102 SL: Sublingual Formulation is Designed for Long-Term Daily Administration at Bedtime and Transmucosal Absorption

- **Cyclobenzaprine (CBP) - Tertiary Amine Tricyclic (TAT)**
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  - Flat pharmacokinetics (PK)
    - No elimination by *N*-glucuronidation
- **TNX-102 SL delivers CBP by transmucosal absorption and is designed to bypass first-pass hepatic metabolism and lower norCBP accumulation**
  - Provides rapid absorption for bedtime dosing

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)

Patents based on TNX-102 SL's eutectic composition and its properties have issued in the U.S., E.U., Japan, China and many other jurisdictions around the world and provide market protection into 2034.

The European Patent Office's Opposition Division maintained Tonix's European Patent EP 2 968 992 in unamended form after an Opposition was filed against it by a Sandoz subsidiary, Hexal AG. Hexal AG did not appeal that decision.

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

Fibromyalgia Market Characteristics

Fibromyalgia: Market Characteristics

Prevalence

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

Diagnosed population

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

Treatment Pattern

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

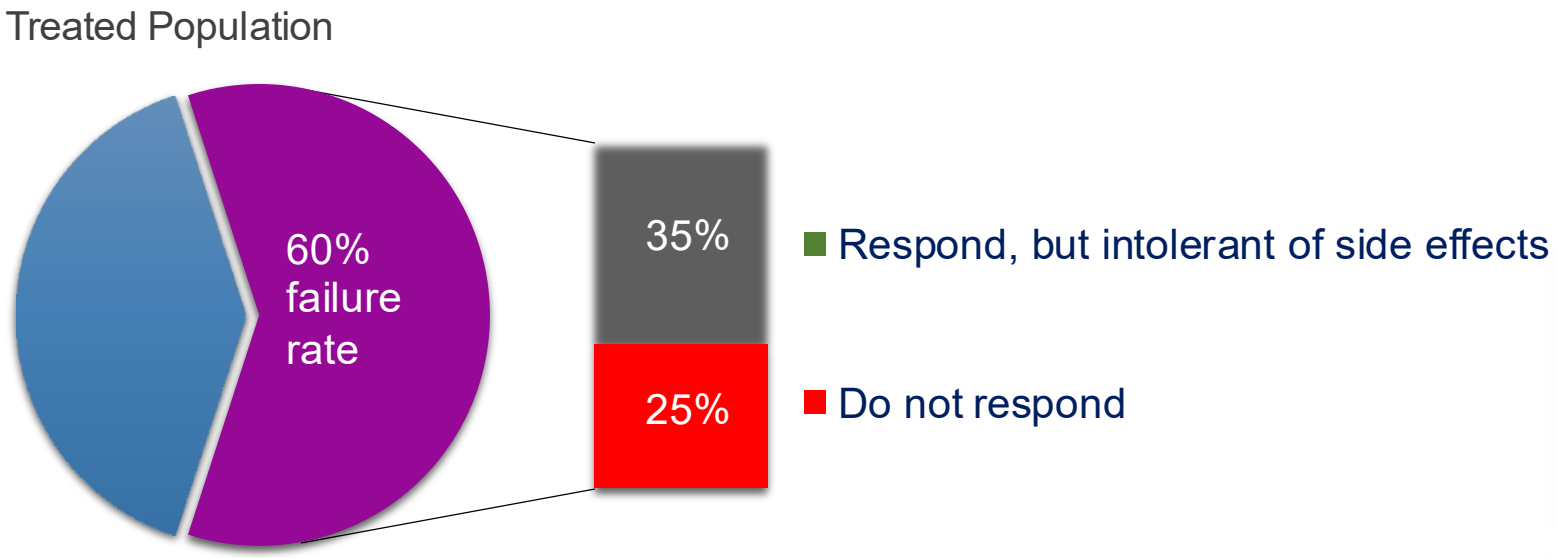
Unmet Need

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

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

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

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



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

Current FDA-Approved Fibromyalgia Drugs[1]

Improvement in fibromyalgia pain was primary endpoint for approval

- No current product addresses pain, poor sleep and fatigue
- Tolerability issues limit long term use for many patients

Drug		Pregabalin	Duloxetine Milnacipran
Class		Gabapentinoid	SNRI
Fibromyalgia Activity	**Pain Reduction**	YES	YES
	Sleep Improvement	YES	-
	Fatigue Reduction	-	YES
Tolerability Issues	Fatigue increase	YES	-
	Sleep problems	-	YES
	Weight gain	YES	-
	Blood Pressure increase	-	YES
	Sexual impairment	-	YES
	GI issues	-	YES
	Hip Fractures[2]	YES	-
	DEA Scheduled	YES	-

[1]The three drugs with FDA approval for the management of fibromyalgia are Pregabalin (Lyrica®); Duloxetine (Cymbalta®); and Milnacipran (Savella®)
[2]Leung MTY, et al. *JAMA Netw Open*. 2024;7(11):e2444488. doi: 10.1001/jamanetworkopen.2024.44488. PMID: 39535796; PMCID: PMC11561685.

TONIX PHARMACEUTICALS

Large Need for New Fibromyalgia Therapies that Provide 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]
- 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.

TNX-102 SL Showed Activity on Pain, Sleep and Fatigue and was Generally Well Tolerated in the RESILIENT Study[1]

Drug		TNX-102 SL
Initial Indication of active ingredient		Muscle spasm[1]
Class		Tricyclic
Mechanism		Antagonist at 4 post-synaptic receptors[2]
Fibromyalgia Activity	Pain	+
	Sleep	+
	Fatigue	+
Tolerability Issues	Sleep	-
	Fatigue	-
	Oral administration site reaction[3]	+

[1]Flexeril® and Amrix® are oral formulations of cyclobenzaprine indicated for short term (2-3 weeks) treatment of muscle spasm

[2]Cyclobenzaprine is an antagonist at: serotonergic-5-HT2A, adrenergic-α1, histaminergic-H1, and muscarinic-M1 cholinergic receptors

[3]TNX-102 SL was generally well tolerated with an adverse event profile comparable to prior studies and no new safety signals were observed. In both pivotal studies, the most common treatment-emergent adverse event was tongue or mouth numbness at the administration site, which was temporally related to dosing, self-limited, never rated as severe, and rarely led to study discontinuation (one participant in each study).

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

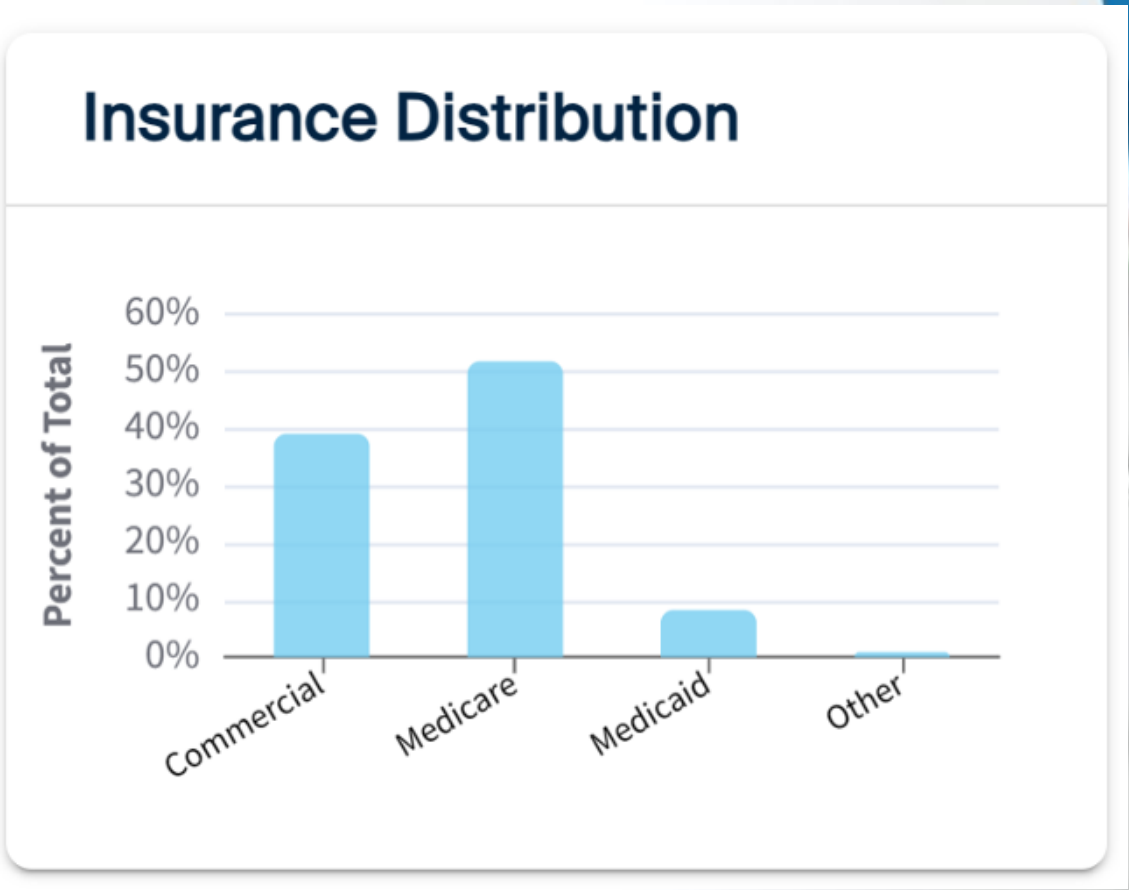
Approximately 50% of fibromyalgia patients are on Medicare

- 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

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

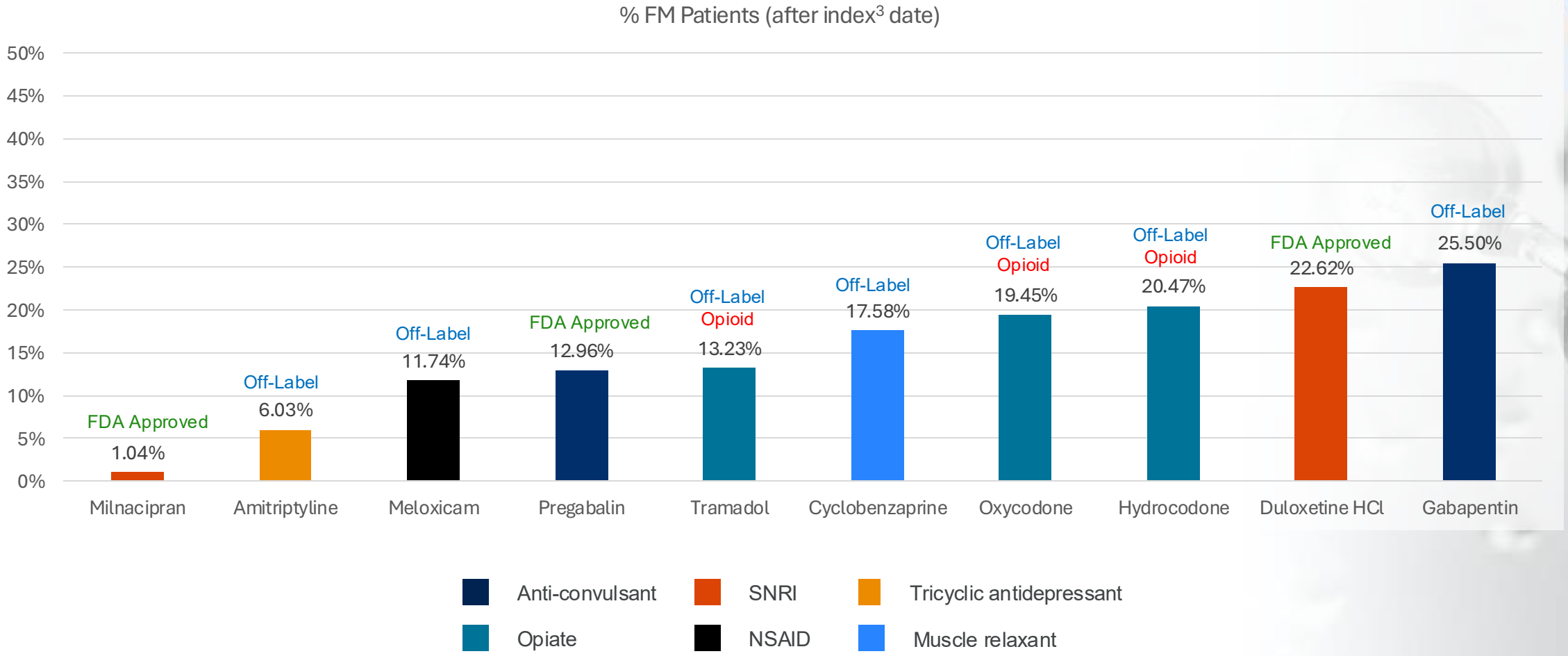
- **Physicians reacted positively to the efficacy and safety profile of TNX-102 SL (based on Phase 3 Study results)**
- Median interest = 4.0 on a 5-point scale
- Driving attributes included **strong efficacy, safety and tolerability**
- Unique & differentiating efficacy features included improvements in **sleep and fatigue**

