

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

FORM 8-K

CURRENT REPORT

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

Date of report (date of earliest event reported): **March 24, 2025**

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada
(State or Other Jurisdiction
of Incorporation)

001-36019
(Commission
File Number)

26-1434750
(IRS Employer
Identification No.)

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

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

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

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

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

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

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

Emerging growth company ☐

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

Item 7.01 Regulation FD Disclosure.

On March 24, 2025, Tonix Pharmaceuticals Holding Corp. (the "Company") announced that the U.S. Food and Drug Administration ("FDA") will not require an Advisory Committee meeting to discuss the Company's New Drug Application ("NDA") for its TNX-102 SL product candidate for the management of fibromyalgia. A copy of the press release that discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference.

The Company updated its investor presentation, which is used to conduct meetings with investors, stockholders and analysts and at investor conferences, and which the Company intends to place on its website, which may contain nonpublic information. A copy of the presentation is filed as Exhibit 99.02 hereto and incorporated herein by reference.

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

Item 8.01

On March 24, 2025, the Company announced that the FDA will not require an Advisory Committee meeting to discuss the NDA for TNX-102 SL for the management of fibromyalgia.

Forward-Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and

markets in which we operate and management’s current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, “expect,” “anticipate,” “intend,” “plan,” “believe,” “estimate,” “potential,” “predict,” “project,” “should,” “would” and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company’s filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)	Exhibit	Description.
	No.	
	<u>99.01</u>	<u>Press Release of the Company, dated March 24, 2025</u>
	<u>99.02</u>	<u>Corporate Presentation by the Company for March 2025</u>
	104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

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

TONIX PHARMACEUTICALS HOLDING CORP.

Date: March 24, 2025

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

Tonix Pharmaceuticals Announces that FDA Will Not Require an Advisory Committee Meeting to Discuss New Drug Application for TNX-102 SL for the Management of Fibromyalgia

On track for August 15, 2025 FDA PDUFA goal date

TNX-102 SL is a non-opioid analgesic; if approved, TNX-102 SL would become the first new drug for treating fibromyalgia in more than 15 years

Commercial planning for TNX-102 SL underway for launch in the fourth quarter of 2025

CHATHAM, N.J., March 24, 2025 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a fully-integrated biopharmaceutical company with marketed products and a pipeline of development candidates, today announced that the U.S. Food and Drug Administration (FDA) will not require an Advisory Committee meeting to discuss the Company's New Drug Application (NDA) for TNX-102 SL for the management of fibromyalgia. If approved, TNX-102 SL (cyclobenzaprine HCl sublingual tablets) would be the first new treatment option for fibromyalgia patients in 15 years.

"We are pleased that FDA will not require an advisory committee meeting as part of the regulatory review process for TNX-102 SL," said Seth Lederman, M.D., President, and Chief Executive Officer of Tonix Pharmaceuticals. "We believe that TNX-102 SL has the potential to be the first member of a new class of medicines for the management of fibromyalgia, a debilitating condition affecting over 10 million adults in the U.S. We believe we are well positioned to launch TNX-102 SL for the management of fibromyalgia in the fourth quarter of 2025 if approved by the FDA."

The FDA previously granted Fast Track designation to TNX-102 SL for the management of fibromyalgia in 2024, a designation intended to expedite FDA review of important new drugs to treat serious conditions and fill an unmet medical need.

About Fibromyalgia

Fibromyalgia is a common chronic pain disorder that is understood to result from amplified sensory and pain signaling within the central nervous system, called central sensitization. Brain imaging studies have localized the functional disorder to the brain's insula and anterior cingulate cortex. Fibromyalgia afflicts more than 10 million adults in the U.S., the majority of whom are women. Symptoms of fibromyalgia include chronic widespread pain, non-restorative sleep, fatigue, and brain fog (or cognitive dysfunction). Other associated symptoms include mood disturbances, including depression, anxiety, headaches and abdominal pain or cramps. Individuals suffering from fibromyalgia often struggle with their daily activities, have impaired quality of life, and frequently are disabled. Physicians and patients report common dissatisfaction with currently marketed products. Fibromyalgia is now recognized as the prototypic nociplastic syndrome and as a chronic overlapping pain condition (COPC)¹⁻³. Nociplastic pain is the third primary type of pain in addition to nociceptive pain and neuropathic pain. Many patients present with pain syndromes that are mixtures of the three primary types of pain. Nociplastic syndromes are associated with central and peripheral sensitization. Fibromyalgia can occur without any identifiable precipitating event. However, many fibromyalgia cases follow one or more precipitating event(s) including: post-operative pain, acute or chronic nociceptive or neuropathic pain states; recovery from an infectious illness; a cancer diagnosis or cancer treatment; a metabolic or endocrine stress; or a traumatic event. In the cases of recovery from an infectious illness, fibromyalgia is considered an Infection-Associated Chronic Condition. In addition to fibromyalgia cases associated with other conditions or stressors, the U.S. National Academies of Sciences, Engineering, and Medicine, has concluded that fibromyalgia is a diagnosable condition that can occur after recovery from COVID-19 in the context of Long COVID. Fibromyalgia is also recognized as a Chronic Overlapping Pain Condition, which is a group of related conditions that include chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), irritable bowel syndrome, endometriosis, low back pain, post-concussive syndrome (also known as mild traumatic brain injury), chronic Lyme Disease, chronic diabetic neuropathy and chronic post-herpetic neuralgia.

About TNX-102 SL

TNX-102 SL is a centrally acting, non-opioid investigational drug, designed for chronic use. The tablet is a patented sublingual formulation of cyclobenzaprine hydrochloride developed for bedtime dosing for the management of fibromyalgia. Cyclobenzaprine potently binds and acts as an antagonist at four different post-synaptic neuroreceptor subtypes: serotonergic-5-HT_{2A}, adrenergic- α_1 , histaminergic-H₁, and muscarinic-M1-cholinergic receptors. Together, these interactions are believed to target the non-restorative sleep characteristic of fibromyalgia identified by Professor Harvey Moldofsky in 1975. Cyclobenzaprine is not associated with risk of addiction or dependence. The TNX-102 SL tablet is based on a eutectic formulation of cyclobenzaprine HCl and mannitol that provides a stable product which dissolves rapidly and delivers cyclobenzaprine by the transmucosal route efficiently into the bloodstream. The eutectic protects cyclobenzaprine HCl from interacting with the basifying agent that is also part of the formulation and required for efficient transmucosal absorption. 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. The formulation of TNX-102 SL was designed specifically for sublingual administration and transmucosal absorption for bedtime dosing to target disturbed sleep, while reducing the risk of daytime somnolence. Clinical pharmacokinetic studies indicated that relative to oral cyclobenzaprine, TNX-102 SL results in higher levels of exposure during the first 2 hours after dosing and in decreased levels of the long-lived active metabolite, norcyclobenzaprine in both single dose and multiple dose studies, consistent with bypassing first pass hepatic metabolism. At steady state after 20 days of dosing TNX-102 SL, the dynamic peak level of cyclobenzaprine is higher than the background level of norcyclobenzaprine. In contrast, after 20 days of dosing oral cyclobenzaprine, the simulated peak level of cyclobenzaprine is lower than the simulated background level of norcyclobenzaprine.

¹Fitzcharles MA, et al. *Lancet*. 2021;397:2098-110

²Clauw DJ. *Ann Rheum Dis*. Published Online First: 2024

³Kaplan CM, et al. *Nat Rev Neurol*. 2024;20, 347-363

an NDA was submitted based on two statistically significant Phase 3 studies for the management of fibromyalgia and for which a PDUFA (Prescription Drug User Fee act) goal date of August 15, 2025 has been assigned for a decision on marketing authorization. The FDA has also granted Fast Track designation to TNX-102 SL for the management of fibromyalgia. TNX-102 SL is also being developed to treat acute stress reaction and acute stress disorder under a Physician-Initiated IND at the University of North Carolina in the OASIS study funded by the U.S. Department of Defense (DoD). Tonix's CNS portfolio includes TNX-1300 (cocaine esterase), a biologic in Phase 2 development designed to treat cocaine intoxication that has FDA Breakthrough Therapy designation, and its development is supported by a grant from the National Institute on Drug Abuse. Tonix's immunology development portfolio consists of biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is an Fc-modified humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. TNX-1500 has completed a positive Phase I trial. Tonix's infectious disease portfolio includes TNX-801, a vaccine in development for mpox and smallpox, as well as TNX-4200 for which Tonix has a contract with the U.S. DoD's Defense Threat Reduction Agency (DTRA) for up to \$34 million over five years. TNX-4200 is a small molecule broad-spectrum antiviral agent targeting CD45 for the prevention or treatment of infections to improve the medical readiness of military personnel in biological threat environments. Tonix owns and operates a state-of-the art infectious disease research facility in Frederick, Md. Tonix Medicines, our commercial subsidiary, markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg for the treatment of acute migraine with or without aura in adults.

* Tonix's product development candidates are investigational new drugs or biologics; their efficacy and safety have not been established and have not been approved for any indication.

Zembrace SymTouch and Tosymra are registered trademarks of Tonix Medicines. All other marks are property of their respective owners.

This press release and further information about Tonix can be found at www.tonixpharma.com.

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of 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," "expect," 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, risks related to the 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. Tonix does not undertake an obligation to update or revise any forward-looking statement. 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 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. The information set forth herein speaks only as of the date thereof.

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Indication and Usage

Zembrace® SymTouch® (sumatriptan succinate) injection (Zembrace) and Tosymra® (sumatriptan) nasal spray are prescription medicines used to treat acute migraine headaches with or without aura in adults who have been diagnosed with migraine.

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

Important Safety Information

Zembrace and Tosymra 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 and Tosymra are 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 or 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
- 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, or dihydroergotamine. Ask your provider for a list of these medicines if you are not sure.
- 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 or Tosymra

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

Zembrace and 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.

Zembrace and 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 Zembrace or 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.
 - 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 and Tosymra include: pain and redness at injection site (Zembrace only); 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; application site (nasal) reactions (Tosymra only) and throat irritation (Tosymra only).

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 and Tosymra. For more information, ask your provider.

This is the most important information to know about Zembrace and Tosymra but is not comprehensive. For more information, talk to your provider and read the Patient Information and Instructions for Use. You can also visit <https://www.tonixpharma.com> or call 1-888-869-7633.

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



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.

Who We Are

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

...Transforming therapies for pain management and vaccines for public health challenges...

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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 1H25			
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 1 st 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

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

➤ **TNX-102 SL¹ for Fibromyalgia: FDA Decision on marketing authorization expected August 15, 2025**

- Granted FDA Fast Track Designation
- Two Phase 3 trials completed with statistical significance on primary endpoint
- Potential product launch in 2025

➤ **Marketed Products**

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

➤ **Pipeline¹**

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

➤ **Strategic Partnerships**

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

➤ **Internal Capabilities**

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

¹All 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.

