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

FORM 8-K

CURRENT REPORT

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

Date of report (date of earliest event reported): June 16, 2025

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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

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

Emerging growth company ☐

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

Item 7.01 Regulation FD Disclosure.

On June 16, 2025, Tonix Pharmaceuticals Holding Corp. (the "Company") presented data in a poster presentation at the Annual European Congress of Rheumatology 2025, held June 11-14, 2025 ("EULAR"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. A copy of the presentation is furnished hereto as Exhibit 99.02, and incorporated herein by reference

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

Item 8.01. Other Events.

On June 16, 2025, the Company presented data in poster presentation at EULAR titled "*Advancing Fibromyalgia Treatment: Transmucosal Sublingual Cyclobenzaprine (TNX-102 SL) Targets Non-restorative Sleep and Provides Sustained Pain Reduction*".

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 No.	Description.
99.01	Press Release of the Company, June 16, 2025
99.02	Advancing Fibromyalgia Treatment: Transmucosal Sublingual Cyclobenzaprine (TNX-102 SL) Targets Non-restorative Sleep and Provides Sustained Pain Reduction
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

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

TONIX PHARMACEUTICALS HOLDING CORP.

Date: June 16, 2025

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

Exhibit 99.01

Tonix Pharmaceuticals Presented Data and Analyses of TNX-102 SL Treatment Effects on Fibromyalgia at the Annual European Congress of Rheumatology (EULAR) 2025

TNX-102 SL is a sublingual formulation of cyclobenzaprine designed for transmucosal delivery and durable activity in treating fibromyalgia: FDA PDUFA goal date of August 15, 2025

TNX-102 SL demonstrated statistically significant improvement in the primary endpoint of reduction in fibromyalgia pain in two double-blind randomized placebo-controlled Phase 3 studies

If approved by FDA, TNX-102 SL would become the first member of a new class of non-opioid analgesic drugs for fibromyalgia and the first new drug for treating fibromyalgia in more than 15 years

CHATHAM, N.J., June 16, 2025 (GLOBE NEWSWIRE) – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company) presented data in a poster presentation at the Annual European Congress of Rheumatology (EULAR) 2025, held June 11-14, 2025, in Barcelona, Spain. A copy of the Company's poster, titled *"Advancing Fibromyalgia Treatment: Transmucosal Sublingual Cyclobenzaprine (TNX-102 SL) Targets Non-restorative Sleep and Provides Sustained Pain Reduction"* is available under the Scientific Presentations tab of the Tonix website at www.tonixpharma.com. TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is a non-opioid analgesic designed for daily bedtime dosing with an FDA Prescription Drug User Fee Act (PDUFA) goal date of August 15, 2025.

"Fibromyalgia is a complex and invisible chronic pain condition which drives many patients to be prescribed chronic opioids which are associated with addiction and overdose," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "To address the chronic symptoms of fibromyalgia, potential therapeutic options must provide durable benefits. TNX-102 SL has shown statistically significant, durable activity (14 weeks) in reducing fibromyalgia pain in two Phase 3 studies. Designed to target the sleep disturbance of fibromyalgia, TNX-102 SL harnesses the therapeutic activity of cyclobenzaprine in part by reducing in the level of the active metabolite norcyclobenzaprine relative to oral cyclobenzaprine. Norcyclobenzaprine is believed to interfere with the durability of oral cyclobenzaprine's treatment effect in off-label chronic dosing regimens and in a failed double-blind randomized placebo-controlled trial.[1] TNX-102 SL now has the potential to be the first new treatment option for fibromyalgia patients in 15 years."

TNX-102 SL is designed for transmucosal absorption to bypass first-pass hepatic metabolism. The poster presentation shows the day 20 steady state blood levels from a study of nightly TNX-102 SL dosing in which the peak level of cyclobenzaprine exceeds the level of the active metabolite norcyclobenzaprine during sleep time. In contrast, with nightly oral cyclobenzaprine dosing, pharmacokinetic simulations show that norcyclobenzaprine accumulates to higher levels, and the cyclobenzaprine peak level does not exceed the norcyclobenzaprine level during sleep time.

The poster includes data from the RESILIENT Phase 3 study evaluating the efficacy and safety of TNX-102 SL with a primary endpoint of reducing daily pain numeric rating scale scores after 14 weeks of treatment. TNX-102 SL significantly reduced pain and improved clinical outcomes in fibromyalgia patients while demonstrating a favorable tolerability profile. TNX-102 SL employs a novel mechanism targeting the sleep disturbance in fibromyalgia by acting as a potent antagonist at four post-synaptic receptors, each of which is known to regulate sleep.