Anticipated Use

- **Physicians indicated intended use in 40% of their FM patients**
- Majority of respondents indicated TNX-102 SL 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

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

Potential for Tonix to Launch and Market TNX-102 SL

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

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

Fibromyalgia experts are a subset of Rheumatologists

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

Channels for distribution of prescription drugs are evolving

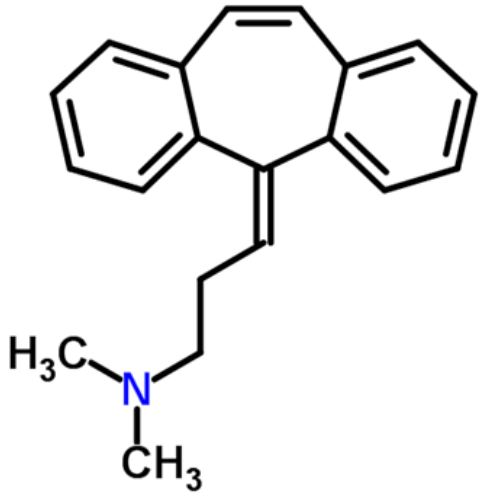
- Growth of specialty pharmacies who distribute products by mail

Tonix markets two prescription products for the acute treatment of migraine

- Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg for the acute treatment of migraine with or without aura in adults

About Cyclobenzaprine and TNX-102 SL

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

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

Multi-Functional Mechanism Involves Antagonism at Four Post-Synaptic Receptors and Inhibition of SERT and NET

Cyclobenzaprine is an antagonist at four post-synaptic receptors

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

Cyclobenzaprine is a SERT inhibitor and weak NET inhibitor

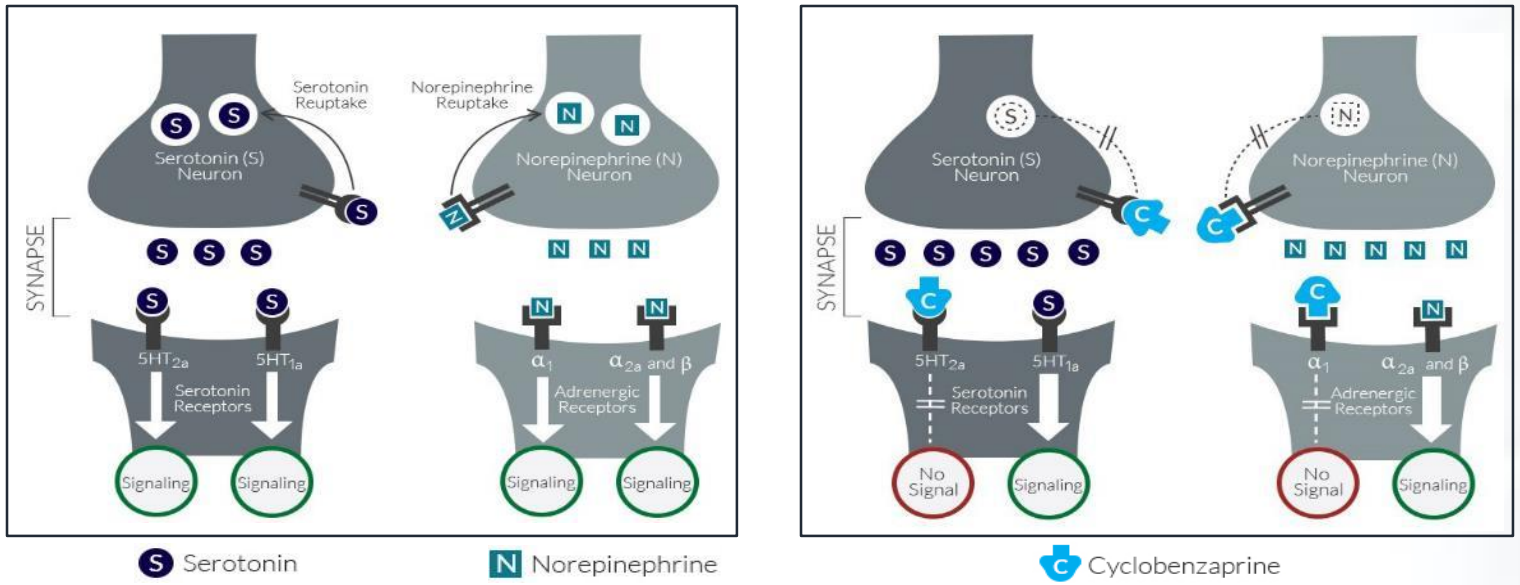
- Inhibitor of SERT
  - Similar activity to SSRIs (e.g., Prozac® [fluoxetine])
- Weak inhibitor of NET
  - Weaker activity than SNRIs (e.g., Cymbalta® [duloxetine] and Savella® [milnacipran])

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

Untreated → **Effects of TNX-102 SL**



SNARI = Serotonin and Norepinephrine receptor Antagonist and Reuptake Inhibitor

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

TNX-102 SL NDA can be filed without drug abuse and dependency assessment studies

- April 2017 meeting minutes from the March 2017 FDA meeting

RESILIENT Phase 3 Study

TNX-102 SL: Phase 3 *RESILIENT* Study Design

RESILIENT Study

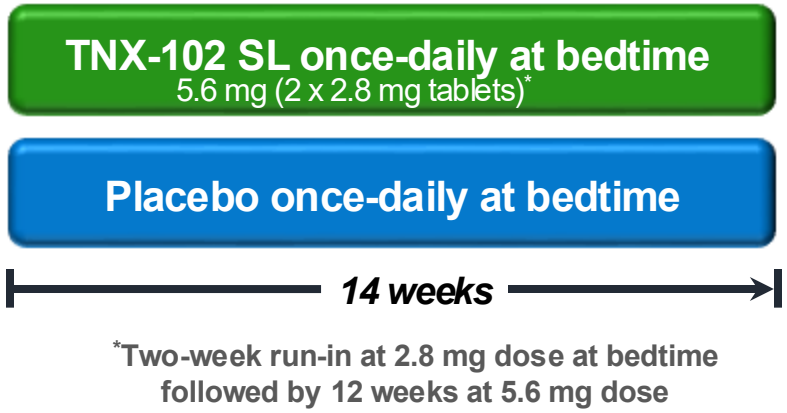
CNS PORTFOLIO

General study characteristics:

- Randomized, double-blind, multicenter, placebo-controlled study in fibromyalgia
- 33 U.S. sites enrolled 457 participants with fibromyalgia as defined by 2016 Revisions to the 2010/2011 FM Diagnostic Criteria[1]

Primary Endpoint:

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



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

ClinicalTrials.gov Identifier: **NCT05273749**

Study Title: A Phase 3 Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily in Patients With Fibromyalgia (RESILIENT)

Trial ID: TNY-CY-F307 ('RESILIENT')

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

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RESILIENT Demographics and Baseline Characteristics

RESILIENT Study

	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

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)

RESILIENT Study Efficacy Findings

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

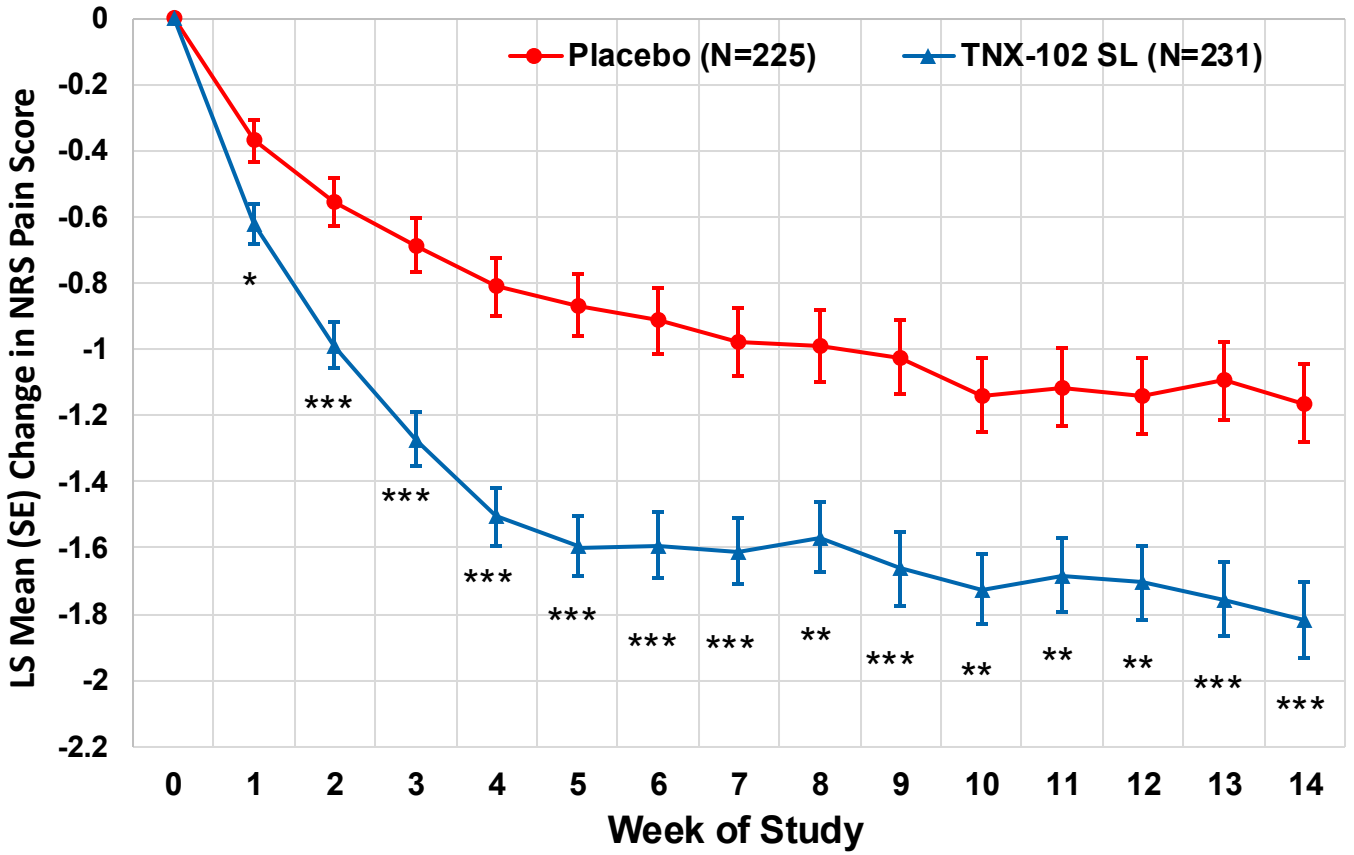
*In order of statistical serial gate-keeping hierarchy (or, “waterfall”) to control overall Type 1 error
**Statistical significance met