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**CNS:
Key Development
Candidates**

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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-HT_{2A}, α 1-adrenergic, histamine H₁)
 - More selective for norepinephrine transporter



CNS PORTFOLIO

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

- **Activity**

- First pivotal Phase 3 study (*RELIEF*) reported – December 2020¹
 - 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%

¹Lederman 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, 2025¹**
 - December 2024
- **FDA guided that no Advisory Committee will be required for this NDA**
 - March 2025

Next Milestone:

FDA decision on marketing authorization expected August 15, 2025

¹PDUFA = 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 **nociceptive pain**¹⁻⁴

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



Multisite
pain



Non-Restorative Sleep

Fatigue



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

Fibromyalgia is the prototypic nociceptive syndrome

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

²Fitzcharles MA, et al. *Lancet* 2021;397:2098-110

³Kaplan CM, et al. *Nat Rev Neurol*. 2024 20(6):347-363.

⁴Clauw DJ. *Ann Rheum Dis*. 2024 arid-2023-225327. doi: 10.1136/ard-2023-225327.

⁵Makner W, et al. *J Pain*. 2016; 17(9 Suppl):T93-T107.

⁶The 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 therapy⁵: 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 therapies⁵
- **~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 Rx product since 2009**
- **The treatment objective is to restore functionality and quality of life while avoiding intolerable side effect burden**

¹American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)

²Vincent 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

³Robinson RL, et al. *Pain Med*. 2012 13(10):1366-76. doi: 10.1111; 85% received drug treatment

⁴The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)

⁵EVERSANA primary physician research, May 2024; commissioned by Tonix

⁶EVERSANA analysis of claims database, May 2024; commissioned by Tonix

⁷Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.

⁸Market research by Frost & Sullivan, commissioned by Tonix, 2011

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Poor Sleep and Pain have Bi-directional Reinforcing Effects¹

- 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}



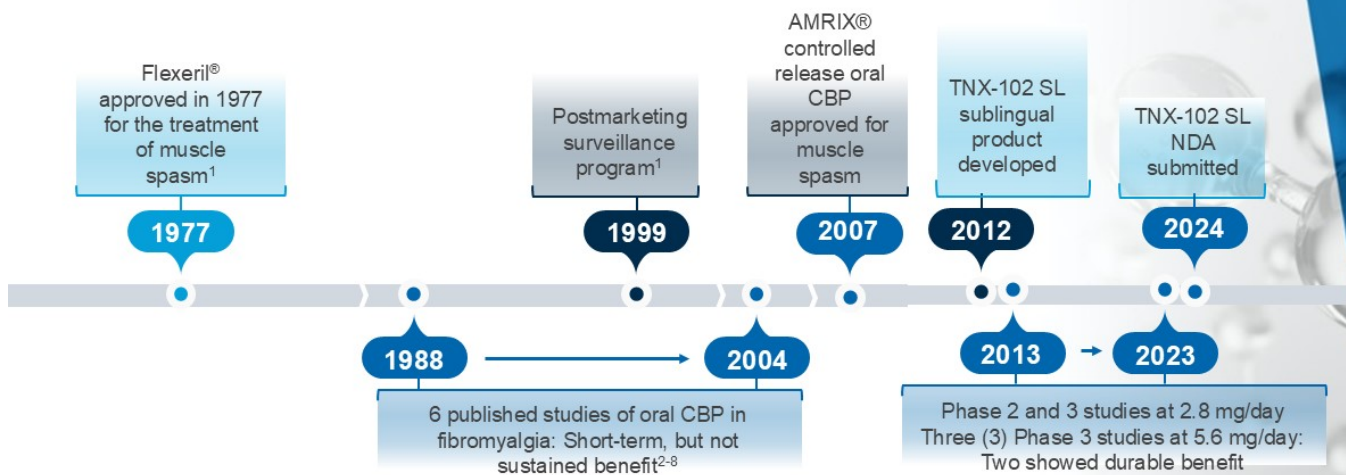
¹Moldofsky H, et al. *J Rheumatol*. 1996;23:529–533.
²Grönblat M, et al. *Clin Rheumatol*. 1993;12(2):186–191

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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 years⁹

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. Toffen JK, et al. *Arthritis Rheum*. 2004; 51:9–13. 9. IMS report 2011 of cyclobenzaprine use in 2009 – Data on File.

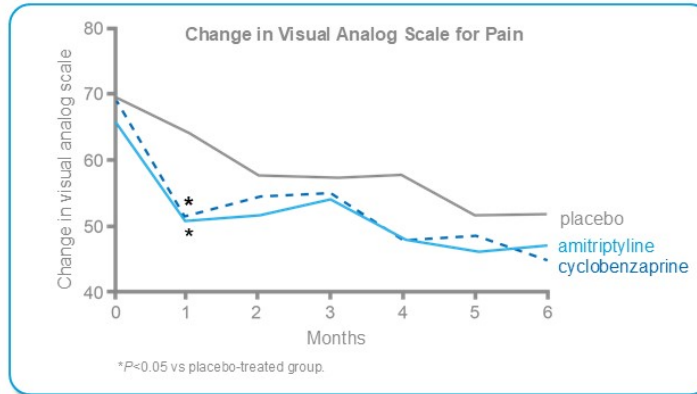
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Neither Cyclobenzaprine nor Amitriptyline Has Durable (>1 Month) Activity on Pain in Fibromyalgia¹



Study

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



Bedtime dosing²

- 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)

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

²Amitriptyline 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.

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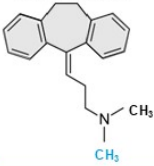
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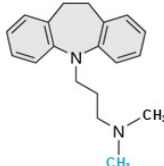
Oral Tertiary Amine Tricyclics (TATs) Are Prodrugs for Active Secondary Amine Tricyclics (SATs) in Depression

Tertiary Amine Tricyclics

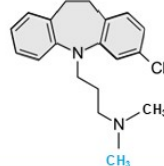
Amitriptyline



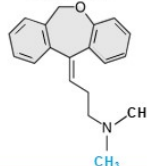
Imipramine



Clomipramine



Doxepin

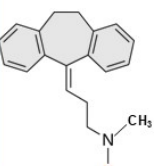


- Dynamic PK profiles with shorter half-lives¹
- **Short-term** utility for bedtime dosing to target nonrestorative sleep at very low dose
- Higher SERT inhibition than NET inhibition^{2,3}

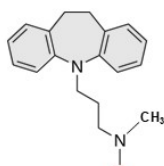
First-pass hepatic metabolism → **CH₃** Demethylation

Secondary Amine Tricyclics

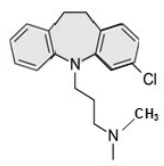
Nortriptyline



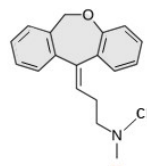
Desipramine



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.

¹Stahl SM. 7th ed. Cambridge University Press; 2020.

²Moraczewski J, et al. StatPearls Publishing; 2025. Updated August 17, 2023. Accessed February 24, 2025. <https://www.ncbi.nlm.nih.gov/books/NBK557791>

³Michell HA, et al. *Biochem Pharmacol*. 2010;79(6):801-809.

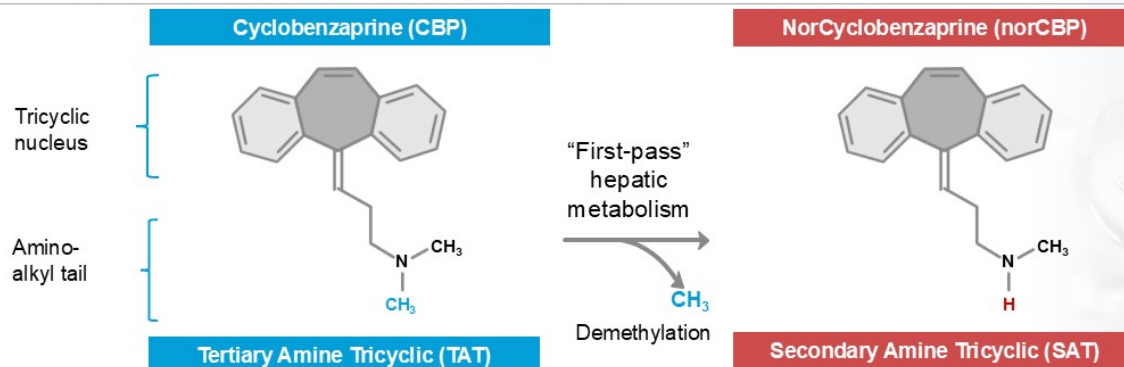
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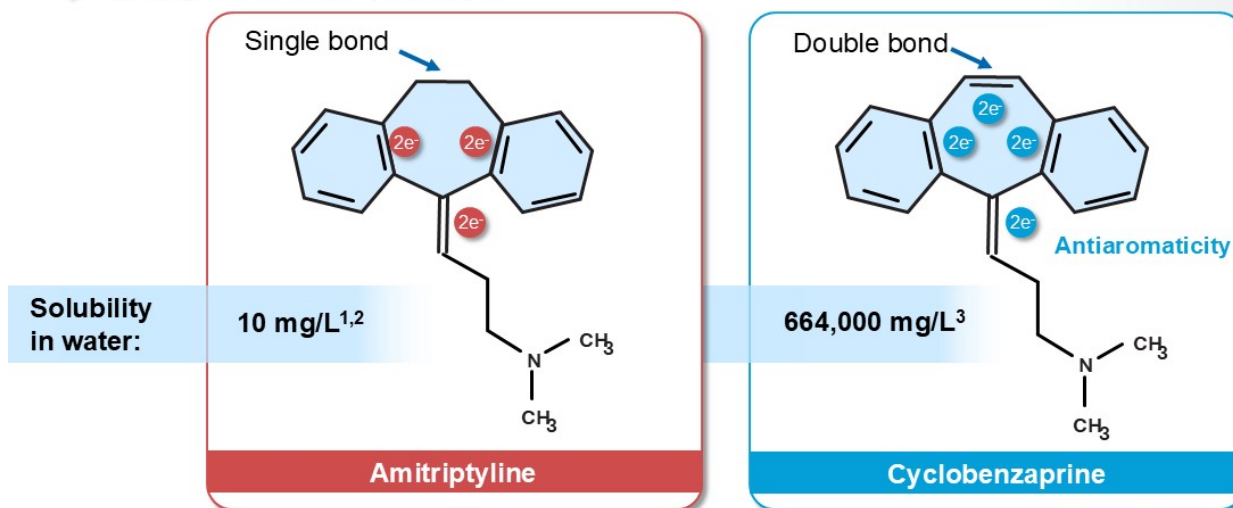
Cyclobenzaprine Is a Tertiary Amine Tricyclic That Was Not Developed as an Antidepressant



