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): May 1, 2023

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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

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

Emerging growth company ☐

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

Item 7.01 Regulation FD Disclosure.

Tonix Pharmaceuticals Holding Corp. (the "Company") updated its investor presentation, which is used to conduct meetings with investors, stockholders and analysts and at investor conferences, and which the Company intends to place on its website, which may contain nonpublic information. The Company also updated its TNX-601 (tianeptine hemioxalate extended-release tablets) product candidate presentation which it intends to place on its website and which may contain nonpublic information. A copy of the presentations are filed as Exhibits 99.01 and 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 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	**Description.**
99.01	Corporate Presentation by the Company for May 2023
99.02	TNX-601 Product Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

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

TONIX PHARMACEUTICALS HOLDING CORP.

Date: May 1, 2023

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

Exhibit 99.01

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; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

TONIX PHARMACEUTICALS

Who We Are

OUR MISSION

Tonix Pharmaceuticals is committed to improving population health by **inventing and developing** innovative therapies and vaccines, through **broad in-house capabilities and creative collaborations**, to help address important unmet needs.

OUR VISION

Tonix strives to be a leader in providing **novel drug therapies and vaccines** to **improve population health around the world.**

Investment Highlights

DIVERSE PIPELINE

Tonix's core focus is on **central nervous system** disorders, but we also target unmet needs across multiple therapeutic areas including **immunology, infectious disease** and **rare disease.**

IN-HOUSE CAPABILITIES

Investment in domestic**, in-house, R&D and manufacturing** to accelerate development timelines and improve the ability to respond to pandemics.

STRATEGIC PARTNERSHIPS

Partnering strategically with other **biotech companies**, **world-class academic and non-profit research organizations** to bring innovative therapeutics to market faster.

FINANCIAL POSITION

Tonix had approximately **$120 M in cash and cash equivalents** as of 12/31/22. Tonix has no debt.

Pipeline: Key Clinical Programs

Candidates*	Indication	Status/Next Milestone
TNX-102 SL[1]	Fibromyalgia (FM) Long COVID (PASC[2])	Mid-Phase 3 - >50% enrolled Phase 2 enrollment complete
TNX-1300[3]	Cocaine Intoxication - *FDA Breakthrough Designation*	Mid-Phase 2, Targeted 3Q 2023 Start
TNX-1900[4]	Prevention of Chronic Migraine	Phase 2 - enrolling[5]
TNX-601 ER	Depression	Phase 2 - enrolling[6]
TNX-2900[7]	Prader-Willi Syndrome - *FDA Orphan Drug Designation*	Phase 2 ready
TNX-1500[8]	Organ Transplant Rejection/ Autoimmune Conditions	Phase 1, Targeted 3Q 2023 Start
TNX-801[9]	Smallpox and mpox vaccine	Phase 1, Targeted 2H 2023 Start

*All of Tonix's product candidates are investigational new drugs or biologics and none has been approved for any indication.
[1]TNX-102 SL (cyclobenzaprine HCl sublingual tablets) also has active INDs for Agitation in Alzheimer's Disease (AAD), Alcohol Use Disorder (AUD), and Posttraumatic Stress Disorder (PTSD). All indications are Phase 2 ready.
[2]Post-Acute Sequelae of COVID-19.
[3]TNX-1300 (double-mutant cocaine esterase) is licensed from Columbia University.
[4]Acquired from Trigemina; license agreement with Stanford University; Planned investigator-initiated Binge Eating Disorder (BED) study is expected start 2Q 2023.
[5]A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900
[6]Phase 1 trial for formulation development was completed outside of the U.S.; Other potential indications include PTSD and neurocognitive dysfunction from steroids
[7]Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)
[8]anti-CD40L humanized monoclonal antibody
[9]Live attenuated vaccine based on horsepox virus

TONIX PHARMACEUTICALS

Five Late-Stage CNS Programs to be in the Clinic by 1H 2023[1]
Three studies Enrolling Now

CNS PORTFOLIO

Active Studies

- **In Phase 3:**
  - TNX-102 SL for fibromyalgia (>50% enrolled) — Potential Pivotal Study
- **In Phase 2:**
  - TNX-102 SL for fibromyalgia-type Long COVID (enrollment complete)
  - TNX-1900 for migraine headache (new mechanism for US patients)
  - TNX-601 ER for major depressive disorder (new mechanism for US patients) — Potential Pivotal Study