RESILIENT Primary Outcome Measure
Reduction in Widespread Pain

RESILIENT Study

CNS PORTFOLIO

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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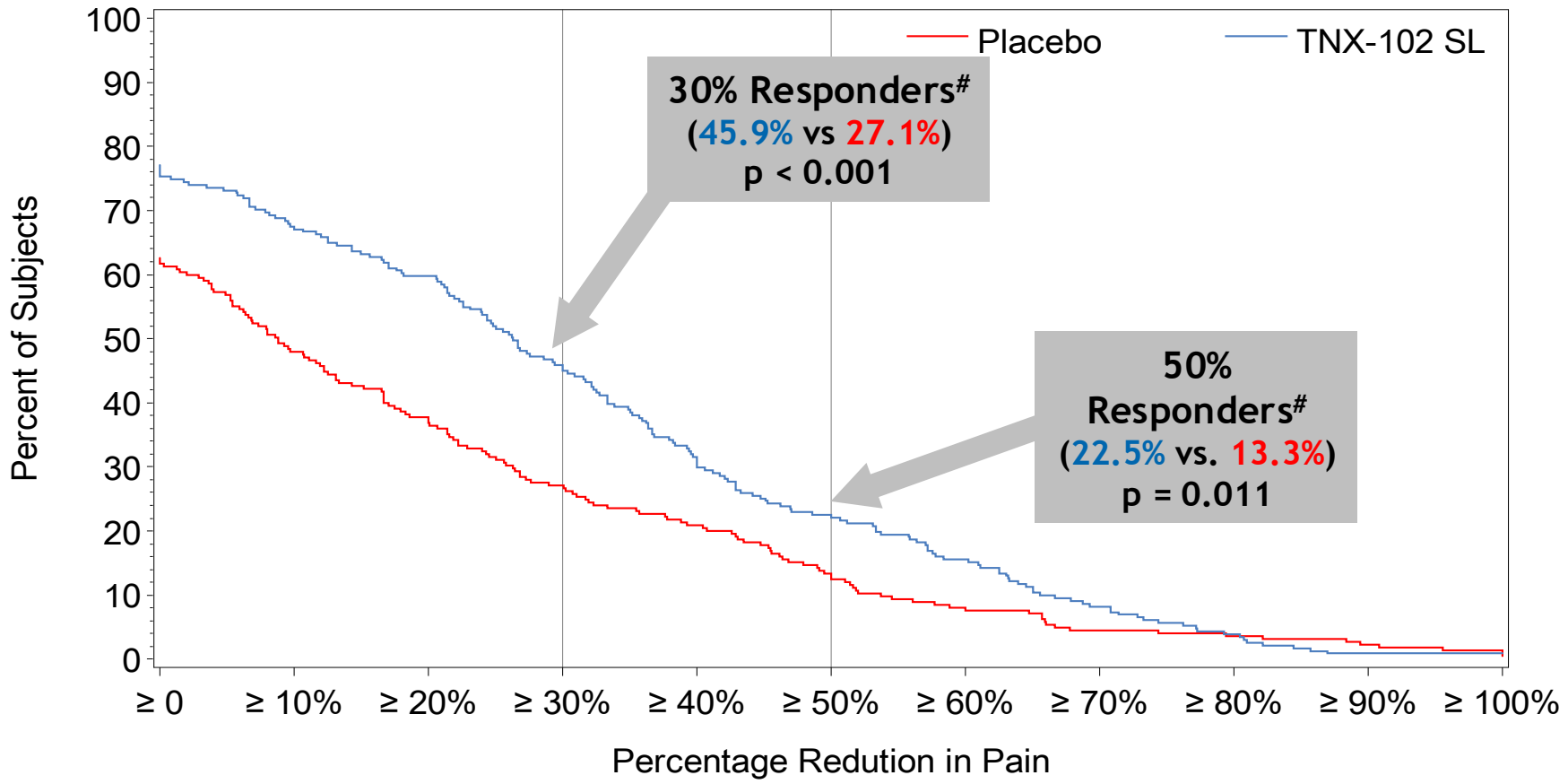
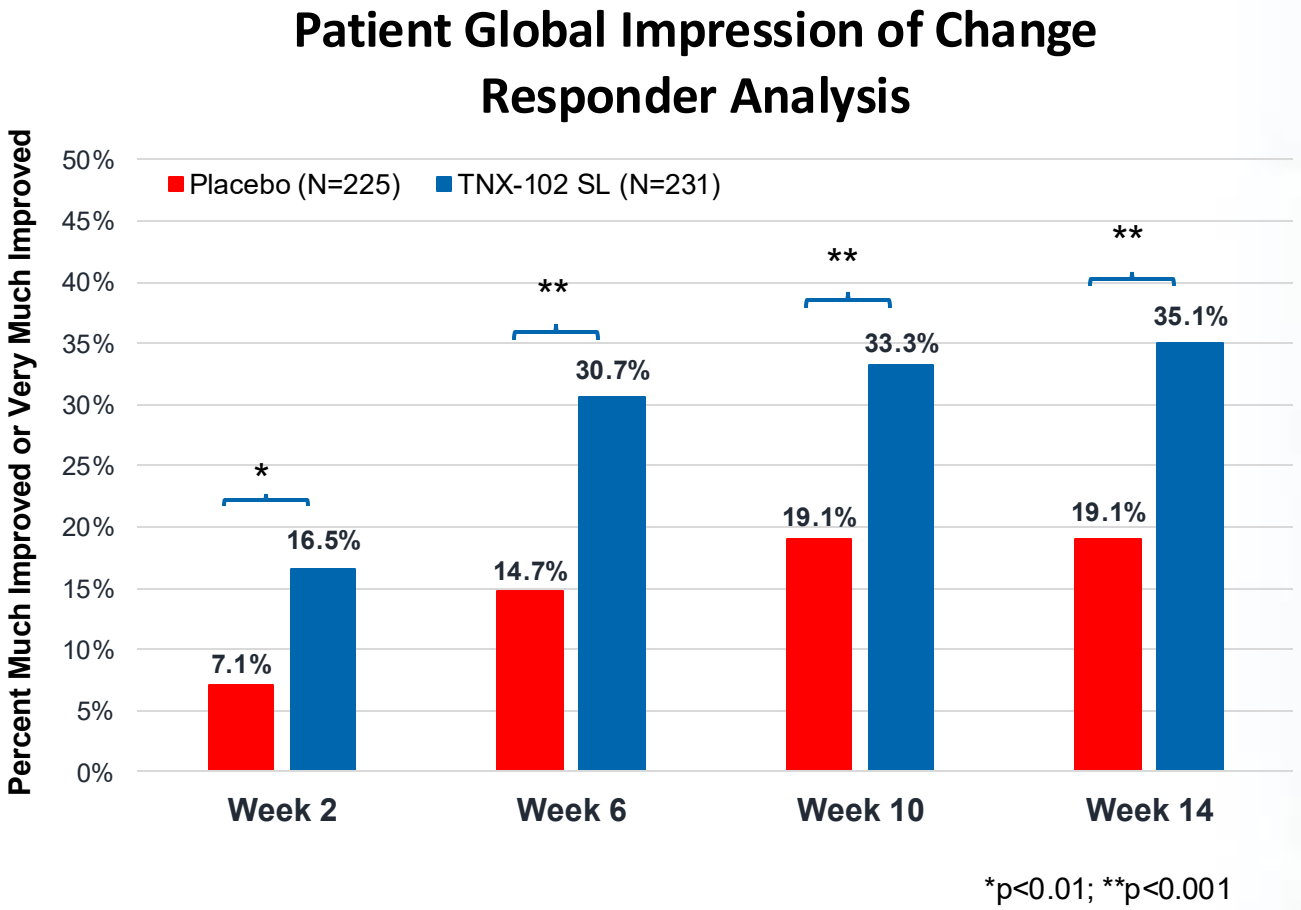
RESILIENT Continuous Pain Responder Graph



#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

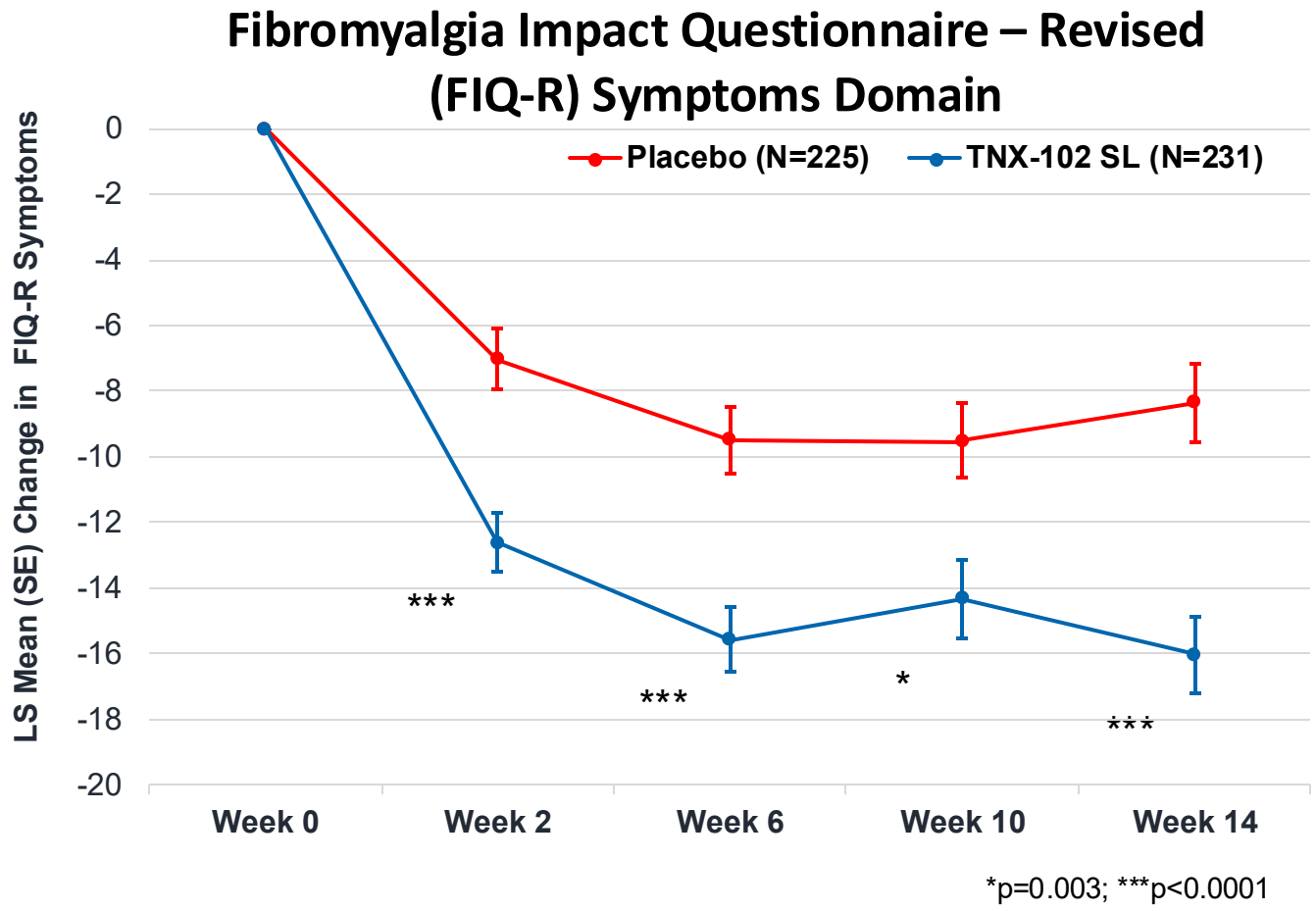
RESILIENT Patient Global Impression of Change
Key Secondary Outcome Measure