- 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

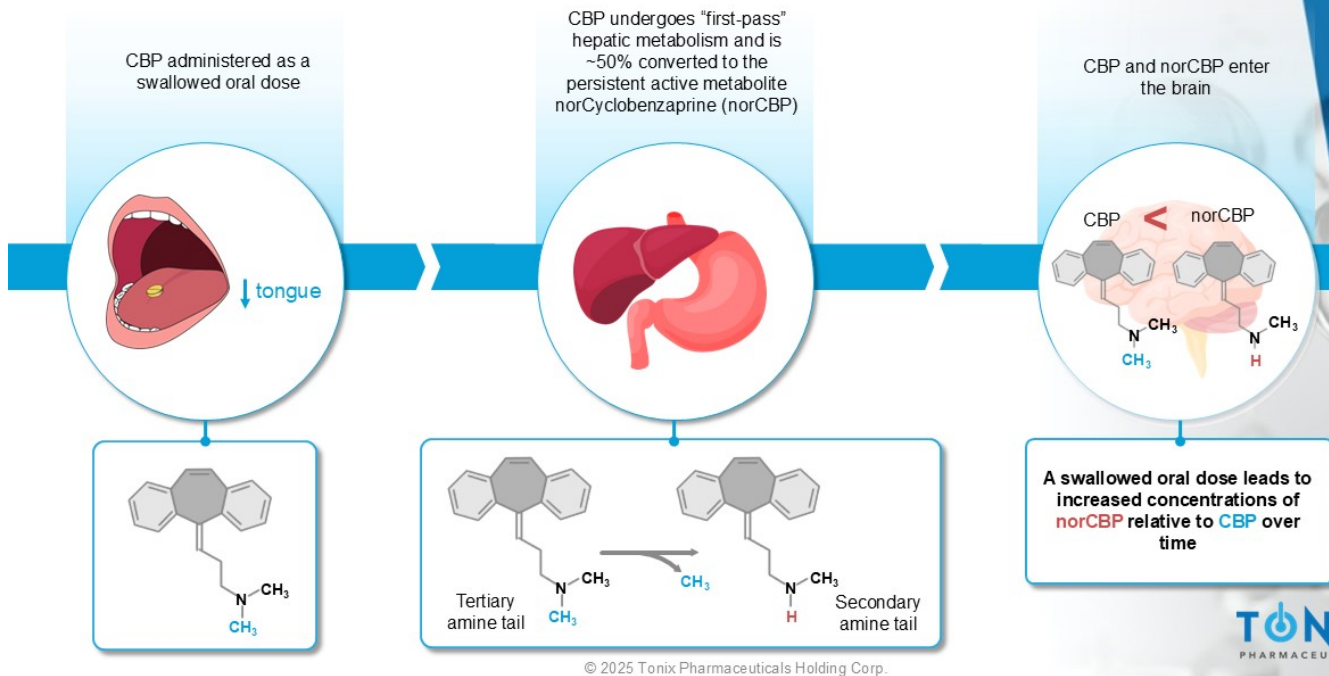


- ▶ Exocyclic double bond in central 7-member ring leads to antiaromaticity in cyclobenzaprine: 4n electron (e⁻) rule

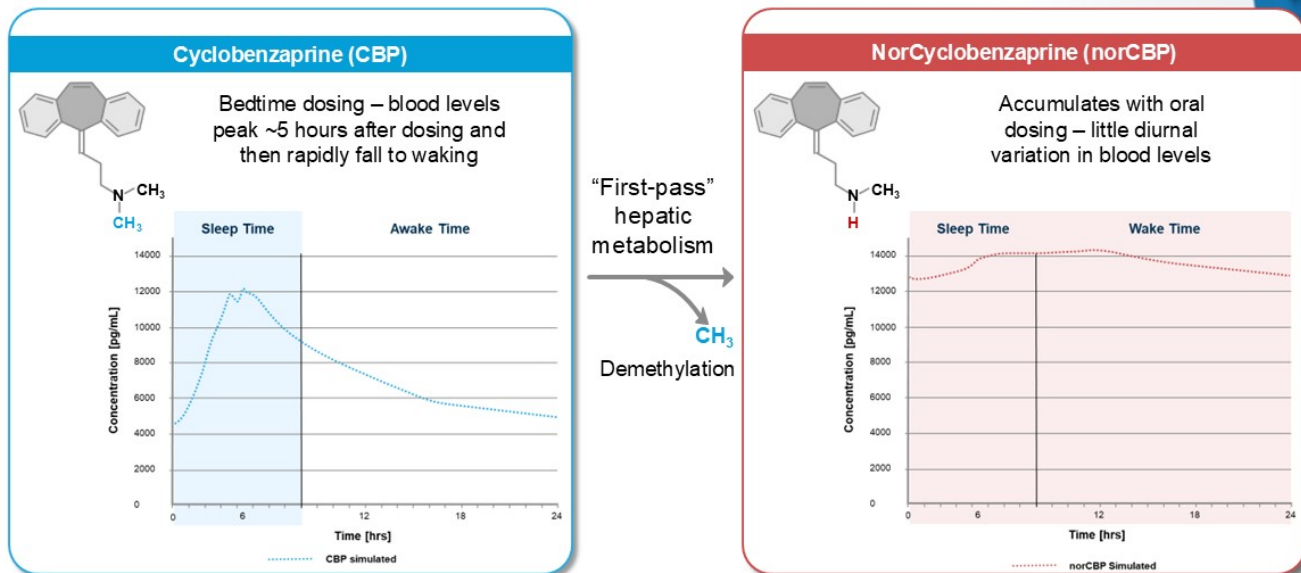
¹Abdollahi M, et al. 3rd ed. Academic Press; 2014:838-845.
²Ledeti A, et al. J Therm Anal Calorim. 2018;131:155-165.
³Brioschi TM, et al. Biomed Res Int. 2013;2013:281392.



Oral Cyclobenzaprine Undergoes First-Pass Metabolism



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



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

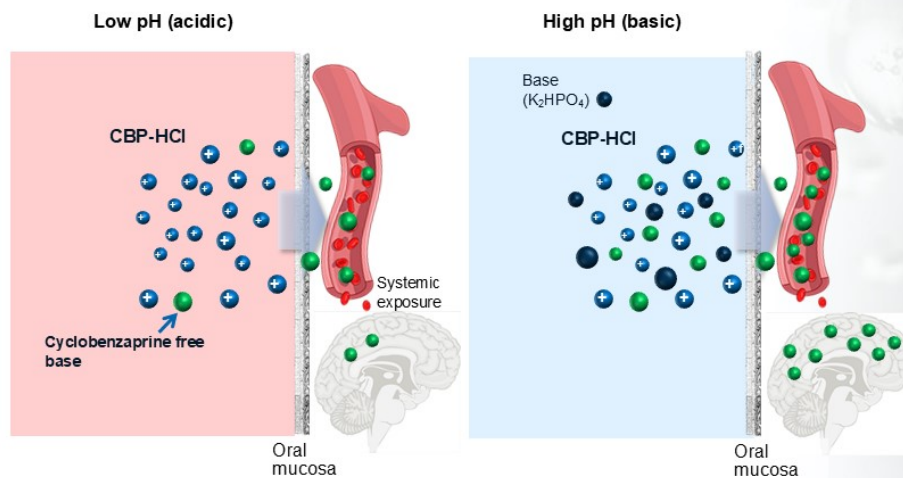
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Formulation with Basic Excipient Increases Transmucosal Absorption of Sublingual Cyclobenzaprine¹

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



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

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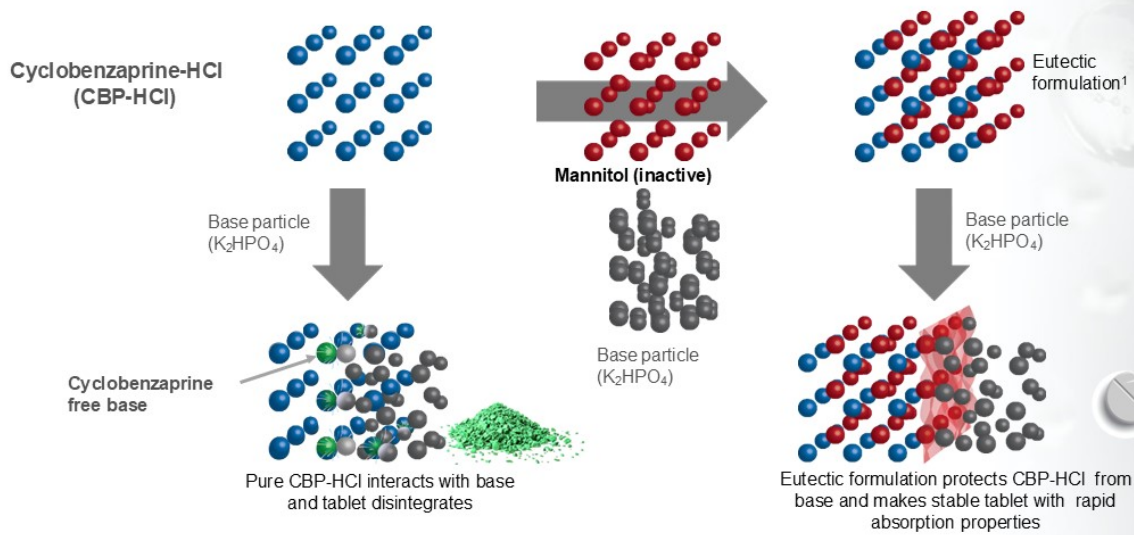
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TNX-102 SL: Proprietary Eutectic Formulation

Proprietary cyclobenzaprine HCl eutectic composition stabilizes sublingual tablet formulation



¹U.S. Patent issued May 2, 2017

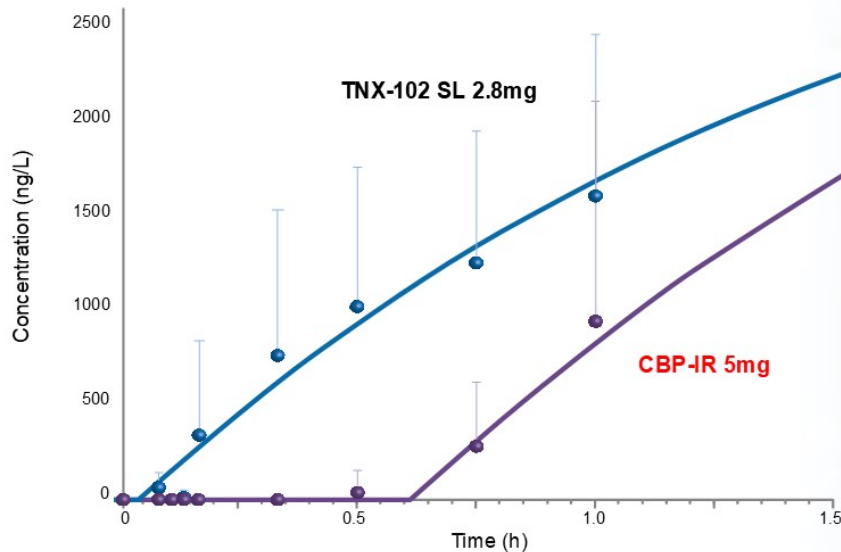
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TNX-102 SL: CBP Detected in Plasma Within Minutes Following Sublingual Administration