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. 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.

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-H_1, and muscarinic-M_1-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 deceased levels of the long-lived active metabolite, norcyclobenzaprine in both single dose and multiple dose studies, consistent with bypassing first pass hepatic metabolism. Cyclobenzaprine is a tertiary amine tricyclic and its active metabolite norcyclobenzaprine is a secondary amine tricyclic. 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 during sleep time. In contrast, after 20 days of dosing oral cyclobenzaprine, the simulated peak level of cyclobenzaprine is lower than the simulated background level of norcyclobenzaprine.

Tonix Pharmaceuticals Holding Corp.*

Tonix is a fully integrated biotechnology company focused on transforming therapies for pain management and vaccines for public health challenges. Tonix's development portfolio is focused on central nervous system (CNS) disorders. Tonix's priority is to advance TNX-102 SL, a product candidate for the management of fibromyalgia, for which 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 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. 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.

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

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.

TONIX PHARMACEUTICALS

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ADVANCING FIBROMYALGIA TREATMENT: TRANSMUCOSAL SUBLINGUAL CYCLOBENZAPRINE (TNX-102 SL) TARGETS NONRESTORATIVE SLEEP AND PROVIDES SUSTAINED PAIN REDUCTION

Iredell Iglehart III[1], Gregory Sullivan[2], Seth Lederman[2]

[1]Private Practice, Baltimore, MD, USA, [2]Tonix Pharmaceuticals, Chatham, NJ, USA

INTRODUCTION

- Fibromyalgia (FM) is characterized by widespread pain, fatigue, cognitive disturbances, mood symptoms, and *nonrestorative sleep*, with the final symptom experienced by over 90% of patients[1,2]
- An anomalous non-rapid eye movement (NREM) arousal rhythm has been observed on electroencephalogram (EEG) recordings during sleep in patients with FM[2]
- Additionally, healthy volunteers subjected to noise that artificially disrupts NREM sleep developed a similar EEG anomaly and complained of non-refreshing sleep, diffuse myalgias, and fatigue[4]
- Cyclobenzaprine (CBP) 10-40 mg/d has been investigated as a treatment for FM
  - Meta-analyses of these studies indicate that while CBP significantly improved sleep, it only transiently improved pain, did not affect fatigue, and led to side effects in 85% of patients[5]
- Low-dose CBP (<5 mg/d) administered before bed was shown to improve pain, tenderness, fatigue, mood, and sleep quality[4]
- The ability of CBP to improve sleep quality may be due to its functional antagonism at the 5-HT2A serotonergic, α1-adrenergic, H1-histaminergic, and M1-muscarinic anticholinergic receptors; CBP also has weak inhibitory effects on the serotonin and norepinephrine transporters (SERT and NET, respectively)
- After oral administration, CBP undergoes first-pass metabolism to norcyclobenzaprine (nCBP)
- Compared with CBP, nCBP has a longer half-life (~3 days), lower affinities for the 5HT2A, α1, H1, and M1 receptors, and a higher affinity for the NET, which can be activating
- TNX-102 SL is a transmucosally absorbed formulation of CBP designed to decrease the accumulation of nCBP by reducing first-pass metabolism
- A previous single-dose pharmacokinetic (PK) study revealed that TNX-102 SL 2.8 mg results in 54% higher CBP bioavailability and a 16% lower nCBP AUC relative to that of dose-adjusted oral immediate-release (IR) CBP 5 mg

AIM

- To test the ability of daily bedtime administration of TNX-102 SL to reduce FM pain by targeting nonrestorative sleep with reduced nCBP accumulation interference