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

RESILIENT FIQ-R Symptoms Domain
Key Secondary Outcome Measure



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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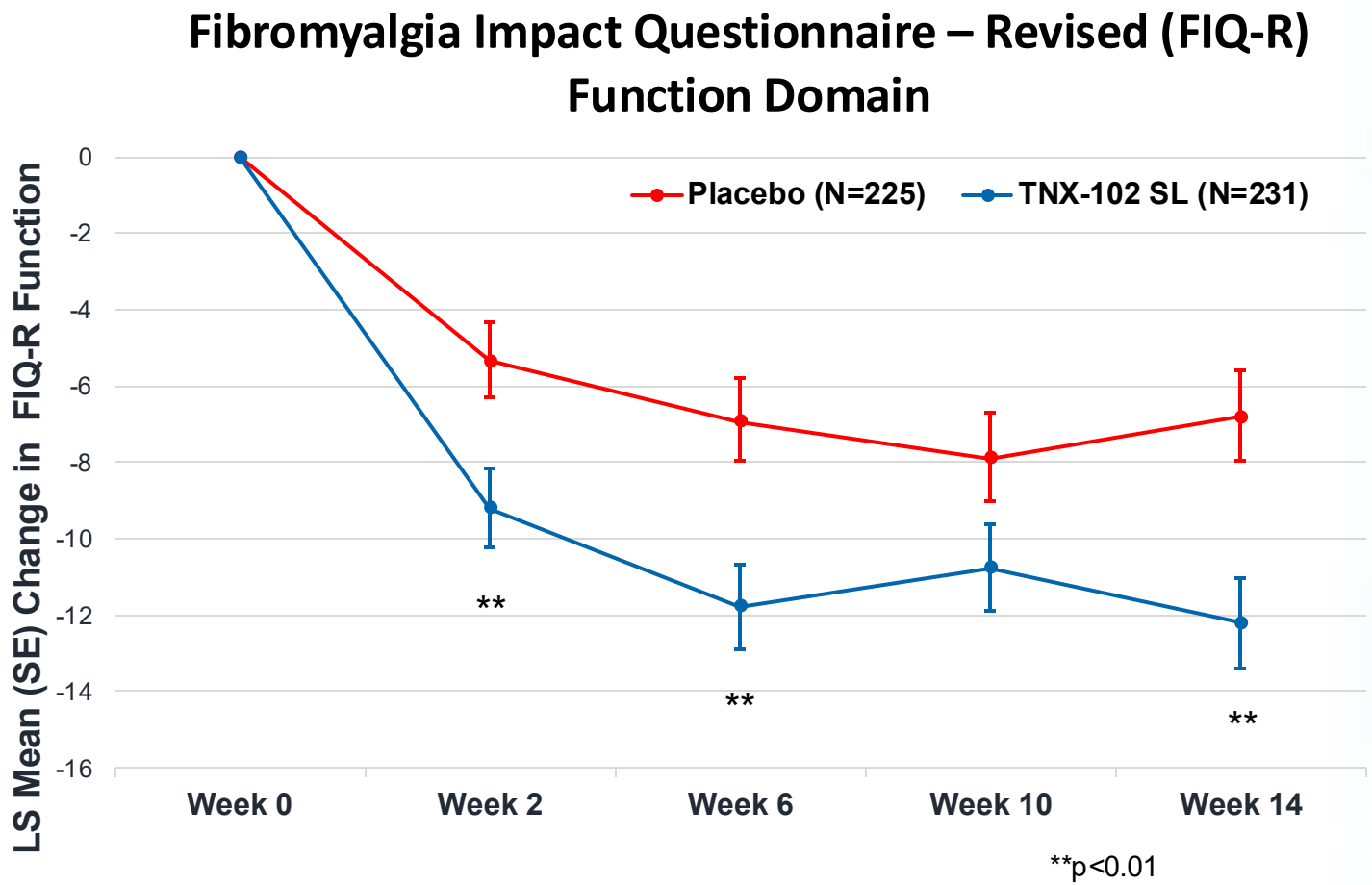
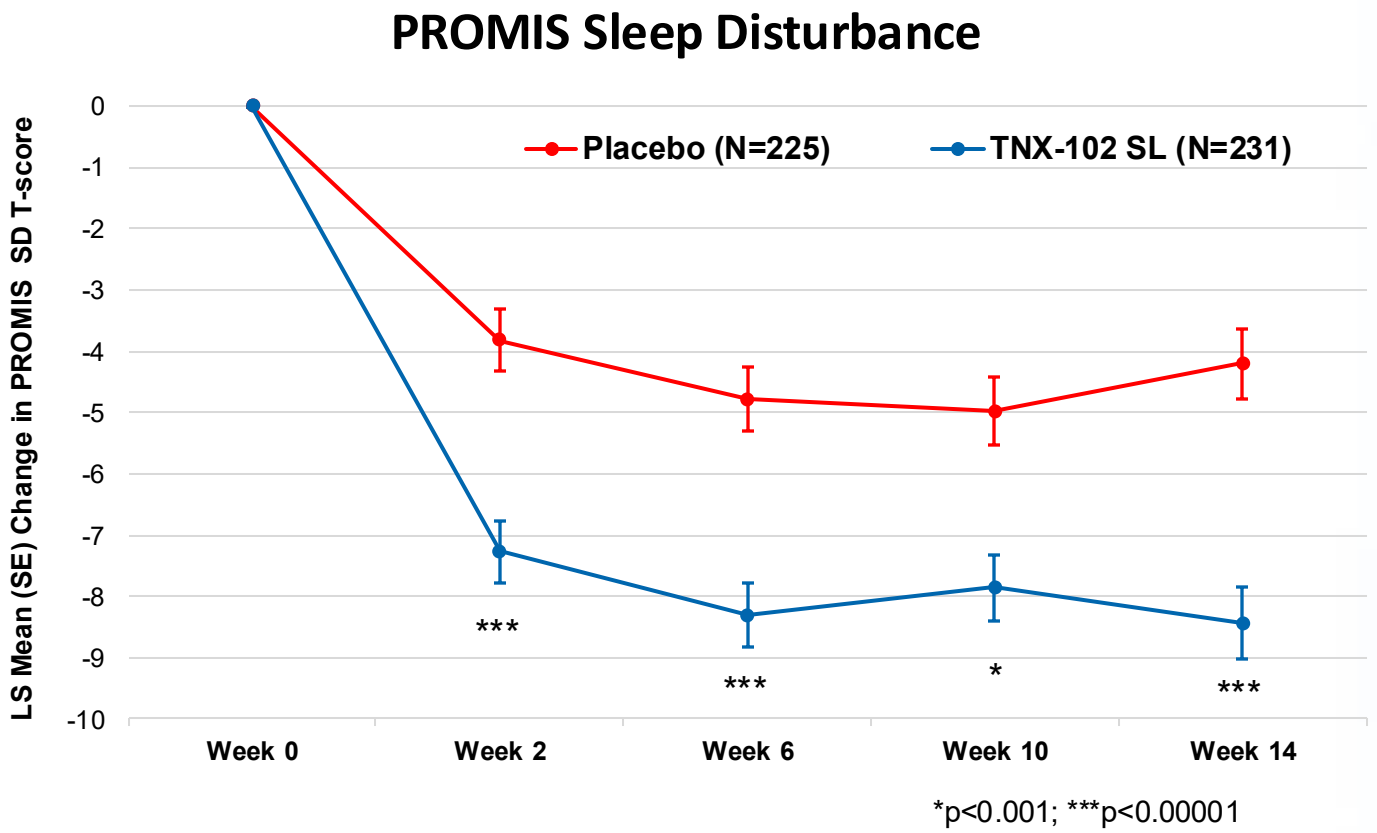
RESILIENT FIQ-R Function Domain
Key Secondary Outcome Measure



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.

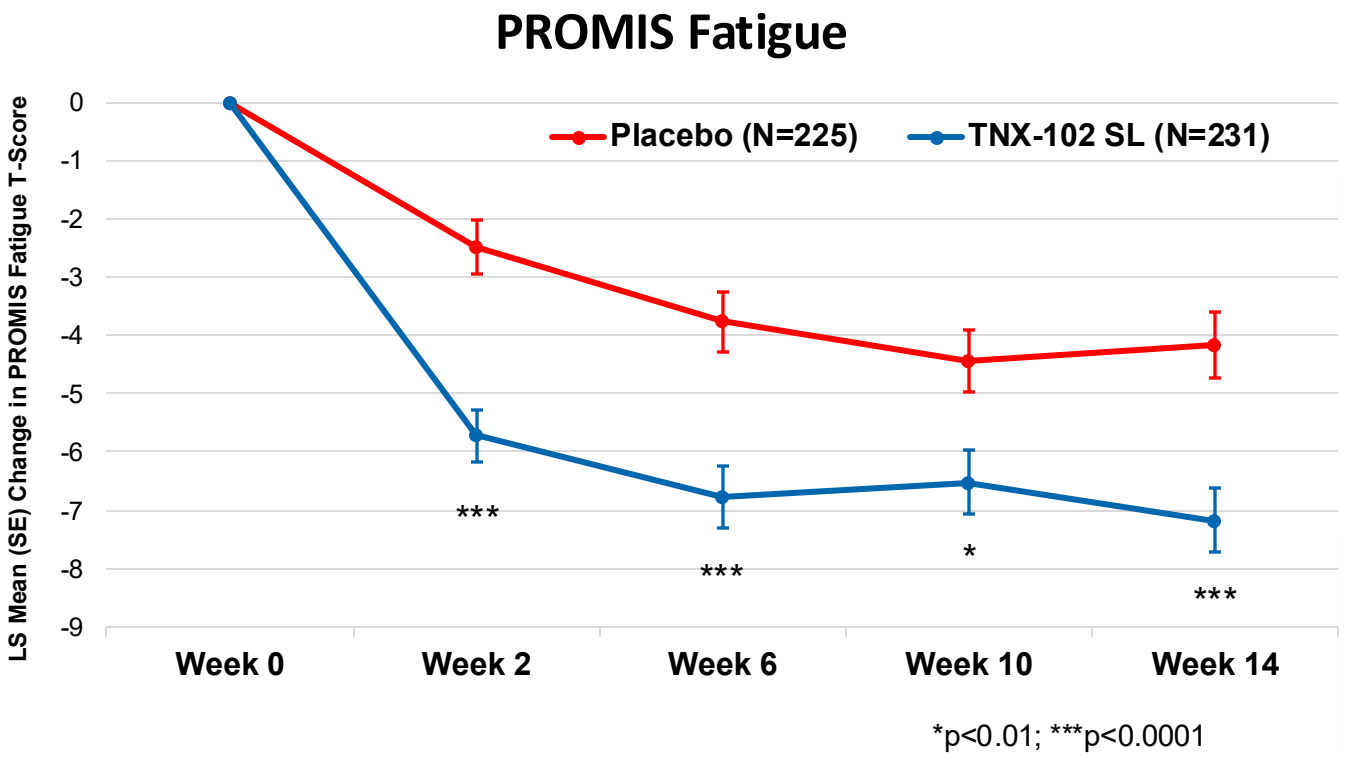
RESILIENT PROMIS Sleep Disturbance Inventory
Key Secondary Outcome Measure