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



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

TNX-102 SL is administered sublingually



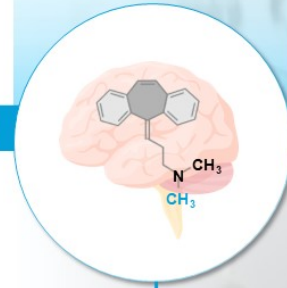
tongue

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**

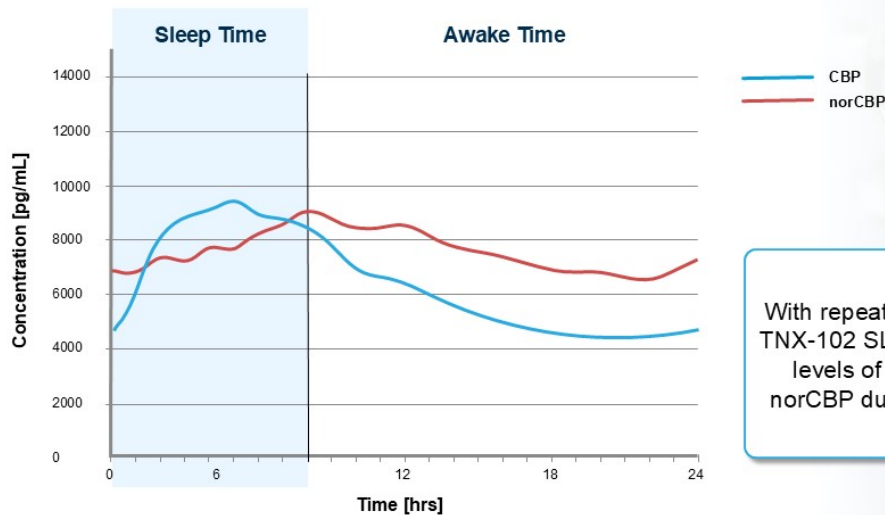
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Steady State Pharmacokinetics of Daily Sublingual TNX-102 SL (5.6 mg) at Bedtime

Steady State PK (after 20 days dosing)



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

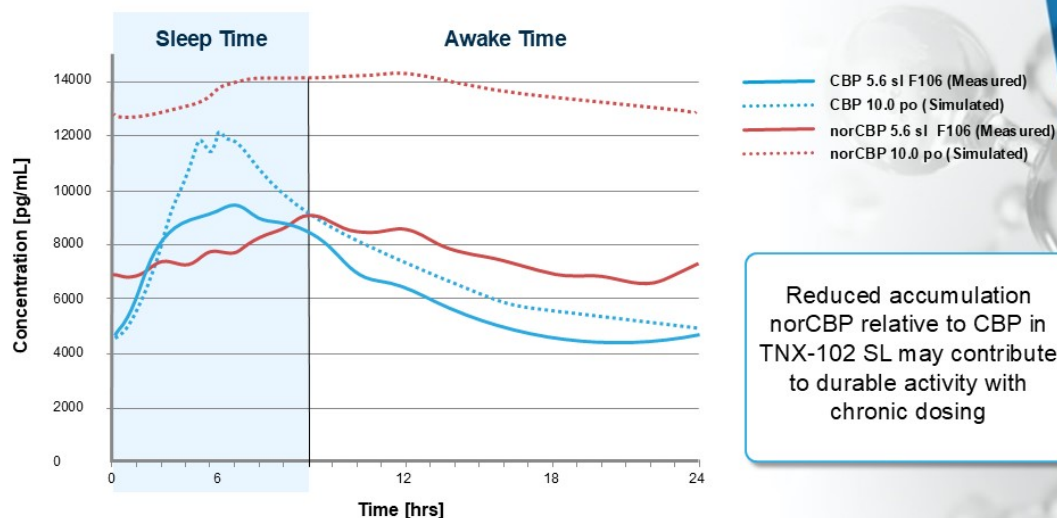
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TNX-102 SL: Multi-Dose PK Differentiation from Simulated Oral Cyclobenzaprine (CBP)-Immediate Release (IR)

Steady State PK (after 20 days dosing)
Day 20 TNX-102 SL 5.6 mg v. Simulated Oral IR 10 mg



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

sl = sublingual
po = by mouth

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CNS PORTFOLIO

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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

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CNS PORTFOLIO

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



The pain system evolved to detect acute pain

- The body's "check engine" light

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

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

Chronic Overlapping Pain Conditions (COPCs) are Nociplastic Syndromes:

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

Stresses that may precede or precipitate FM include:

- Chronic nociceptive pain
 - e.g., osteoarthritis
- Chronic neuropathic pain
 - e.g., diabetic neuropathy
- Infectious
 - e.g., viral illness
- Cancer
 - e.g., breast cancer
- Chemical
 - e.g., cancer chemotherapy
- Traumatic
 - e.g., motor vehicle accident
- Head trauma
 - e.g., post-concussive syndrome
- Physiologic
 - e.g., disturbed sleep

Common Chronic Conditions are a Challenge for Pharma



Fibromyalgia is a common chronic disease¹

- 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

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



Common Chronic Conditions are a Challenge for Society

The Opioid 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 opioids
- Many individuals who are opioid dependent have transitioned to illegal street heroin and fentanyl
- Illegal drugs contribute to homelessness

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

- No new drug for fibromyalgia has been approved since 2009



Current FDA-Approved Fibromyalgia Drugs¹

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		Lyrica® (pregabalin) - Pfizer	Cymbalta® (duloxetine) - Lilly Savella® (milnacipran) - AbbVie
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	-

¹The three drugs with FDA approval for the management of fibromyalgia are Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)

²Leung MTY, et al. JAMA Netw Open. 2024;7(11):e2444488. doi: 10.1001/jamanetworkopen.2024.44488. PMID: 39535796; PMCID: PMC11561685.

~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

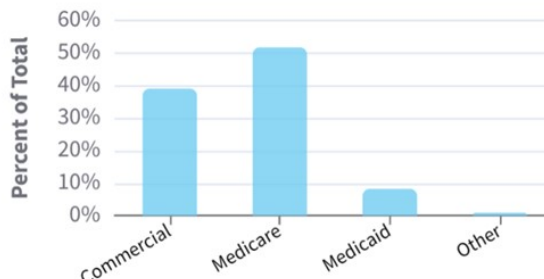
- EVERSANA analysis of claims database consisting of 2.2M patients, for which 1.2M claims were submitted throughout March 2002-March 2023¹

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 Coverage¹

Insurance Distribution



¹EVERSANA analysis of claims database, May 2024; commissioned by Tonix

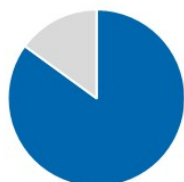
²Source: [Final CY 2025 Part D Redesign Program Instructions Fact Sheet I CMS](#)



Prescribers Interviewed Expressed Broad Dissatisfaction with Available Fibromyalgia Medications: Results of Primary Research¹

Perspectives on FM Therapies from Prescribers Interviewed

Drug	Positives	Negatives
Duloxetine (Cymbalta, generic)	<ul style="list-style-type: none"> Relatively high efficacy (compared to alternatives) Can be titrated slowly from 20mg to 120mg 	<ul style="list-style-type: none"> Tolerability issues: worsening depression, insomnia Seldom used as a monotherapy; often requires adjunct
Pregabalin (Lyrica, generic)	<ul style="list-style-type: none"> Relatively high efficacy (compared to alternatives) Can often be safely combined with other medications 	<ul style="list-style-type: none"> Suboptimal for long-term use (e.g., weight gain) Schedule V status makes some HCPs more cautious to Rx
Savella (milnacipran)	<ul style="list-style-type: none"> Offers another option if patient fails Cymbalta or Lyrica 	<ul style="list-style-type: none"> Subpar efficacy does not counterbalance tolerability issues High cost and access constraints (~\$50/month)
Cyclobenzaprine (Flexeril, generic; oral formulation, off-label)	<ul style="list-style-type: none"> Active for initiating and sustaining sleep; can be titrated up Active for pain driven by stiffness and muscle spasms 	<ul style="list-style-type: none"> Mixed perspectives on pain benefit independent of sleep Suboptimal long-term results as efficacy wanes



85% of patients (avg) fail first line therapy



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

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



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

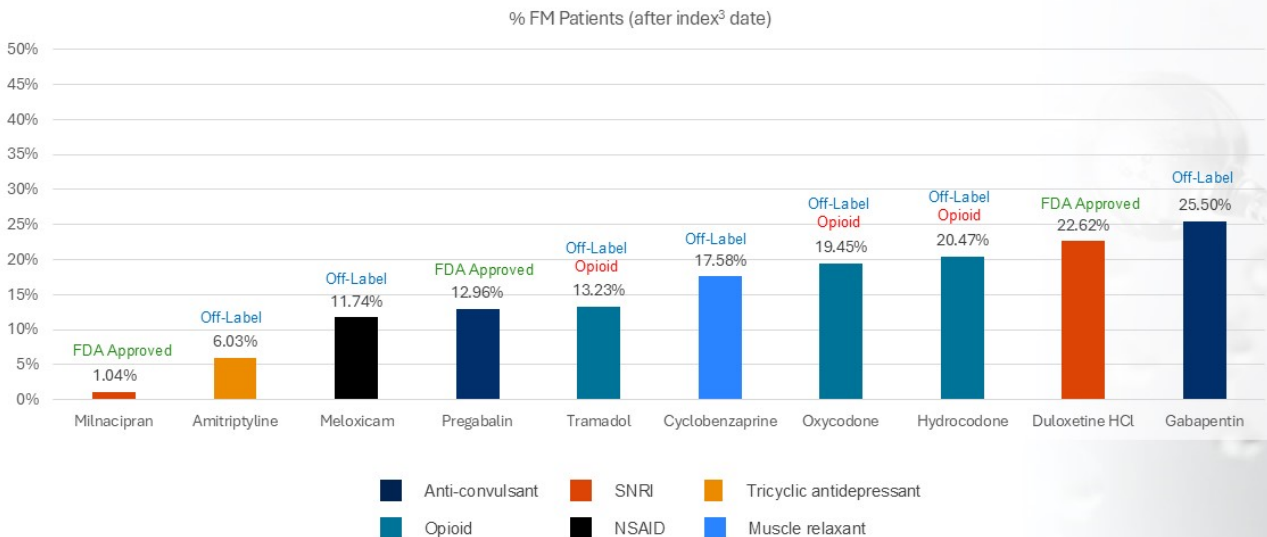
- **Physicians indicated intended use in 40% of their FM patients**
- Majority of respondents indicated TNX-102 SL would be their first choice, if accessible
- Physicians surveyed indicated they are well-equipped to deal with access restrictions including prior authorizations and step-edits

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-Label¹



¹ 2022-2023

² EVERSANA analysis of claims database, May 2024; commissioned by Tonix





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 lives¹
- In the US alone, one-third of emergency department visits (40-50 million patients per year) are for evaluation after trauma exposures²

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

¹National Center for PTSD. How Common is PTSD in Adults? https://www.ptsd.va.gov/understand/common/common_adults.asp

²Wisco 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; received IND clearance from FDA

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)

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

Placebo once-daily at bedtime

2 weeks

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

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

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

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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 sites¹

- 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}

¹Thaweethai T, et al. JAMA. 2023 329(22):1934-1946.

²Feb 22, 2023 Tonix Pharmaceuticals Press Release. URL: <https://ir.tonixpharma.com/news-events/press-releases/detail/1369/tonix-pharmaceuticals-describes-emerging-research-on-the>

³September 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

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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 COVID¹
- 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 US²

Long-COVID prevalence: 5.3% or ~14M adults in the US³

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

¹U.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>.