METHODS

Phase 1 PK Study and PK Modeling

- A single-center, open-label, randomized, multiple-dose, 2-arm, parallel study (N=24) compared the PKs of TNX 102 SL 5.6 mg (2 × 2.8 mg) tablets with AMRIX extended-release (ER) capsules at the maximum recommended daily dose of 30 mg/d
- The study included a 30-day screening period and a 21-day confinement period with 20-day daily dosing to reach steady state; PK blood collection was performed up to 648 hours (27 days) after the last dose
- The following PK parameters were calculated by standard noncompartmental methods for CBP and nCBP:
  - Day 1: $AUC_{0\text{-}24}$, C_{max}, T_{max}
  - Day 20: $AUC_{0\text{-}tau}$, AUC_{ss}, $AUC_{0\text{-}inf}$, $C_{max\ ss}$, $C_{min\ ss}$, residual area, T_{max}, $T_{½\ el}$, K_{el}, FI (%)
- The TNX-102 SL 5.6 mg PK data were compared against PK simulations of steady-state oral IR CBP 10 mg
  - Concentration-time profiles of CBP and nCBP during multiple dosing of oral IR CBP 10 mg once daily at steady state were simulated from single-dose oral IR CBP 5 mg data from a previous study using nonparametric superposition methodology assuming linear PKs for CBP and nCBP

Phase 3 Confirmatory Registrational Study

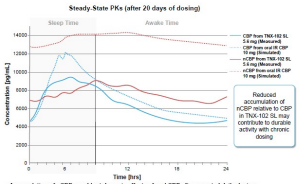
- The RESILIENT study randomized patients with FM 1:1 to receive TNX-102 SL 2.8 mg for 2 weeks followed by 5.6 mg for 12 weeks or matching placebo for 14 weeks.
- The primary endpoint was change from baseline to Week 14 in weekly average of daily diary pain numeric rating scale (NRS) scores analyzed by mixed model repeated measures (MMRM), with multiple imputation (MI) for missing data
- Key secondary endpoints included evaluations of the effects of TNX-102 SL on sleep (PROMIS Sleep Disturbance and daily sleep quality NRS scores) and fatigue (PROMIS Fatigue scores) at Week 14, which were analyzed in the same manner as the primary endpoint
- Safety was assessed by adverse events, vital signs/weight, physical exams, clinical lab tests, C-SSRS, and Beck Depression Inventory II (BDI-II)

RESULTS

PK Study and Modeling

- PK results showed that following the first (Day 1) and last (Day 20) dose of TNX-102 SL 5.6 mg, exposure to CBP and its long-lasting major metabolite, nCBP, was less than with AMRIX ER 30 mg
- In a 20-day multiple-dose PK study, TNX-102 SL achieved a higher dynamic peak CBP level at steady state compared with the background level of nCBP
- A total of 9 phase I metabolites and 8 phase II metabolites were detected in human plasma after dosing with CBP
  - All metabolites detected after TNX-102 SL 5.6 mg dosing were also detected in the samples after dosing with AMRIX 30 mg ER capsules, no new metabolites were noted with the SL formulation
- Day 20 concentration-time profiles of CBP and nCBP after TNX-102 SL 5.6 mg administration and simulated oral CBP 10 mg administration are displayed in **Figure 1**
- In the 8 hours following bedtime administration of TNX-102 SL 5.6 mg, steady-state CBP AUC and C_{max} were higher than nCBP AUC and C_{max}; after simulated oral CBP administration, nCBP AUC and C_{max} were higher than those of CBP

Figure 1. Multiple-Dose PKs of TNX-102 SL 5.6 mg (Measured) Compared With Immediate-Release Oral Cyclobenzaprine 10 mg (Simulated)



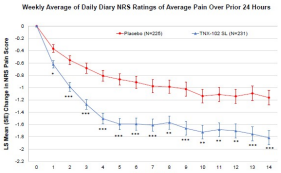
Accumulation of nCBP may blunt dynamic effects of oral CBP after repeated daily dosing

CBP, cyclobenzaprine; IR, immediate release; nCBP, norcyclobenzaprine; SL, sublingual.

RESILIENT Efficacy

- In the Phase 3 RESILIENT study, a total of 457 patients with FM were randomized to TNX-102 SL 5.6 mg administered before bedtime (n=231) or placebo (n=226)
- In total, 436 (95.4%) were females, 386 (84.5%) were White/Caucasian, mean (SD) duration of FM disease was 9.2 (9.0) years, and mean (SD) baseline NRS pain score was 5.9 (1.1)
- TNX-102 SL demonstrated a highly statistically significant improvement in the primary endpoint, ie, mean weekly average of daily NRS pain scores vs placebo at Week 14 (p<0.0001, **Figure 2**)
  - Significant pain score improvements vs placebo were observed beginning at Week 1 and continued each week through Week 13 (p-values descriptive for Weeks 1-13)

Figure 2. In the RESILIENT Study, TNX-102 SL Significantly Improved Weekly Average Pain Scores vs Placebo at Week 14[#]



Week 14 LS mean (SE) change from baseline for TNX-102 SL, -1.82 (0.12) and for placebo, -1.16 (0.12); LSMD from placebo, -0.65 (0.16); p=0.00005[#]

*p<0.01, **p<0.001, ***p<0.0001

[#]Based on mixed model repeated measures with multiple imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction.