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

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

RESILIENT PROMIS Fatigue Inventory
Key Secondary Outcome Measure



*p<0.01; ***p<0.0001

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

[#]Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

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RESILIENT Sleep Quality by Daily Diary
Key Secondary Outcome Measure

RESILIENT Study

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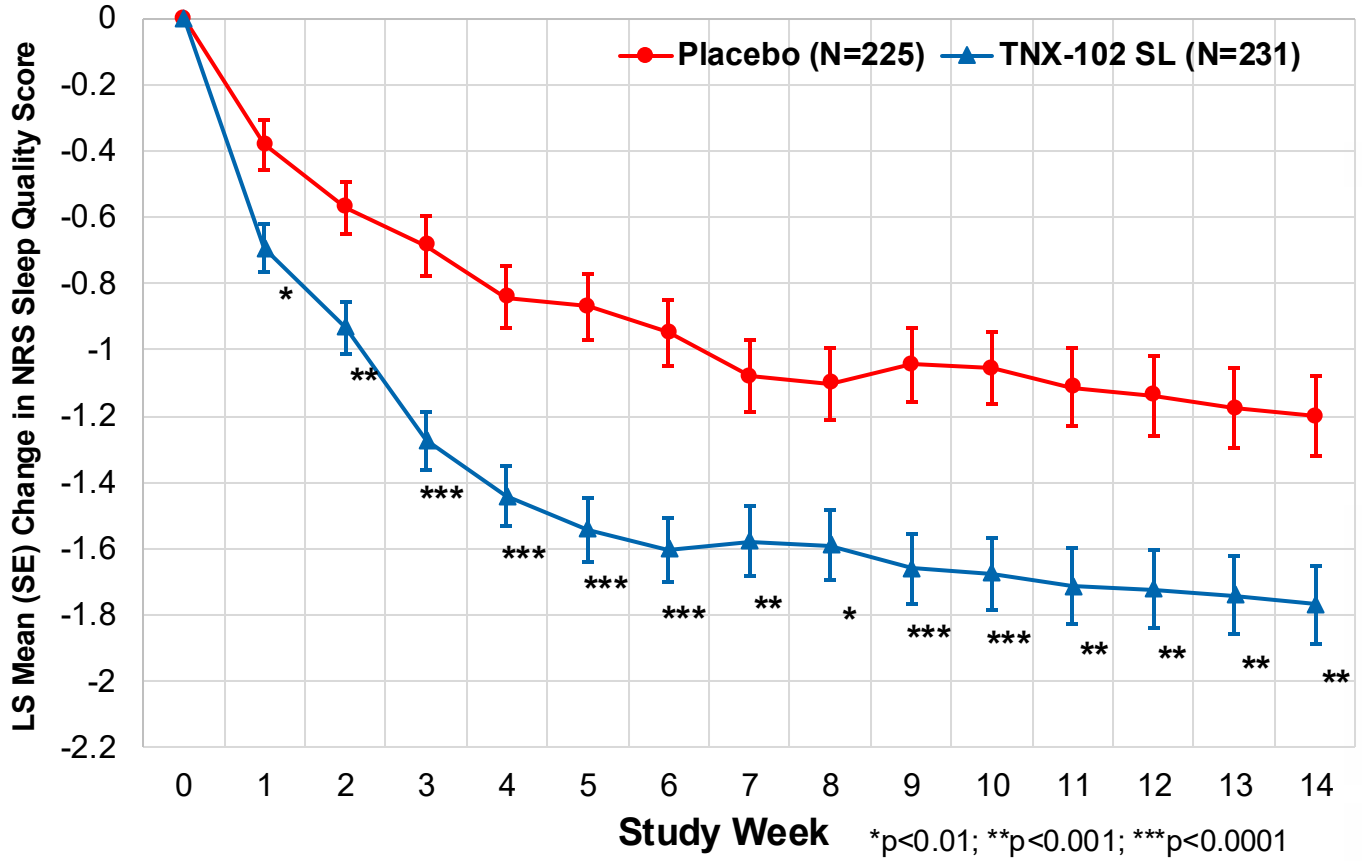
Weekly Average of Daily Diary NRS Ratings of Prior Night Sleep Quality



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

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: TNX-102 SL 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”

RESILIENT Study

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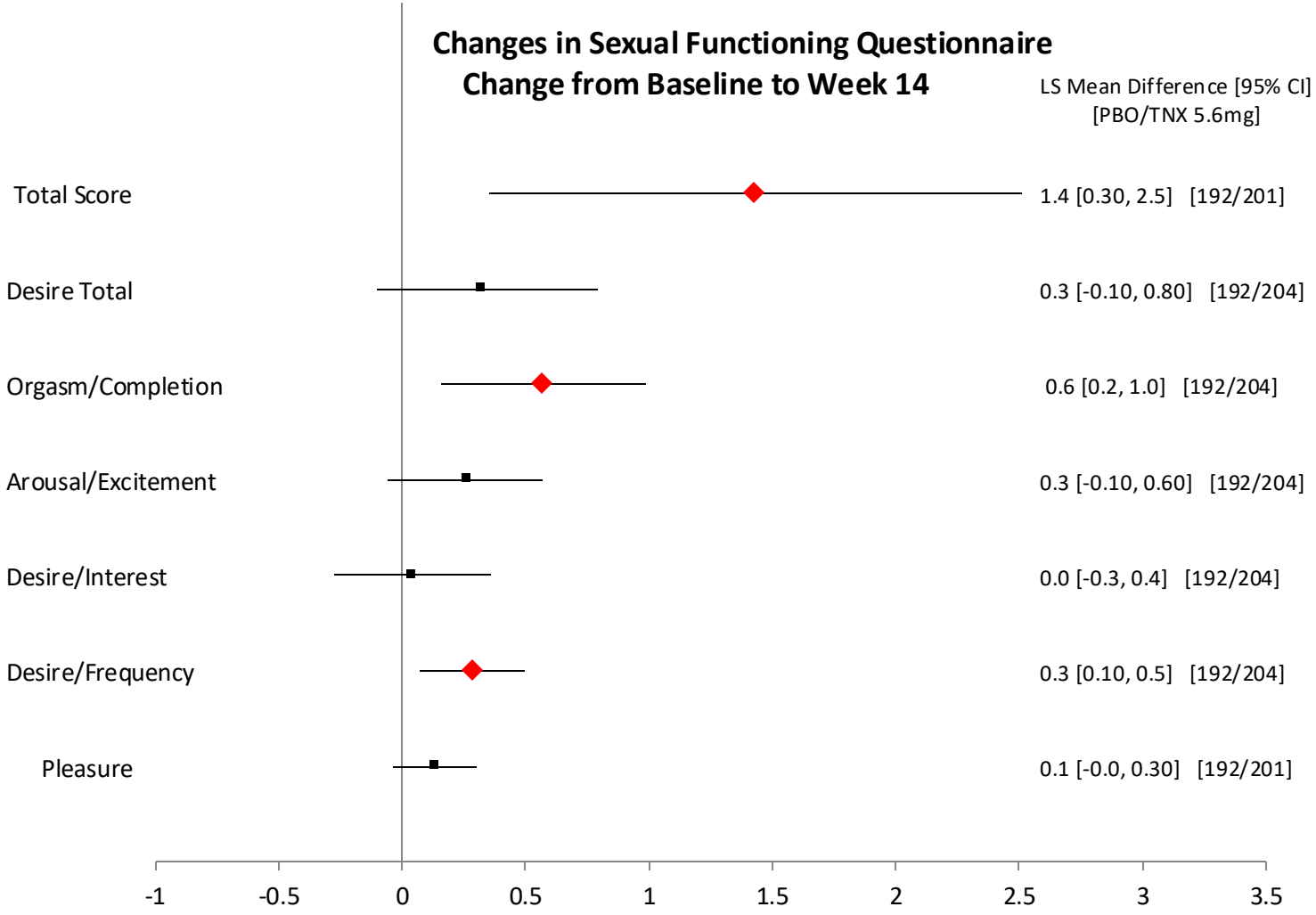
RESILIENT: CSFQ-14 Females

Pre-specified exploratory endpoint



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

RESILIENT Study

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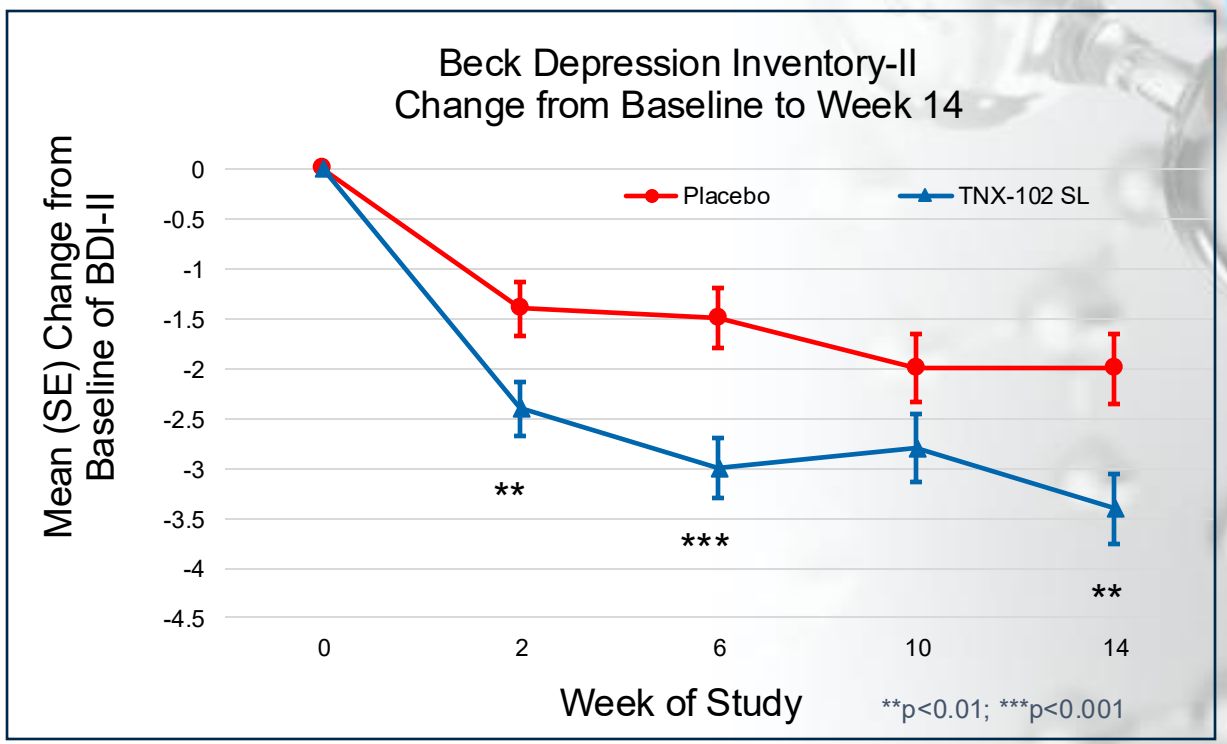
RESILIENT: Beck Depression Inventory-II
Pre-specified Exploratory Endpoint

	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

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.