²Vincent A, et al. *Arthritis Care Res (Hoboken)*. 2013 65(5):786-92. doi: 10.1002

³National 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>

Tonix Medicines: Marketed Products



Tonix Medicines: Commercial-Stage Specialty Pharma Subsidiary

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



Tonix Medicines Markets Two Proprietary Migraine Drugs Non-oral Formulations of Sumatriptan

Zembrace® Sym Touch® (sumatriptan injection) 3 mg¹



- Each indicated for the *treatment of acute migraine with or without aura in adults*
- Sumatriptan remains the acute migraine 'gold standard' treatment for many patients and continues to represent the largest segment of the market in terms of unit sales³
- Each may provide migraine *pain relief in as few as 10 minutes* for some patients^{1,2,4,5}
- Patents to 2036 (Zembrace) and 2031 (Tosymra)

Tosymra® (sumatriptan nasal spray) 10 mg²



Tonix Medicines Commercial Subsidiary

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

¹Zembrace SymTouch [package insert]. For more information, talk to your provider and read the [Patient Information](#) and [Instructions for Use](#). – Important Safety Information is provided in the appendix

²Tosymra [package insert]. For more information, talk to your provider and read the [Patient Information](#) and [Instructions for Use](#). – Important Safety Information is provided in the appendix

³Tonix Medicines, Inc.; Data On File, 2023

⁴Mathew NT, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49(12):1271-1276.

⁵Wendt J, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. Clinical Therapeutics. 2006;28(4):517-526.

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





Zembrace and Tosymra Bypass the GI Tract

Bypassing gastrointestinal (GI) tract is *potential advantage for treating acute migraine*

- GI absorption may be inconsistent in migraineurs due to gastric stasis (also called “gastroparesis”)¹⁻⁴
- Nausea and vomiting are symptoms of migraine⁵ which can complicate oral treatment

Existing Subcutaneous injectable products

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

Existing intranasal products

- Imitrex® nasal spray (sumatriptan)
- Migranal® (dihydroergotamine) nasal spray – developed by Novartis, sold by Bausch Health
- Zavzpret® (zavegepant) nasal spray, FDA approved in March, 2023⁵ is the first intranasal gepant-marketed by Pfizer
- Zomig® nasal spray (zolmitriptan)
- Onzetra® Xsail® (sumatriptan nasal powder) marketed by Currax
- Trudhesa® (dihydroergotamine) nasal spray

¹Zembrace SymTouch [package insert]. Maple Grove, MN: Upsher-Smith Laboratories, LLC; February 2021.

²Mathew NT, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49(12):1271-1276.

³Landy, S. et al. Efficacy and safety of DFN-11 (sumatriptan injection, 3 mg) in adults with episodic migraine: a multicenter, randomized, double-blind, placebo-controlled study. J Headache Pain. 19, 69 (2018).

⁴Brand-Schieber E, Munjal S, Kumar R, et al. Human factors validation study of 3 mg sumatriptan autoinjector, for migraine patients. Med Devices (Auckl). 2016;9:131-137.

⁵Pfizer Press Release March 10, 2023. – <https://www.pfizer.com/news/press-release/press-release-detail/pfizers-zavzpretm-zavegepant-migraine-nasal-spray>

Pipeline

Programs and Strategy for Partnerships

Pipeline Development Strategy

Focusing on government and academic collaborations

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

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External Partnerships

Government partners providing direct funding, cost sharing or in-kind support include¹:

- **National Institutes of Health (NIH)**
- **National Institute of Allergy and Infectious Disease (NIAID)**
 - TNX-1800 selected for Project NextGen
- National Institute on Drug Abuse (NIDA)
 - TNX-1300 for cocaine intoxication; Phase 2 study funding
- **Department of Defense (DoD)**
 - TNX-4200 for the prevention or treatment of infections to improve the medical readiness of military personnel in biological threat environments
 - TNX-102 SL for ASD; investigator-initiated Phase 2 study funding

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

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

¹Tonix's product development candidates are investigational new drugs or biologics; their efficacy and safety have not been established and have not been approved for any indication.

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Key Partnerships

TNX-1500: ALLOGRAFT REJECTION



TNX-102 SL: ACUTE STRESS DISORDER



U.S. Department of Defense



THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

TNX-2900: PRADER-WILLI SYNDROME



TNX-1300: COCAINE INTOXICATION



TNX-1800: COVID-19 VACCINE



TNX-4200: BROAD-SPECTRUM ANTIVIRAL



U.S. Department of Defense



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TNX-801

Live Virus Vaccine

Live virus vaccine platform with multitude of potential applications



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Mpox Declared Public Health Emergency of International Concern (PHEIC) by WHO* on August 14, 2024: New Clade I = "Clade Ib"

- **Clade Ib - first wave in Democratic Republic of Congo (DRC)**
 - Affects children
 - New mutations
 - ~0.5% mortality
 - Affects both MSM (men who have sex with men) + heterosexual transmission primarily in adults
 - 2024 mpox epidemic has spread to 16 countries in Africa
 - Outside of Africa cases identified in Sweden, Thailand, Singapore, India, Germany and England
- **Two FDA**-approved vaccines:**
 - Jynneos® (Bavarian-Nordic) – requires 2 dose regimen
 - Durability of neutralization antibody titers being studied¹⁻³
 - Also approved for use in adults by the WHO⁴
 - ACAM 2000 (Emergent) – single-dose, reactogenic
 - Provides durable protection
 - Approved for people at high risk of mpox infection⁵

*WHO = World Health Organization

¹Zaack LM, *Nat Med*. 2023 29(1):270-278. doi: 10.1038/s41591-022-02090

²Berens-Riha N, et al. *Euro Surveill*. 2022 27(48):2200894. doi: 10.2807/1560-7917.ES.2022.27.48.2200894.

³Collier AY, et al. *JAMA*. 2024 Oct 3. doi: 10.1001/jama.2024.20951. Epub ahead of print. PMID: 39361499. <https://pubmed.ncbi.nlm.nih.gov/39361499/>

⁴Keaton, J. Sept. 13, 2024. *Associated Press*. "WHO grants first mpox vaccine approval to ramp up response to disease in Africa." URL: <https://bit.ly/4e4yyeb>

⁵<https://www.fda.gov/vaccines-blood-biologics/vaccines/key-facts-about-vaccines-prevent-mpox-disease#:~:text=ACAM2000%20Vaccine,for%20smallpox%20or%20mpox%20infection.>

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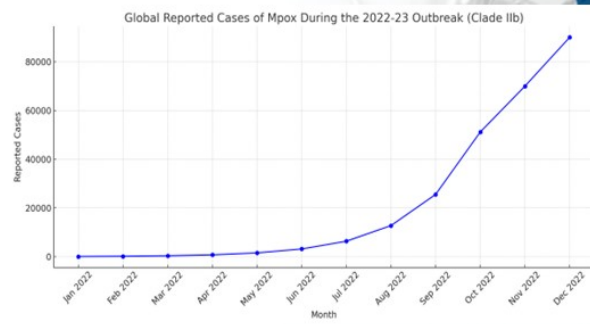
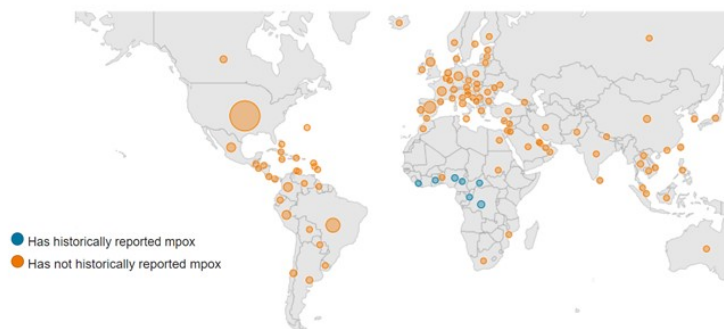
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Mpox Outbreak 2022-23: Clade IIb Public Health Emergency Global Health Concern

Risk of Spread and Lethality of Clade IIb

- Case Fatality Rate (CFR): 0.1% to 3.6% → Lower compared to Clade I
- Primarily spread through sexual contact among MSM (men who have sex with men)
- Rapid and significant spread beyond endemic regions → Over 90,000 cases reported in more than 100 countries by the end of 2022
- Systemic symptoms and rash leading to medical interventions in up to 40% of cases



Total Cases: 95,912; 92,982 were in locations that have not historically reported Mpox
Total Location: 118; 111 has not historically reported Mpox

Sources: WHO, European CDC, US CDC, and Ministries of Health

[2022 U.S. Map and Case Count | Mpox | Poxvirus | CDC](#)

WHO = World Health Organization

FDA = U.S. Food and Drug Administration

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Monkeypox Headlines

- Multiple recent statements by U.S. Agencies warning about smallpox and monkeypox¹⁻⁶
- U.S. National Academy of Sciences Consensus Report (March 2024)⁶
 - “Additionally, safer, single-dose vaccines and a diverse set of therapeutic options against smallpox would improve the U.S. readiness and response posture for immediate containment and long-term protection in a smallpox emergency.
 - “Smallpox vaccines that have improved safety across different population subgroups and are available as a single dose would support faster and more effective response to contain smallpox and other orthopoxvirus outbreaks. The development of novel smallpox vaccines using multi-vaccine platforms (i.e., use common vaccine vectors, manufacturing ingredients, and processes) would improve the capacity for rapid vaccine production in response to a smallpox event and reduce the need for stockpiling in the SNS at current levels.
 - “Given the lack of commercially available orthopoxvirus diagnostics, vaccines, and therapeutics, planning for logistics and supply chain management considerations is critical. Efforts could give consideration to developing plans to increase the number of smallpox vaccine and therapeutics manufacturers as well as optimizing current manufacturing capacities should they be needed in the shorter term.”

¹ Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021

² National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023

³ Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021

⁴ National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023

⁵ BARDA Strategic Plan 2022-2026.

⁶ U.S. National Academy of Sciences. March 28, 2024. “Consensus Study Report: Future State of Smallpox Medical Countermeasures.” <https://nap.nationalacademies.org/catalog/27652/future-state-of-smallpox-medical-countermeasures>

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

Cloned version of horsepox¹ purified from cell culture

TNX-801*
(Horsepox)

Horsepox

**ANTIGEN
CODING**

• Mpox and Smallpox

• COVID-19

• Future Pandemics & New Infectious Diseases

• Biodefense

• Oncology

Key Differentiators

Live virus vaccines are the most established vaccine technology

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

Economical to manufacture at scale

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

Standard refrigeration for shipping and storage

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



TNX-801: Pre-IND Ready Candidate Mpox Vaccine

- Based on synthetic horsepox-vector, believed related to first smallpox vaccine used by Dr. Edward Jenner in 1796¹
- Single-dose percutaneous²
- Attenuated live virus³
- Expected durable T-cell immunity similar to 19th Century vaccinia
- Believed to be thermo-stable in ultimate lyophilized formulation
- Eventual presentation using Microneedle Array Patch – working with developers



R&D Center- Maryland
Operational BSL-3 capable
Bio Hub and Innovation Center



Advanced Manufacturing Center- MA
GMP-manufacturing capability*

*GMP Suites currently decommissioned

¹Noyce RS, et al. *PLoS One*. 2018 Jan 19;13(1):e0188453. doi: 10.1371/journal.pone.0188453. PMID: 29351298; PMCID: PMC5774680.