LS, least-squares; LSMD, least-squares mean difference; NRS, numerical rating scale; SE, standard error.

- Furthermore, differences in key secondary endpoints evaluating sleep and fatigue were statistically significant (all p-values <0.001) vs placebo (**Table 1**). Effect size for the primary endpoint was 0.38, and those for sleep and fatigue secondary endpoints ranged from 0.32–0.50.

Table 1. Key Secondary Efficacy Endpoints Evaluating Sleep and Fatigue Outcomes at Week 14

Secondary Endpoint	TNX-102 SL LS Mean (SE)	Placebo LS Mean (SE)	LS Mean (SE) Difference	P-value	Effect Size*
PROMIS Sleep Disturbance	-8.44 (0.58)	-4.20 (0.56)	-4.24 (0.79)	<0.0001	0.50
Diary Sleep Quality Ratings	-1.77 (0.12)	-1.20 (0.12)	-0.57 (0.17)	<0.001	0.32
PROMIS Fatigue	-7.18 (0.55)	-4.16 (0.56)	-3.01 (0.77)	<0.0001	0.37

*Effect size calculated as: effect size = (difference in LS means/standard error) x square root ($1/N_{placebo} + 1/N_{active}$). MMRM with MI, LS, least-squares; SE, standard error.

RESILIENT Safety and Tolerability

Table 2. Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥3% of Patients in Any Treatment Group

System Organ Class Preferred Term*, n (%)	TNX-102 SL (n=231)	Placebo (n=226)
Systemic Adverse Events		
COVID-19	10 (4.3)	7 (3.1)
Somnolence	7 (3.0)	3 (1.3)
Headache	7 (3.0)	4 (1.8)
Oral Cavity Adverse Events		
Hypoesthesia, oral	55 (23.8)	1 (0.4)
Product taste abnormal	27 (11.7)	2 (0.9)
Paresthesia, oral	16 (6.9)	2 (0.9)
Tongue discomfort	16 (6.9)	0 (0.0)

*Adverse events are coded using MedDRA, version 23.0.

- 81.0% of patients on TNX-102 SL and 79.2% on placebo completed the study
- TEAEs led to discontinuation in 6.1% and 3.6% of patients in the TNX-102 SL and placebo groups, respectively
- Two patients (0.9%) on TNX-102 SL and 3 patients on placebo had serious adverse events; only ↑ (acute pancreatitis) in a patient taking TNX-102 SL was considered possibly related to treatment
- There were no safety signals by vital signs, weight, clinical labs, or physical exams or on C-SSRS or BDI-II

CONCLUSIONS

- Given the intended daily therapeutic administration of TNX-102 SL* at bedtime, these data indicate that at steady state, CBP AUC and C_{max} values are higher from 0-8 hours post-dose than are nCBP AUC and C_{max} values
- In contrast, simulation of steady state PK parameters following bedtime administration of oral IR CBP 10 mg predicts higher nCBP AUC and C_{max} compared with CBP AUC and C_{max}
- The dynamic changes in CBP and nCBP PKs that occur over 24 hours following administration of TNX-102 SL are believed to optimize its effects on the brain, with higher predicted occupancy at relevant receptors (5-HT2A, α1, H1and M1) during typical sleep hours
- From a clinical perspective, pharmacologically targeting nonrestorative sleep using TNX-102 SL administered at bedtime resulted in a statistically significant reduction in the primary pain efficacy endpoint in RESILIENT while also providing statistically significant improvement in sleep and fatigue outcomes vs placebo and was generally well-tolerated
- These findings highlight the potential of TNX-102 SL as a novel, non-opioid analgesic for patients with FM

*TNX-102 SL is an investigational new drug and has not been approved for any indication.

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CONFLICT OF INTEREST

Iredell Iglelhart III is an independent consultant.
Gregory Sullivan and Seth Lederman are employees of Tonix Pharmaceuticals.

ACKNOWLEDGEMENT

This study was supported by Tonix Pharmaceuticals (Chatham, NJ). Medical writing assistance was provided by Woven Health Collective (New York, NY) and was funded by Tonix Pharmaceuticals.

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