RESILIENT Study

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RESILIENT Summary of Efficacy

RESILIENT Study

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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

Conclusion: TNX-102 SL 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”

RESILIENT Study Safety Findings

RESILIENT Subject Disposition

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

RESILIENT Prior Medication Use

RESILIENT Study

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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

TONIX PHARMACEUTICALS

RESILIENT Washout Medications

RESILIENT Study

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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%)
Amphetamine (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

TONIX PHARMACEUTICALS

RESILIENT Safety Summary

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

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

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

RESILIENT Safety

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%)

TONIX PHARMACEUTICALS

RESILIENT Analysis by Sensory Adverse Events (AEs)
TNX-102 SL group divided for presence/absence of 3 sensory AEs

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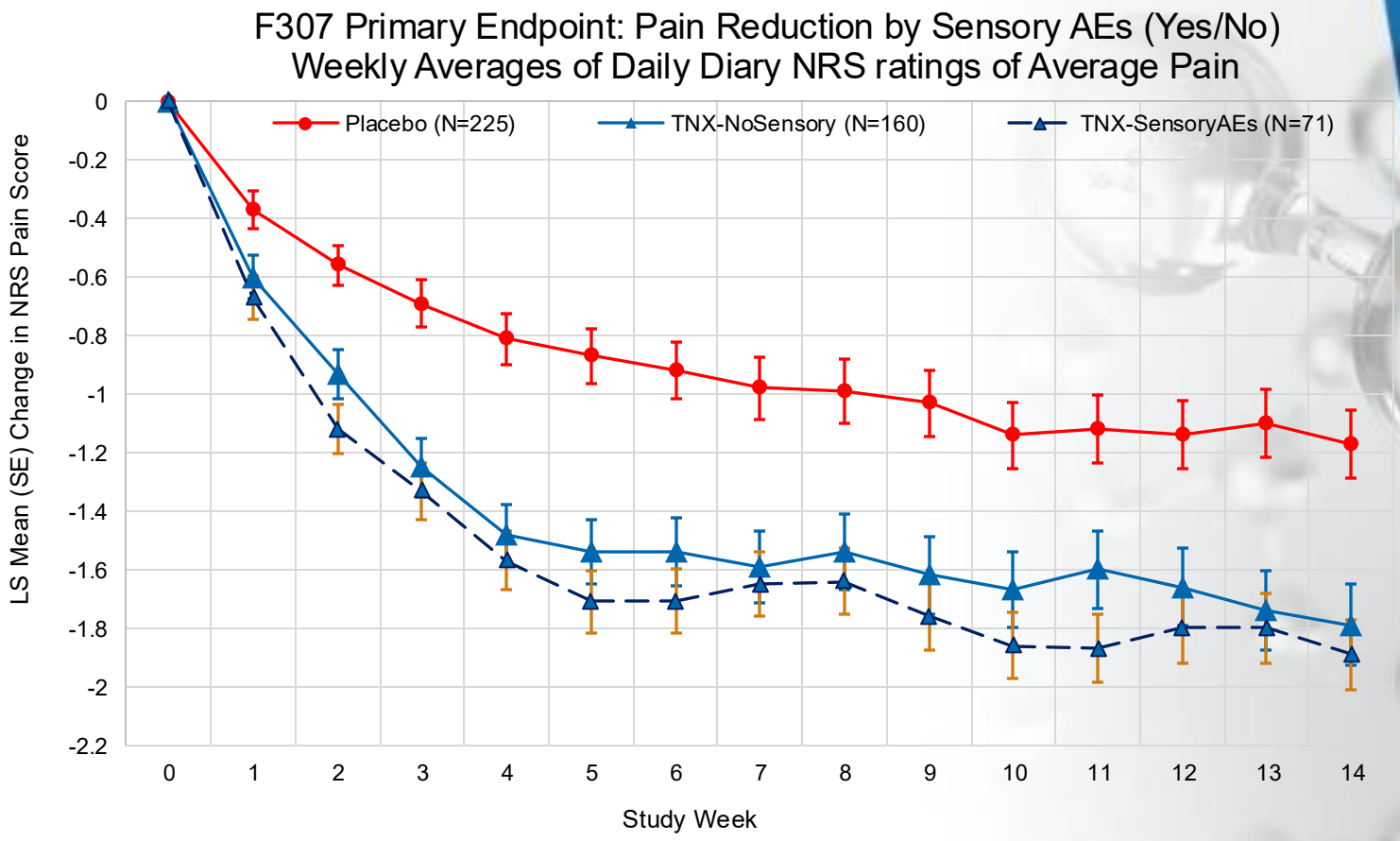
- AEs of oral numbness, oral tingling, and bitter aftertaste named ‘Sensory AEs’*
- Graph shows negligible advantage for presence of sensory AEs
- At Week 14:
  - TNX-NoSensory v Placebo
    - Diff in LS Mean (SE): -0.62 (0.179)
    - p<0.001
  - TNX-SensoryAEs v Placebo
    - Diff in LS Mean (SE): -0.72 (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

TONIX PHARMACEUTICALS

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

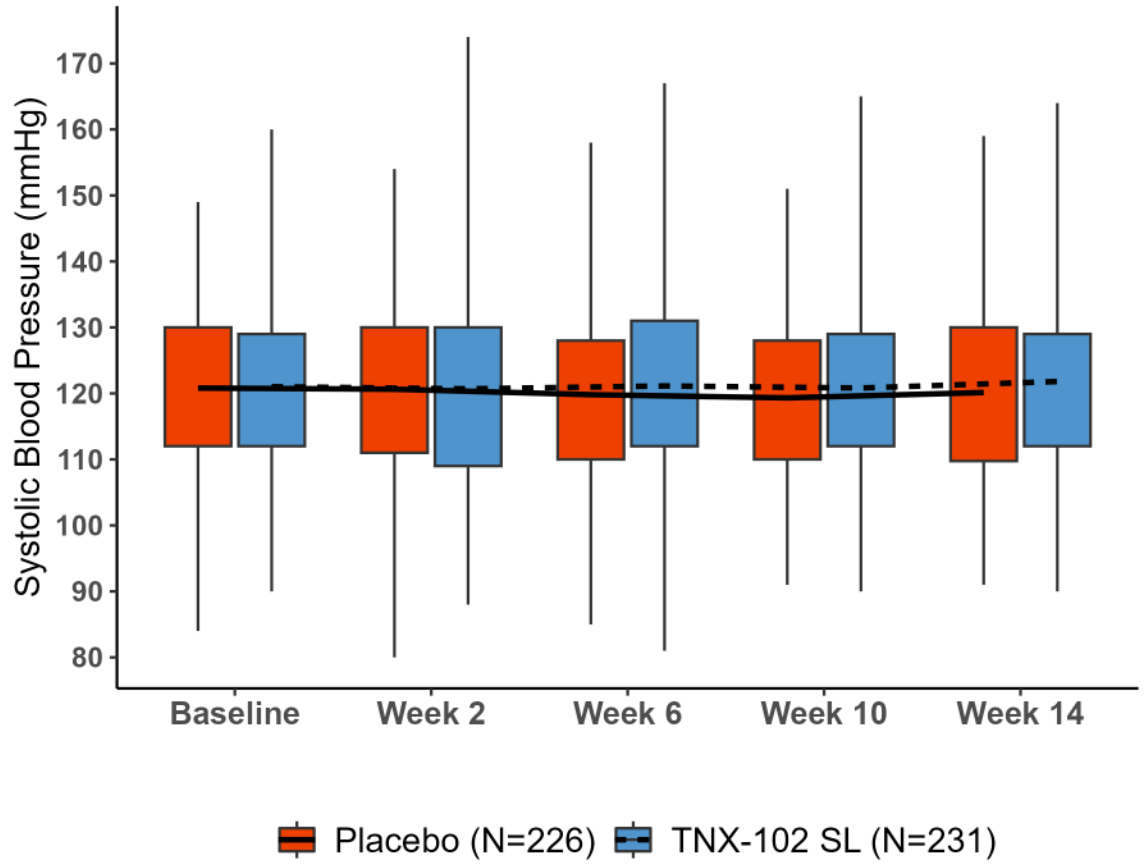
*No clinically meaningful difference in mean **weight** between treatment groups*

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.02 (2.940) kg

Placebo = 0.20 (2.932) kg

RESILIENT Systolic blood pressure
Safety Measure



No clinically meaningful difference in mean systolic blood pressure between groups

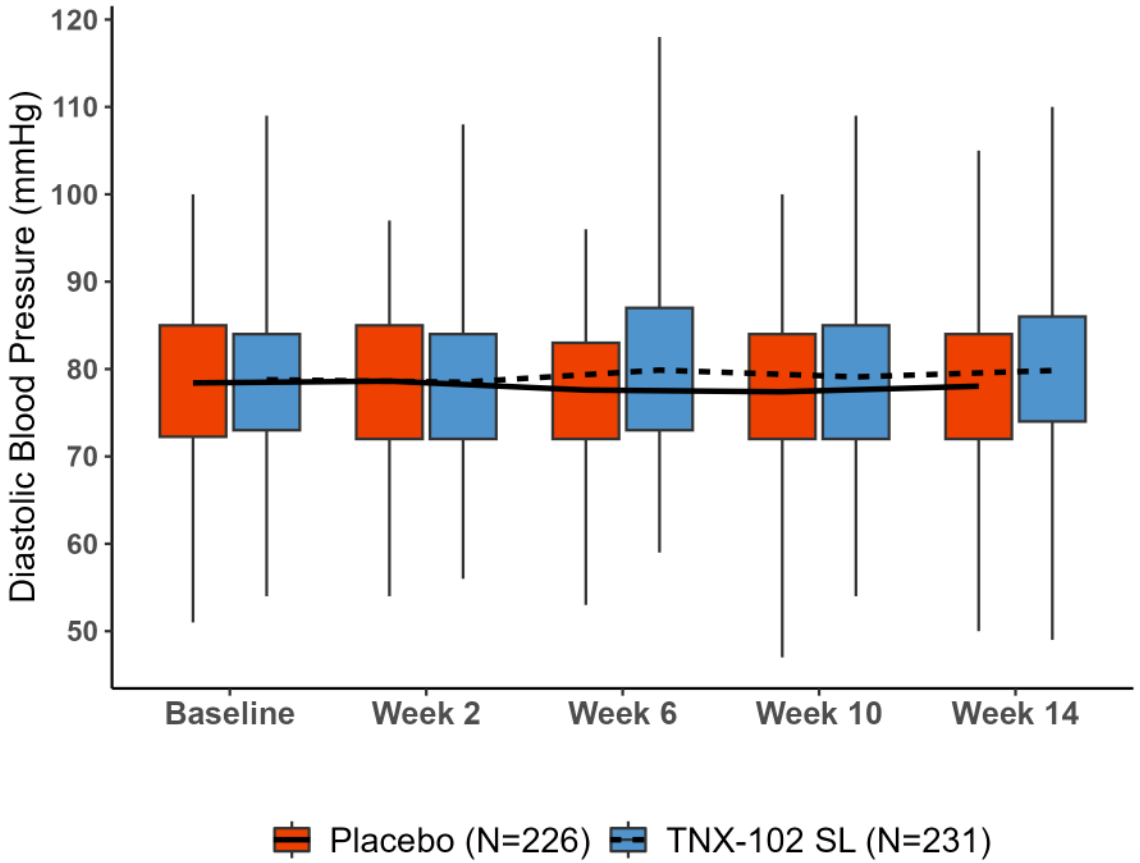
Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.7 (12.38) mmHg

Placebo = 0.5 (10.42) mmHg

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

RESILIENT Diastolic blood pressure
Safety Measure



No clinically meaningful difference in mean diastolic blood pressure between groups