²Noyce RS, et al. *Viruses*. 2023 Jan 26;15(2):356. Doi: 10.3390/v15020356. PMID: 36851570; PMCID: PMC9965234.

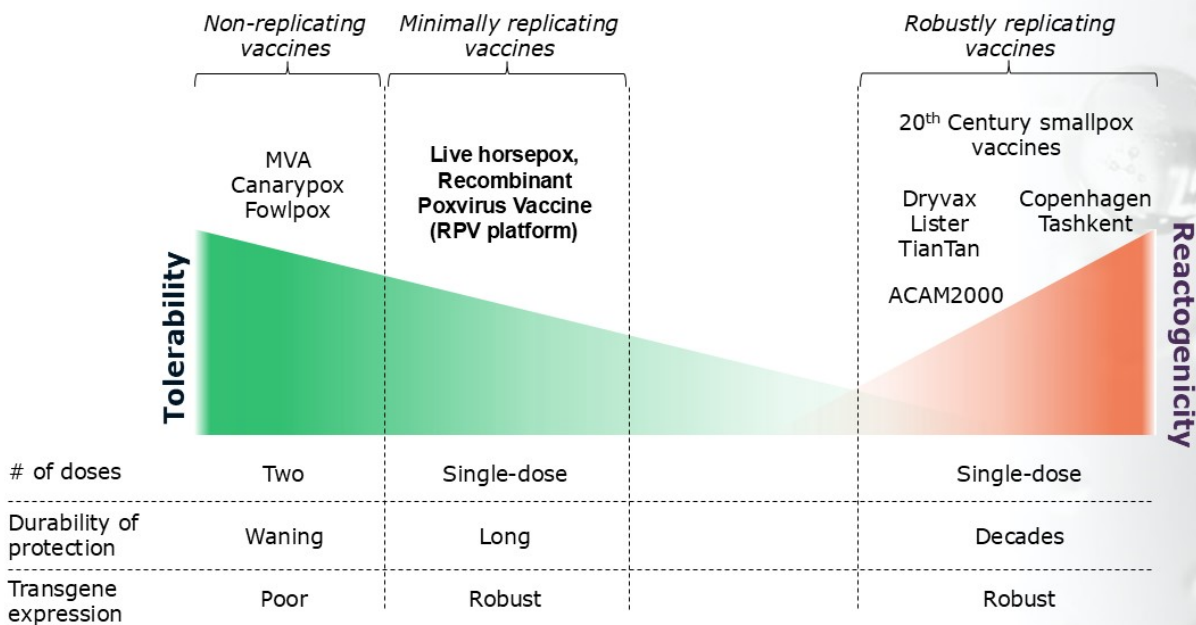
³Trefry SV, et al. *mSphere*. 2024 Nov 13:e0026524. doi: 10.1128/msphere.00265-24. Epub ahead of print. PMID: 39535212.

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Illustrative Safety Spectrum Of Pox-based Vaccine Vectors as Live Virus Vaccines



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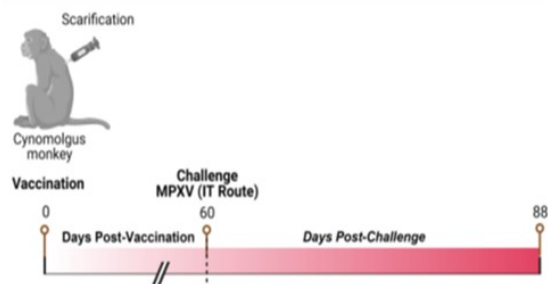
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TNX-801: Immunogenicity and Efficacy in Animals – Study Design

Vaccination					Challenge		
Group	Vaccine	N	Dose (Log ₁₀ PFU)	Route	Virus	Dose (Log ₁₀ PFU)	Route
1	TNX-801 (High)	4	6.6	Percutaneous	MPXV (Zaire) Clade Ia	5.0	IT
2	TNX-801 (Low)	4	5.7	Percutaneous			
3	rVACV*	4	5.0	Percutaneous			
4	Mock	4	-	Percutaneous			

*rVACV = Synthetic vaccinia virus (VACV) similar to ACAM2000 (FDA Approved smallpox and mpox vaccine)



“Take” observed in all TNX-801 vaccinated NHPs except one.

- If no take by day 7 NHPs were revaccinated on day 14.

Post-vaccination, no NHP showed lesions during first 60 days

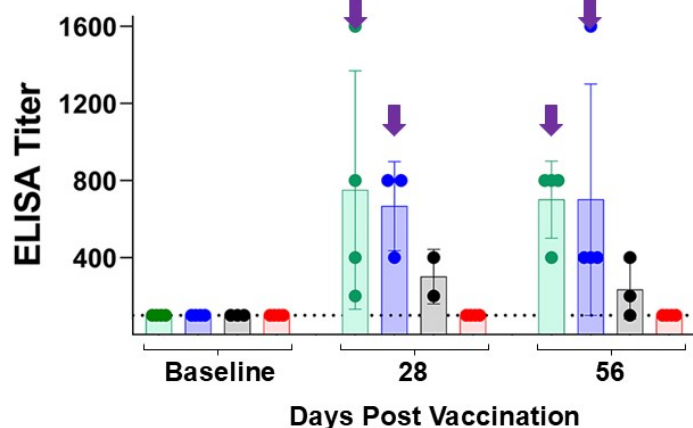
Noyce RS, et al. *Viruses*. 2023; 15(2):356. doi: 10.3390/v15020356.

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TNX-801 Vaccination – Followed by Lethal Monkeypox Clade I Challenge, Immunogenicity: Total IgG (ELISA)



100% Seroconversion in
TNX-801 vaccinated groups

HD = "High Dose"
LD = "Low Dose"

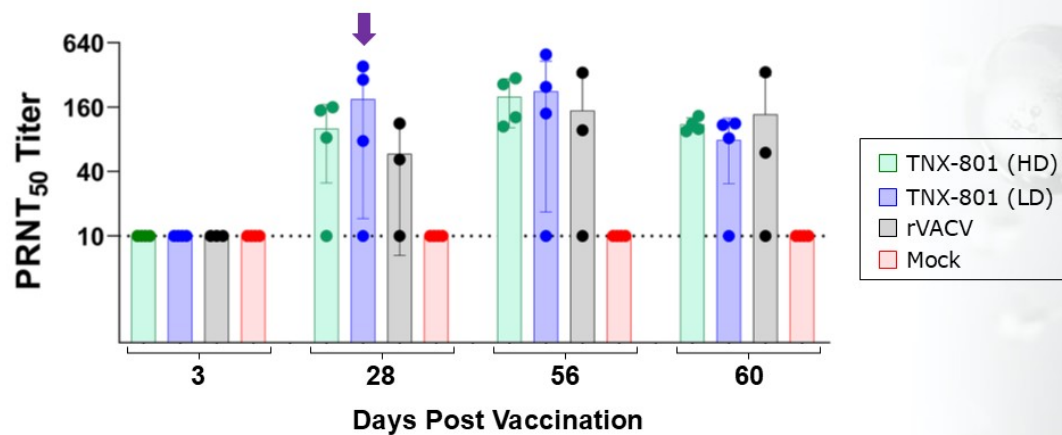
Noyce RS, et al. *Viruses*. 2023; 15(2):356. doi: 10.3390/v15020356.

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TNX-801 Vaccination – Followed by Lethal Monkeypox Clade I Challenge, Immunogenicity: Neutralizing Antibody (PRNT₅₀ Assay)



100% Seroconversion and 88% of TNX-801 vaccinated NHPs had neutralizing antibody responses 8- to 50-fold from baseline

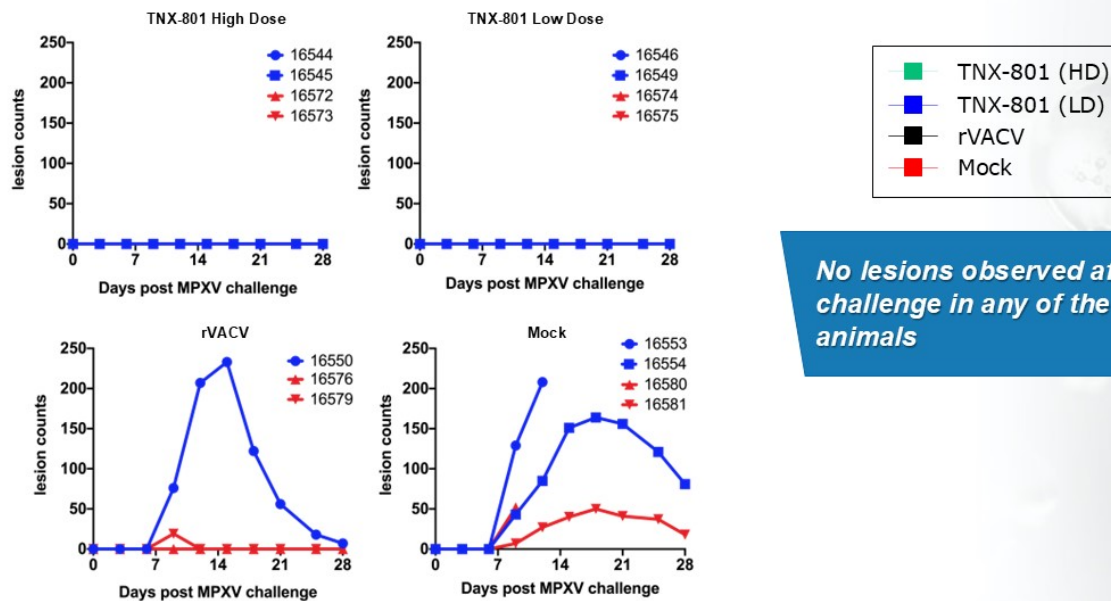
Noyce RS, et al. *Viruses*. 2023; 15(2):356. doi: 10.3390/v15020356.

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TNX-801 Vaccination – Followed by Lethal Monkeypox Clade I Challenge, Clinical Signs (Lesions)



No lesions observed after MPXV challenge in any of the vaccinated animals

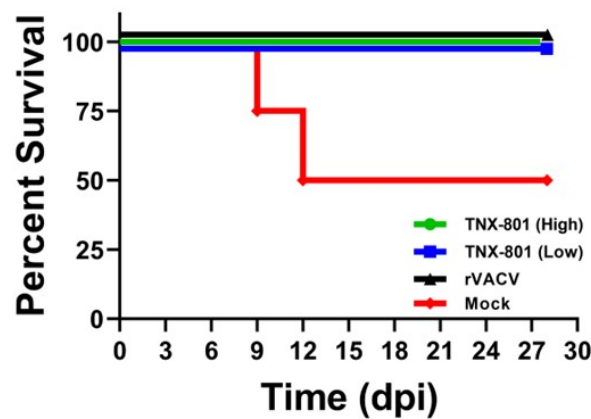
¹Noyce RS, et al. *Viruses*. 2023 Jan 26; 15(2):356. doi: 10.3390/v15020356. PMID: 36851570; PMCID: PMC965234.

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TNX-801 Vaccination – Followed by Lethal Monkeypox Clade I Challenge, Clinical Disease: Lethality



100% survival in TNX-801 vaccinated animals

Noyce RS, et al. *Viruses*. 2023;15(2):356. doi: 10.3390/v15020356.

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

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

- Immunogenic and well tolerated¹
- Showed promise in protecting animals from challenge with SARS-CoV-2 delivered directly into the lungs¹

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

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

*TNX-1800 is in the pre-IND stage of development and has not been approved for any indication

¹Awasthi, M. et al. *Viruses*. 2023. 15(10):2131.

²Awasthi, M. et al. *Vaccines (Basel)*. 2023. 11(11):1682.

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INFECTIOUS DISEASE PORTFOLIO



Broad-Spectrum Antiviral Discovery Programs

Host-directed antiviral discovery programs

- **TNX-4200*: CD45 targeted therapeutics**
 - Small molecule therapeutics that reduce endogenous levels of CD45, a protein tyrosine phosphatase
 - Reduction in CD45 protects against many viruses including the Ebola virus
- **Cathepsin inhibitors**
 - Small molecule therapeutics that inhibit **essential cathepsins** which are required by viruses such as coronaviruses and filoviruses to infect cells
 - Activity as monotherapy and in combination with other antivirals

Virus-directed antivirals discovery program

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

R&D Center (RDC): Frederick, MD

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

*TNX-4200 is in the pre-IND stage of development and has not been approved for any indication

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INFECTIOUS DISEASE PORTFOLIO

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Tonix Awarded Contract from DoD



U.S. Department of Defense



INFECTIOUS DISEASE PORTFOLIO

Defense Threat Reduction Agency (DTRA) contract is expected to advance development of Tonix's broad-spectrum oral antiviral program, TNX-4200, for medical countermeasures

- Other Transaction Agreement (OTA) with a potential for up to \$34 million over five years
- Objective is to develop small molecule, broad-spectrum antiviral agents for the prevention or treatment of infections to improve the medical readiness of military personnel in biological threat environments
- Tonix's focus is to develop an orally available CD45 antagonist with broad-spectrum efficacy against a range of viral families through preclinical evaluation
 - Program is expected to establish physicochemical properties, pharmacokinetics, and safety attributes to support an IND submission and to fund a first-in-human Phase 1 clinical study

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TNX-1300

Cocaine Esterase

Fast acting antidote for life threatening cocaine intoxication

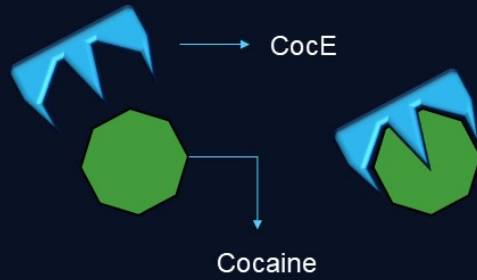
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TNX-1300: Recombinant Protein Rapidly Degrades Cocaine in the Bloodstream

Drops plasma exposure by 90% in 2 minutes



FDA Breakthrough Therapy Designation

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

Phase 2 study enrolling

Key Differentiators

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

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

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About Cocaine Intoxication

Over 5 million Americans reported current cocaine use in 2020, which is almost 2% of the population¹. In 2021, more than 24,900 individuals in the US died from drug overdose deaths involving cocaine²

500k Over 500,000 emergency department visits for cocaine, annually^{3,4}

Current standard of care:

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

Large unmet need:

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

¹Substance Abuse and Mental Health Services Administration. (2021). Results from the 2020 National Survey on Drug Use and Health: Detailed Tables: Prevalence Estimates, Standard Errors, and Sample Sizes.

²Centers for Disease Control and Prevention (CDC) - <https://www.cdc.gov/nchs/nvss/vsm/drug-overdose-data.htm>

³Substance Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

⁴Drug Abuse Warning Network, 2011: Selected Tables of National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA, 2013.

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CNS PORTFOLIO



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Immunology: Key Candidates

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TNX-1500

Anti-CD40L Monoclonal Antibody

*Next Generation mAb preserves efficacy with reduced risk
of thrombosis*

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TNX-1500: Next Generation anti-CD40L mAb

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

Clinical Stage of Phase 1 study topline results positive

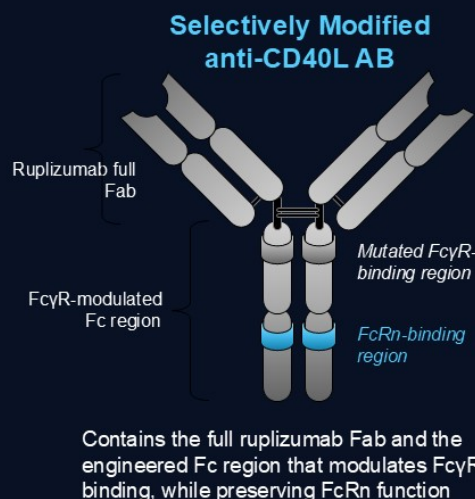
Key Differentiators

Expected to deliver efficacy without compromising safety

First Generation: Development halted due to thromboembolic (TE) complications—blood clots—traced to Fc gamma receptor (FcγR)

Second Generation: Eliminated the FcγR TE complication but potency and half life was reduced, limiting utility

Third Generation (TNX-1500): Re-engineered to better modulate the binding of FcγR.



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

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TNX-1500 Phase 1 Topline Results and Conclusions

Phase 1 design – single ascending dose study in healthy participants

- Goals: Evaluate safety, pharmacodynamics and pharmacokinetics
- At total of 26 participants were enrolled in three cohorts
 - 3 mg/kg, 10 mg/kg, and 30 mg/kg *i.v.*

Topline results

- Pharmacodynamics:** TNX-1500 blocked the primary and secondary antibody responses to a test antigen (KLH) at the 10 and 30 mg/kg *i.v.* doses
- Pharmacokinetics:** mean half-life ($t_{1/2}$) for the 10 mg/kg and 30 mg/kg doses of 34-38 days
- TNX-1500 was generally well-tolerated with a favorable safety profile
- Tolerability:** TNX-1500 was generally well-tolerated with a favorable safety and tolerability profile. The only TEAE occurring in ≥ 3 participants among all TNX-1500 groups was Aphthous ulcer, occurring in one participant each in the 3 mg/kg, 10 mg/kg, and 30 mg/kg groups; all were rated as mild, possibly related, and resolved in 2-10 days.

Conclusions

- Results support proceeding to develop Phase 2 trial for the prevention of kidney transplant rejection
- Fc modifications we engineered to TNX-1500 for safety did not attenuate the potency of TNX-1500 relative to humanized 5c8 (hu5c8, ruplizumab, BG9588)¹⁻³
- We believe the results of this study and our prior animal studies^{4,5} indicate that TNX-1500 is potentially best-in-class among anti-CD40L mAbs in development

- Lederman S, et al. *J Exp Med*. 1992 Apr 1;175(4):1091-101. doi: 10.1084/jem.175.4.1091. PMID: 1348081; PMCID: PMC2119166.
- Boumpas DT, et al. *Arthritis Rheum*. 2003;48(3):719-27. doi: 10.1002/art.10856. PMID: 12632425.
- Pierson RN 3rd, et al. *Transplantation*. 1999;68(11):1800-5. doi: 10.1097/00007890-199912150-00026. PMID: 10609959.
- Lassiter G, et al. *Am J Transplant*. 2023;23(8):1171-1181. doi: 10.1016/j.ajt.2023.03.022.
- Miura S, et al. *Am J Transplant*. 2023;23(8):1182-1193. doi: 10.1016/j.ajt.2023.03.025.

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IMMUNOLOGY PORTFOLIO



TNX-1500 Phase 1 Results and Methods

Topline Results

- **Tolerability:** TNX-1500 was generally well-tolerated with a favorable safety and tolerability profile. The only TEAE occurring in ≥ 3 participants among all TNX-1500 groups was Aphthous ulcer, occurring in one participant each in the 3 mg/kg, 10 mg/kg, and 30 mg/kg groups; all were rated as mild, possibly related, and resolved in 2-10 days. There were no TEAEs assessed as related to KLH administration. No TEAEs led to study discontinuation. There were no serious adverse events. There were no thromboembolic events, which were prespecified as TEAEs of special interest.
- **Pharmacodynamics:** TNX-1500 at 10 mg/kg and 30 mg/kg blocked both the primary and secondary anti-KLH Ab responses, evidenced by the mean Ab level at all sampled timepoints (through Day 120) being below the lower limit of quantitation (400 $\mu\text{g/L}$). TNX-1500 at 3 mg/kg blocked the primary response to KLH Day 2 challenge and reduced the peak secondary response to KLH Day 29 challenge by approximately two thirds (69%) relative to the peak response to placebo.
- **Pharmacokinetics:** The mean (SD) half-life ($t_{1/2}$) of TNX-1500 was: 3 mg/kg, 19.6 (9.29) days; 10 mg/kg, 37.8 (5.46) days; and 30 mg/kg, 33.7 (4.83) days.

Methods

- **Dosing:** TNX-1500 solution was infused *i.v.* over a period of one hour to achieve doses of 3, 10, and 30 mg/kg. Participants were observed in the clinic for one day and followed with periodic clinic visits to Day 120.
- **Keyhole Limpet Hemocyanin (KLH) Challenge:** To evaluate the immune modulation potency of TNX-1500, participants received an antigen challenge with KLH (Immucothel[®]) administered intramuscularly (*i.m.*) on Day 2 and Day 29 of the study. Samples for anti-KLH antibody (Ab) were obtained on Days 1 (pre-challenge), 8, 15, 29, 36, 50, 64, 78, and 120.
- **Disposition:** At total of 26 participants were enrolled in three Cohorts (Cohort 1: n=4 at 3 mg/kg, n=2 placebo; Cohort 3: n=8 at 10 mg/kg, n=2 placebo; Cohort 3: n=8 at 30 mg/kg, n=2 placebo). A total of 24 participants completed the study and two discontinued early (one placebo participant was lost to follow-up and one on TNX-1500 withdrew consent).

TNX-1500 Preclinical Data and Publications

Non-human Primate Kidney Allo-Transplantation

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

Non-human Primate Heart Heterotopic Allo-Transplantation

- TNX-1500 monotherapy consistently prevents heart transplant rejection. Similar activity to chimeric hu5c8¹ during treatment phase in prior studies
- April 2023 Publication: Miura, S., et al. (2023) TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Cardiac Allograft Survival. *American Journal of Transplantation*. www.sciencedirect.com/science/article/pii/S1600613523003969

Non-Human Primate Kidney Xenograft Transplantation

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

¹Pierson RN 3rd, et al. *Transplantation*. 1999;68(11):1800-5. doi: 10.1097/00007890-199912150-00026. PMID: 10609959.