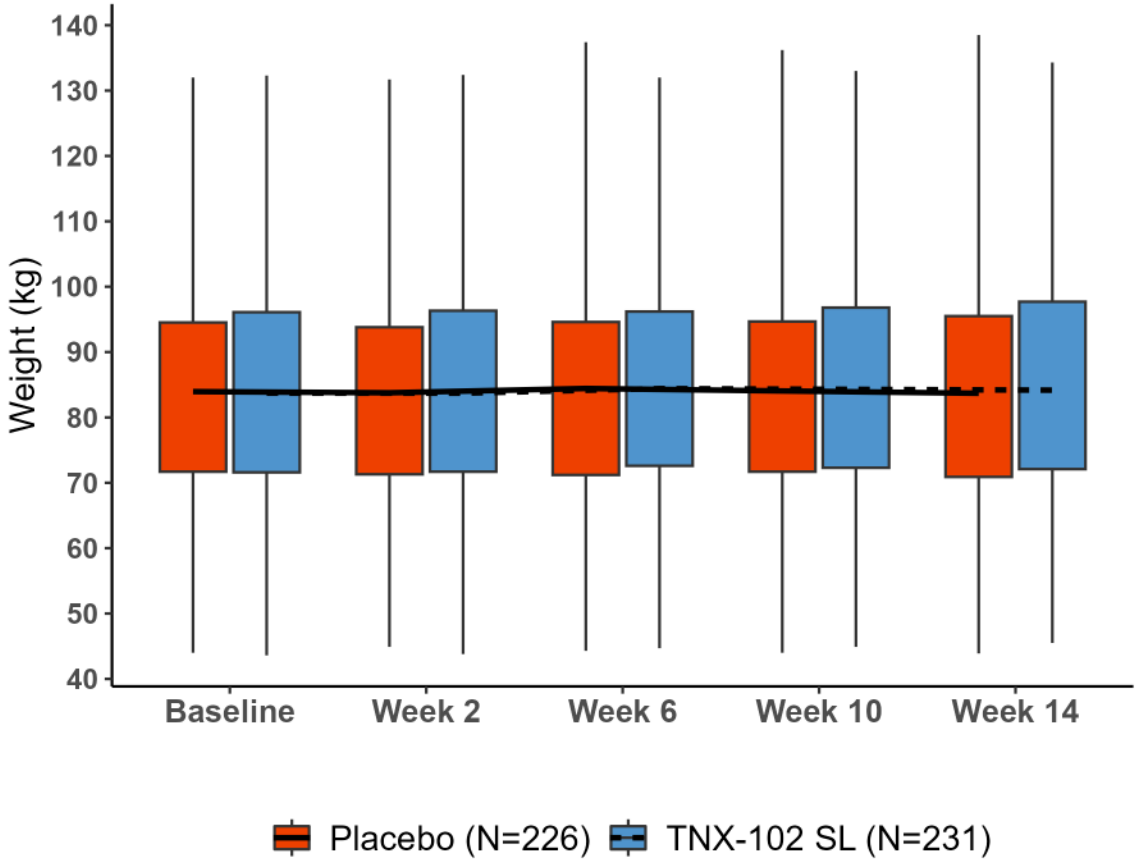
Week 14 mean (SD) change from baseline:

TNX-102 SL = 1.1 (8.60) mmHg

Placebo = 0.2 (8.22) mmHg

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

RESILIENT Weight
Safety Measure



No clinically meaningful difference in mean weight between treatment groups

Week 14 mean (SD) change from baseline:

TNX-102 SL = 0.02 (2.940) kg

Placebo = 0.20 (2.932) kg

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

CNS PORTFOLIO

RALLY Results

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.

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

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

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

* MMRM with MI was the pre-specified primary analysis

**MMRM without MI was a pre-specified analysis

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

TNX-102 SL*
Cyclobenzaprine HCl

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

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

*TNX-102 SL is an investigational drug and has not been approved for any indication.
**5mg once-daily at bedtime.

Indications with Active Programs

Fibromyalgia

Status: Two statistically significant Phase 3 studies completed; FDA granted Fast Track Designation

- First pivotal Phase 3 study (RELIEF) completed
- Second Phase 3 study (RALLY) missed primary endpoint
- Confirmatory pivotal Phase 3 study (RESILIENT) completed
- Submitted New Drug Application (NDA) to FDA in October 2024
- FDA decision on market authorization expected August 15, 2025

Next Steps: Support FDA review; pre-launch activities

Acute Stress Reaction/ Acute Stress Disorder

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

Next Steps: Expect to start Phase 2 in 1H 2025

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TNX-102 SL for Other Indications In Development: *Acute Stress Disorder*

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

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

Large unmet need:

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

Current standard of care:

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

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

TNX-102 SL for ASR/ASD: Program Status

Status: Expect to start investigator-initiated Phase 2 in 1H 2025

Investigator-initiated 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 generally well-tolerated and may promote recovery from PTSD via a pharmacodynamic facilitation of sleep-dependent emotional memory processing

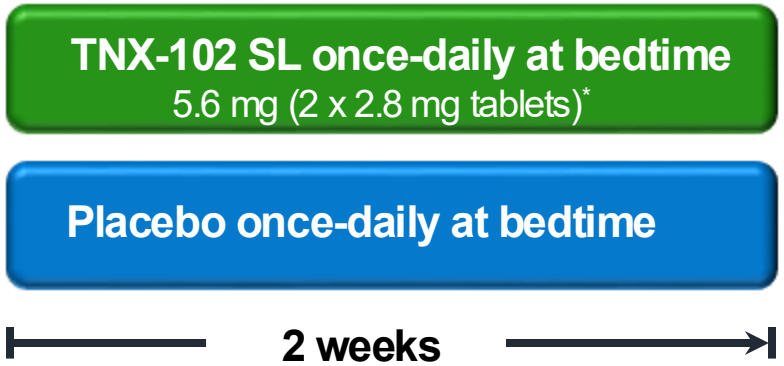
TNX-102 SL for ASR/ASD: Phase 2 OASIS Study Design

General study characteristics:

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

Objective:

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



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

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

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

Fibromyalgia and Long-COVID

Significant Overlap between Fibromyalgia and Long-COVID

National Institutes of Health (NIH)-sponsored RECOVER study found many Long COVID patients suffer from pain at multiple sites[1]

- Suggests that many Long-COVID patients may meet the diagnostic criteria for fibromyalgia

Tonix has previously presented its analysis of real-world evidence from the TriNetX claims database suggesting that ***over 40% of Long COVID patients present with a constellation of symptoms that overlap with fibromyalgia***[2,3]

[1]Thaweethai T, et al. *JAMA*. 2023 329(22):1934-1946.
[2]Feb 22, 2023 Tonix Pharmaceuticals Press Release. URL: https://ir.tonixpharma.com/news-events/press-releases/detail/1369/tonix-pharmaceuticals-describes-emerging-research-on-the
[3]September 21, 2022, Tonix Pharmaceuticals Poster at the IASP, "Retrospective observational database study of patients with Long COVID with multi-site pain, fatigue and insomnia". URL: www.tonixpharma.com/wp-content/uploads/2022/09/Retrospective-Observational-Database-Study-of-Patients-with-Long-COVID-with-Multi-Site-Pain-Fatigue-and-Insomnia_A-Real-World-Analysis-of-Symptomatology-and-Opioid-Use.pdf

NASEM Definition of Long-COVID

- In June 2024, the US National Academies of Sciences, Engineering and Medicine (NASEM) described **fibromyalgia as a 'diagnosable condition' in people suffering from Long COVID**[1]
- This definition provides guidance to government, healthcare professionals and industry that fibromyalgia can arise after infection with the SARS-CoV-2 virus and can be diagnosed in Long COVID patients

Fibromyalgia prevalence prior to COVID-19 pandemic: >10M adults in the US[2]

Long-COVID prevalence: 5.3% or ~14M adults in the US[3]

Tonix believes that diagnosing fibromyalgia in Long COVID patients will increase the potential market for TNX-102 SL as compared to market estimates from before the COVID-19 pandemic

[1]U.S. National Academies of Sciences, Engineering, and Medicine. 2024. *A Long COVID Definition: A chronic, systemic disease state with profound consequences.* Washington, DC: The National Academies Press. https://doi.org/10.17226/27768. http://www.nationalacademies.org/long-covid-definition.
[2]Vincent A, et al. Arthritis Care Res (Hoboken). 2013 65(5):786-92. doi: 10.1002
[3]National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID. Generated interactively: July 22, 2024 from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

NASEM Language Highlighted by Senate Labor-HHS Appropriations Subcommittee (August 1, 2024)

"Long COVID Treatments.—The Committee remains concerned about the economic and overall health impact that Long COVID inflicts on the Nation. It is currently estimated that between 6 percent and 19 percent of those infected with SARS–CoV–2 go on to develop Long COVID, resulting in up to 20 million Americans suffering from this set of debilitating chronic symptoms. Long COVID is characterized by a wide range of symptoms including severe fatigue, non-restorative sleep, cognitive dysfunction, and widespread pain. Further, it resembles other post-acute infection syndromes [PAISs], such as fibromyalgia, myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS] and related conditions, known as 146 chronic overlapping pain conditions [COPCs] or nociplastic syndromes. While the Committee is pleased that NIH's HEAL and RECOVER initiatives plan to target some specific symptoms of Long COVID, the Committee is concerned that NIH has not expanded the evaluation of treatments to address many common symptoms associated with Long COVID either individually or that present as syndromes which are combinations of symptoms. Furthermore, NIH's research program has defined Long COVID narrowly, excluding many of the common symptoms plaguing Long COVID sufferers. In June 2024, NASEM released the 2024 NASEM Long COVID Definition, which encompasses extensive lists of the symptoms and diagnosable conditions that current science attributes to Long COVID. The Committee urges NIH to rebalance its research program to prioritize clinical trials in pursuit of effective treatments and to use the NASEM Long COVID definition to guide its choice of symptoms and conditions to be address by the candidate treatments. Such trials should target key symptoms and symptom complexes associated with Long COVID including widespread pain, fatigue, non-restorative sleep, brain fog, dizziness, post-exertional malaise [PEM], postural orthostatic tachycardia syndrome [POTS] and loss of taste and smell. Further, the Committee urges NIH to prioritize the support of clinical trials evaluating therapies for Long COVID including therapies that have demonstrated efficacy in treating COPCs or nociplastic syndromes that overlap with Long COVID."