TNX-1500 Strategy and Status

1 Proposed Initial Indication: Prevention of Allograft Rejection

Status: *Clinical stage Phase 1 completed – positive topline reported in 1st Quarter 2025*

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

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

Next Steps: Proceed to develop Phase 2 study in Kidney Transplant Recipients

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

- Potential to reduce GvHD

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

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



Other α -CD40L Monoclonal Antibodies in Development

Sanofi – Frexalimab, Indications: Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE)

- Sjögren's Syndrome (SjS) (NCT04572841) program discontinued¹
- Phase 2 Trial in Relapsing MS reported in the *NEJM* (NCT04879628)²
- Phase 2 Trial Currently Enrolling in SLE (NCT05039840)
- Frexalimab, f.k.a. SAR441344 (Fc-modified)

Eledon – Tegoprubart, Indication: Kidney Transplant

- Phase 2 Trial Completed in ALS (NCT04322149)
- Phase 1/2 Trial Currently Enrolling in Kidney Transplant (NCT05027906)
- Tegoprubart, f.k.a. AT-1501 (Fc-modified)

Biogen/UCB – Dapirolizumab pegol, Indication: Systemic Lupus Erythematosus (SLE)

- Phase 3 Trial (NCT04294667) reported positive topline results³
- Dapirolizumab pegol (pegylated Fab)

Amgen (acquired with Horizon) – Dazodalibep, Indication: Sjögren's Syndrome (SjS)

- Two Positive Phase 2 studies reported^{4,5}
- Dazodalibep (tn03 fusion protein)

Lundbeck and AprilBio – Lu AG22515, Indication: Neurology

- Phase 1 Trial in Healthy Adults complete (NCT05136053)
- APB-A1 or Lu AG22515 (HAS fusion protein)

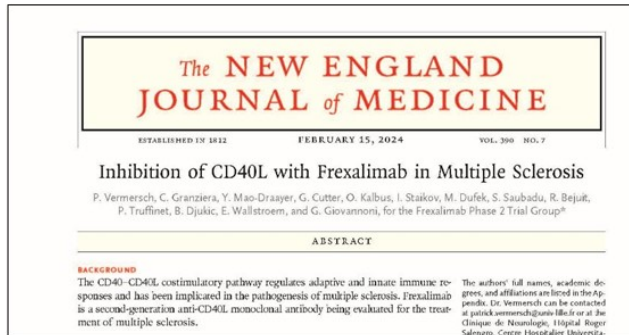
¹Tong, A. April 25, 2024. Endpoints. "Sanofi spotlights early-stage cancer assets, counts on grandfather clause on Biosecure"
²Vermersch P, et al. N Engl J Med. 2024 Feb 15;390(7):589-600. doi: 10.1056/NEJMoa2309439. PMID: 38354138

³Gelman, M. Endpoints. "Biogen, UCB detail response rates in Phase 3 lupus trial after surprising Success" Nov. 19, 2024
<https://www.biospace.com/article/releases/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-dazodalibep-for-the-treatment-of-sjogren-s-syndrome-meets-prima-endpoint/>
⁴<https://www.businesswire.com/news/home/20230118005359/en/Horizon-Therapeutics-plc-Announces-Phase-2-Trial-Evaluating-Dazodalibep-for-the-Treatment-of-Sj%C3%A0gren%E2%80%99s-Syndrome-Meets-Primary-Endpoint-in-the-Second-Study-Population->



Anti-CD40L Headlines

- Sanofi published their Phase 2 data on their frexalimab in multiple sclerosis in the *New England Journal of Medicine*¹
 - Sanofi projects its Fc-modified humanized anti-CD40L mAb frexalimab will exceed €5 B per year in peak sales²
- Like frexalimab, TNX-1500 is Fc-modified to reduce/eliminate the risk of thrombosis seen with “first generation” anti-CD40L mAbs.



¹ Vermersch P, et al. N Engl J Med. 2024 Feb 15;390(7):589-600. doi: 10.1056/NEJMoa2309439. PMID: 38354138.

² Dunn, A. Endpoints. December 7, 2023. "Sanofi CEO Paul Hudson pitches 12 blockbusters in a bid to convince investors on boosting R&D spend". <https://endpts.com/sanofi-rd-day-ceo-paul-hudson-touts-12-blockbusters-ups-rdspend/>

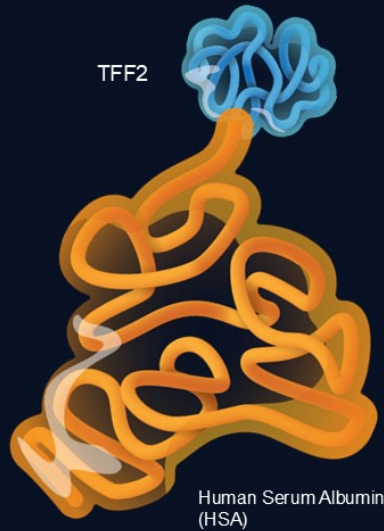
TNX-1700

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

Targeting the toxic tumor micro-environment

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

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



Key Differentiators

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

Preclinical Evidence

- mTNX-1700 (mTFF2-MSA fusion protein) and anti-PD-1 monotherapy each was able to evoke anti-tumor immunity in the MC38 model of colorectal cancer¹
- mTNX-1700 augmented the anti-tumor efficacy of anti-PD-1 therapy in both the MC38 and the CT26.wt models¹

*TNX-1700 is in the pre-IND stage of development and has not been approved for any indication.

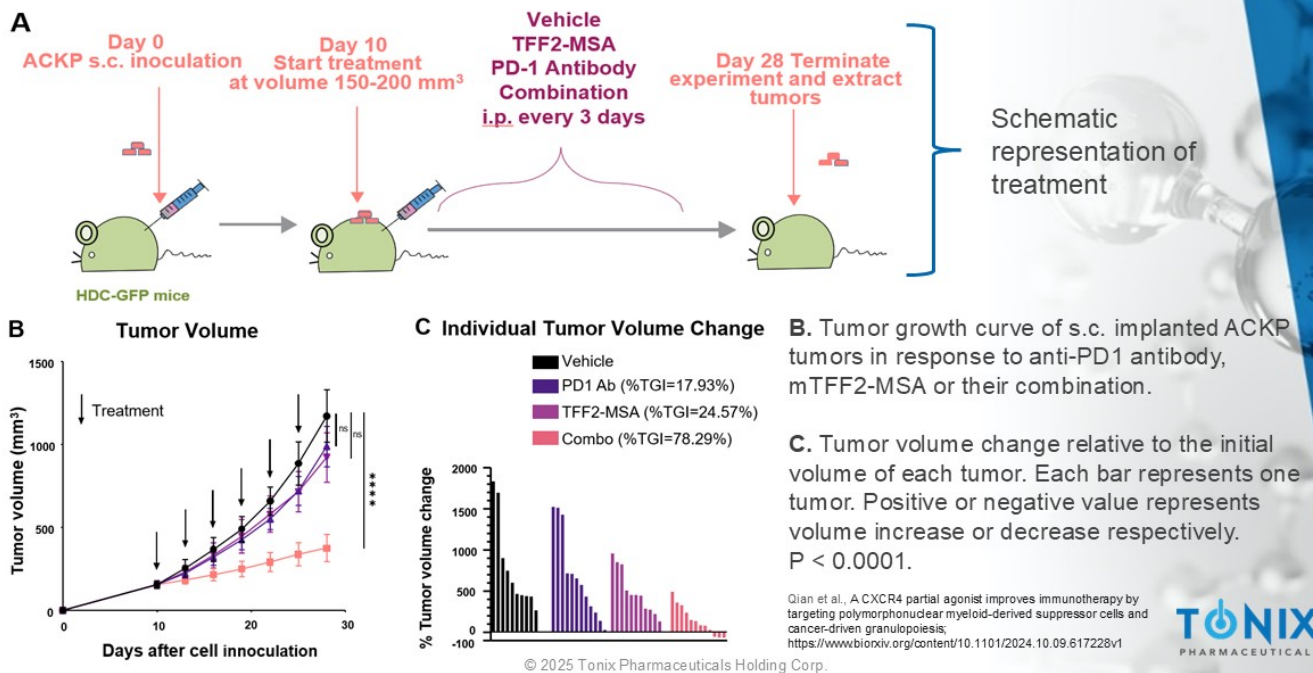
¹Daugherty, B. et al. March 6, 2023 Keystone Poster <https://doi.org/10.1186/1745-6216-149-n1-R1-H1>

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mTNX-1700 (mTFF2-MSA) Showed Synergy with anti-PD1 Antibody in Inhibition of s.c. ACKP Xenograft Growth in Animals





About Gastric and Colorectal Cancer

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

>1.3M People living with colorectal cancer in the US²

>125k People living with gastric cancer in the US³

Current standard of care:

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

Large unmet need:

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

¹American Cancer Society, accessed September 2023 - <https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html>

²NIH, accessed September 2023 - <https://seer.cancer.gov/statfacts/html/colorect.html>

³NIH, accessed September 2023 - <https://seer.cancer.gov/statfacts/html/stomach.html>



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Jessica Morris
Chief Operating Officer



Siobhan Fogarty
Chief Technical Officer



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Milestones: Recently Completed and Upcoming

TNX-102 SL for the Management of Fibromyalgia Milestones

- ✓ 3rd Quarter 2024 FDA Fast Track Designation granted by FDA
- ✓ 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
- August 15, 2025 FDA decision expected on marketing authorization

Other Key Program Milestones

- ✓ 3rd Quarter 2024 U.S. DoD / DTRA Awarded up to \$34 M contract (over 5 years) for broad spectrum antiviral development (TNX-4200)
- ✓ 3rd Quarter 2024 Initiate Phase 2 study of TNX-1300 for the treatment of cocaine intoxication
- ✓ 1st Quarter 2025 Topline results from First in Human Phase 1 Pharmacokinetic and Pharmacodynamic study of TNX-1500 (in development for prevention of organ transplant and treatment of autoimmunity)
- 1st Half 2025 Initiate Phase 2 Investigator-Initiated study at UNC of TNX-102 SL for the treatment of Acute Stress Disorder (ASD) / Acute Stress Reaction (ASR)

*PDUFA = Prescription Drug User Fee Act

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Zembrace® Important Safety Information (1 of 2)

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

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

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

Do not use Zembrace if you have:

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

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

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



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Zembrace® Important Safety Information (2 of 2)

Zembrace may cause serious side effects including:

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

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

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

This is the most important information to know about Zembrace but is not comprehensive. For more information, talk to your provider and read the [Patient Information](#) and [Instructions for Use](#). For full Prescribing Information, visit:

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6e5b104f-2b9e-416e-92fb-ef1bdaea867d>

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

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

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

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Tosymra® Important Safety Information (1 of 2)

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

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

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

Do not use Tosymra if you have:

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

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

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Tosymra® Important Safety Information (2 of 2)

Tosymra may cause serious side effects including:

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

The most common side effects of Tosymra include:

tingling, dizziness, feeling warm or hot, burning feeling, feeling of heaviness, feeling of pressure, flushing, feeling of tightness, numbness, application site (nasal) reactions, abnormal taste, and throat irritation.

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

This is the most important information to know about Tosymra but is not comprehensive. For more information, talk to your provider and read the [Patient Information and Instructions for use](#). For full Prescribing Information, visit:

<https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=015a5cf9-f246-48bc-b91e-cd730a53d8aa>.

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

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

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

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

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