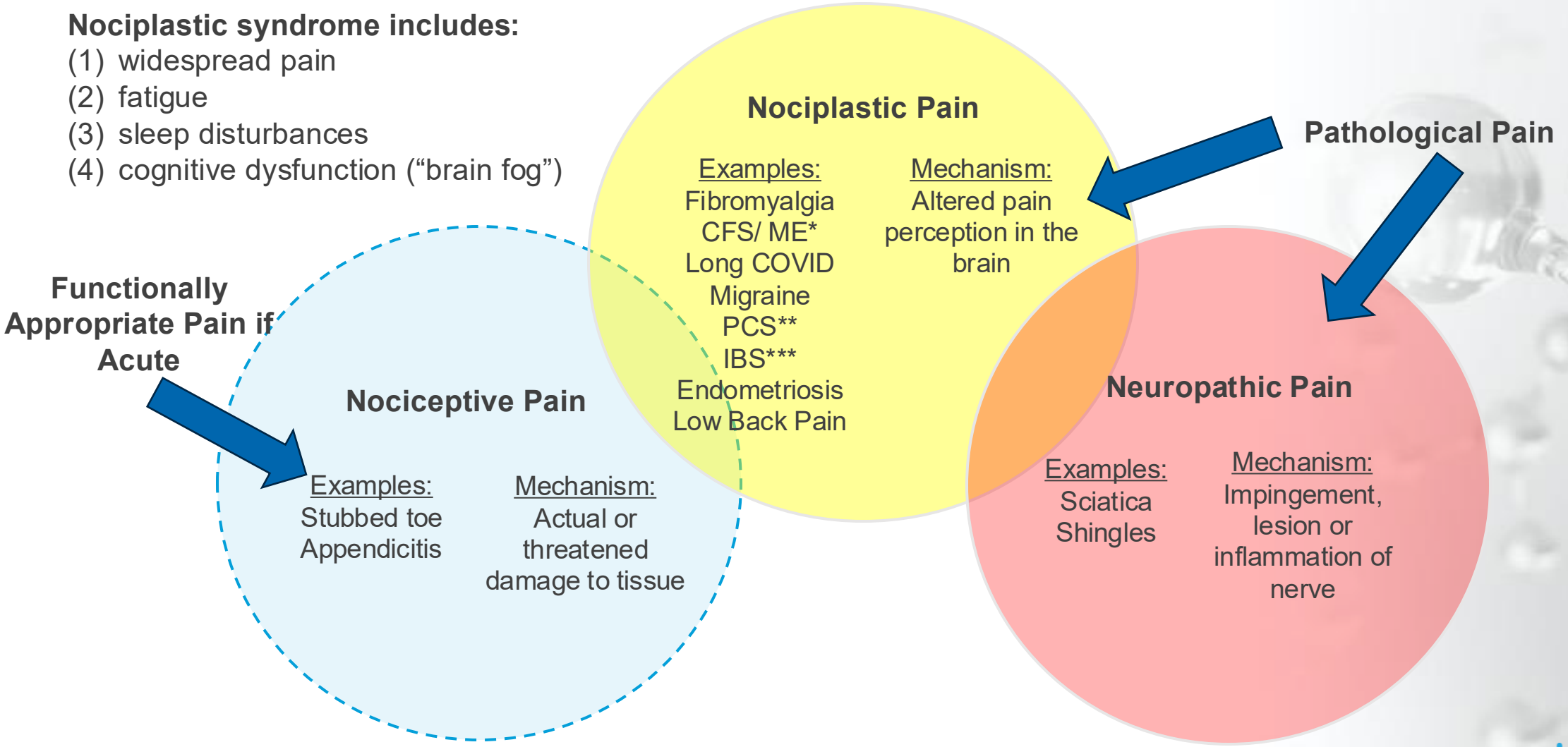
- Senate Appropriations Committee report on FY25 Labor, Health, and Human Services Appropriations Act includes language on Long COVID, fibromyalgia and nociplastic syndromes[1]

[1]FY25 Labor-HHS Senate Report, p145-146. Accessed Aug 7, 2024: https://www.appropriations.senate.gov/download/fy25-lhhs-senate-report

About Fibromyalgia and Nociplastic Pain

The Third Primary Type of Pain: Nociplastic Pain[1-5]

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.
[2]Fitzcharles MA, et al. *Lancet* 2021;397:2098-110
[3]Kaplan CM, et al. *Nat Rev Neurol.* 2024 20(6):347-363..
[4]Clauw DJ. *Ann Rheum Dis.* 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.
[5]Kureshi S et al. *Healthcare* (Basel) 2024 12(3): 289.

*ME/CFS = chronic fatigue syndrome / myalgic encephalomyelitis
**PCS = post concussive syndrome.
**IBD – irritable bowel syndrome

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Fibromyalgia is Believed to Result from Chronic Pain or Prior Stress Experiences[1-2]

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:

Acute pain
- *e.g.*, post-operative pain

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

[1]Kaplan CM, et al. *Nat Rev Neurol.* 2024 20(6):347-363..
[2]Clauw DJ. *Ann Rheum Dis.* 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.

Common Chronic Conditions are a Challenge for Pharma

Fibromyalgia is a common chronic disease[1-3]

- 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)
[2]Kaplan CM, et al. *Nat Rev Neurol.* 2024 20(6):347-363..
[3]Clauw DJ. *Ann Rheum Dis.* 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.

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

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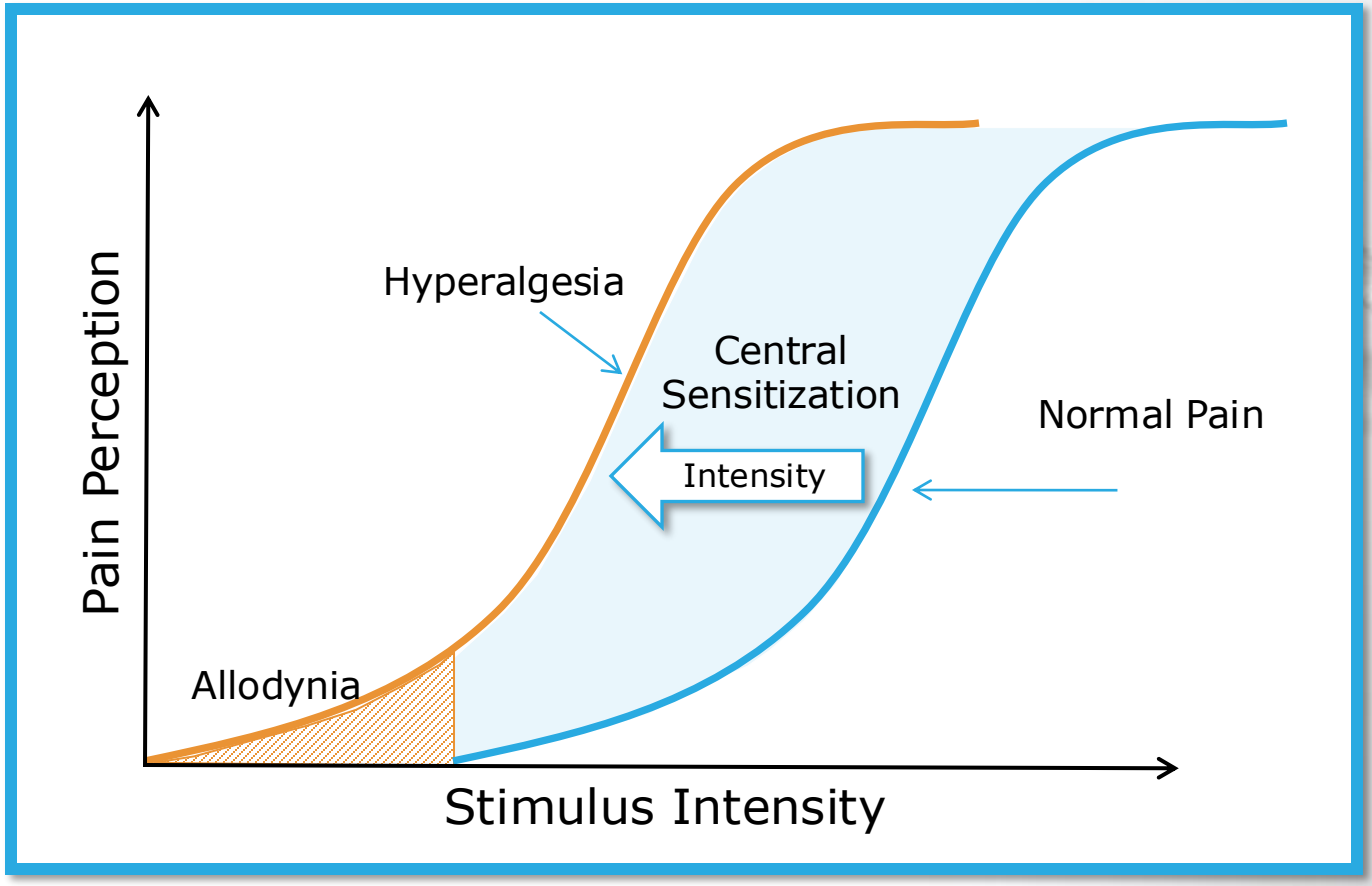
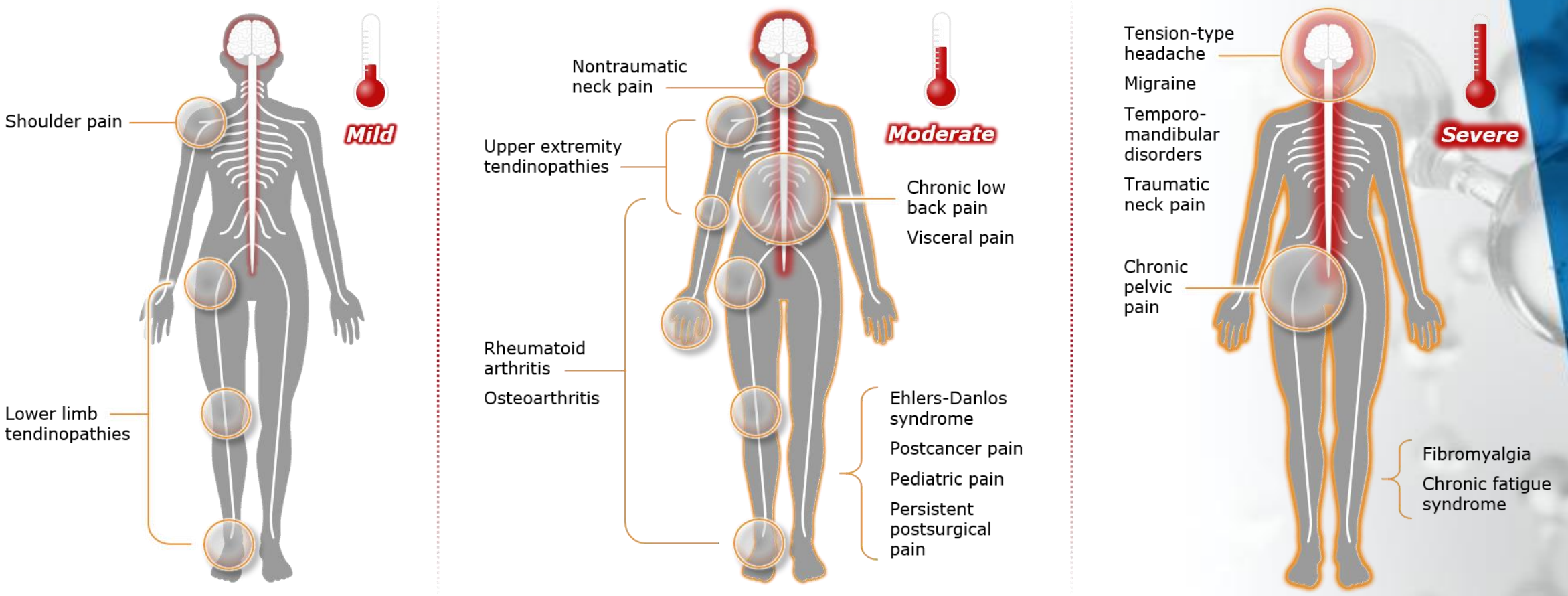
Central Sensitization (CS)
A Feature of Many Nociplastic Pain Syndromes

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



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

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



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

Milestones and Summary

Milestones: Recently Completed and Upcoming

TNX-102 SL for the Management of Fibromyalgia Milestones

☑ 4th Quarter 2023	Statistically significant topline results of Phase 3 RESILIENT study – 2nd statistically significant Phase 2 trial
☑ 2nd Quarter 2024	Type B CMC and clinical pre-NDA meetings with FDA
☑ 3rd Quarter 2024	FDA granted Fast Track Designation
☑ October 2024	Submitted NDA to FDA for TNX-102 SL for fibromyalgia in October 2024
☑ December 2024	FDA assigned a PDUFA* goal date of August 15, 2025
☑ March 2025	FDA determined that no Advisory Committee Meeting will be required
❑ August 15, 2025	FDA decision expected on marketing authorization

*PDUFA = Prescription Drug User Fee Act

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THANK YOU

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.

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. 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.

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. 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.