Entering Phase 2

- **In 3Q 2023:**
  - TNX-1300 for cocaine intoxication (FDA Breakthrough Therapy Designation) — Potential Pivotal Study

[1]Not approved for any indication

TONIX PHARMACEUTICALS

TNX-102 SL*
Cyclobenzaprine (Protectic®) Pipeline in a Product

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

Potent binding and antagonist activities at the serotonergic-5-HT2A, adrenergic-α1, histaminergic-H1, and muscarinic-M1 cholinergic receptors to facilitate restorative sleep

Innovative and proprietary PROTECTIC® Rapid drug exposure following nighttime administration

Differentiators:

Relative to Oral Cyclobenzaprine
- Lower daytime exposure
- Avoids first-pass metabolism
- Reduces risk of pharmacological interference from major metabolite

Relative to Standard of Care
- Potential for better tolerability while maintaining efficacy

Patents Issued

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

Fibromyalgia
Status: Mid-Phase 3
- One positive Phase 3 study (RELIEF) completed
- Second Phase 3 study (RALLY) missed primary endpoint
- Confirmatory Phase 3 study (RESILIENT) is currently enrolling
  - >50% enrolled

Next Steps: Topline results expected 4Q 2023

Fibromyalgia-Type Long COVID
Status: Phase 2
- Phase 2 study (PREVAIL) has completed enrollment of 60 patients

Next Steps: Topline results expected 3Q 2023

TONIX PHARMACEUTICALS

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

CNS PORTFOLIO

PROFILE

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

- Afflicts an estimated 6-12 million adults in the U.S., approximately 90% of whom are women[1]
- Symptoms include chronic widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction
- Patients struggle with daily activities, have impaired quality of life, and frequently are disabled
- Physicians and patients report common dissatisfaction with currently marketed products

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

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Fibromyalgia

Additional Indications: Long COVID, PTSD, Agitation in Alzheimer's, Alcohol Use Disorder

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

Second Phase 3 study RALLY missed primary endpoint

Confirmatory Phase 3 study RESILIENT is currently enrolling

Next Steps: Topline results expected 4Q 2023

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

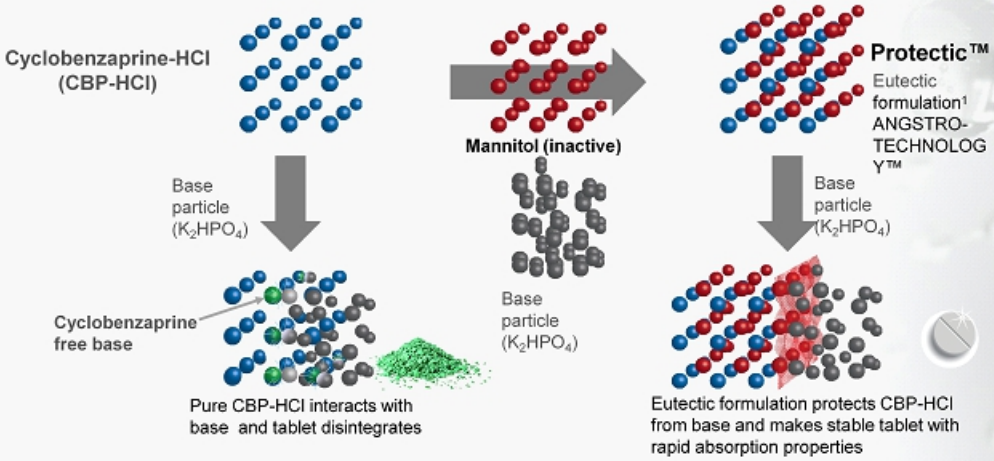
[1]American Chronic Pain Association (www.theacpa.org, 2019)
[2]Lederman et al., (2023) *Arthritis Care & Research* "Efficacy and Safety of TNX-102 SL (Sublingual Cyclobenzaprine) for the Treatment of Fibromyalgia: Results From the RELIEF Trial", in press

TONIX PHARMACEUTICALS

TNX-102 SL (Sublingual Cyclobenzaprine HCl tablets*)

CNS PORTFOLIO

Proprietary cyclobenzaprine HCl eutectic mixture stabilizes sublingual tablet formulation



*U.S. Patent issued May 2, 2017

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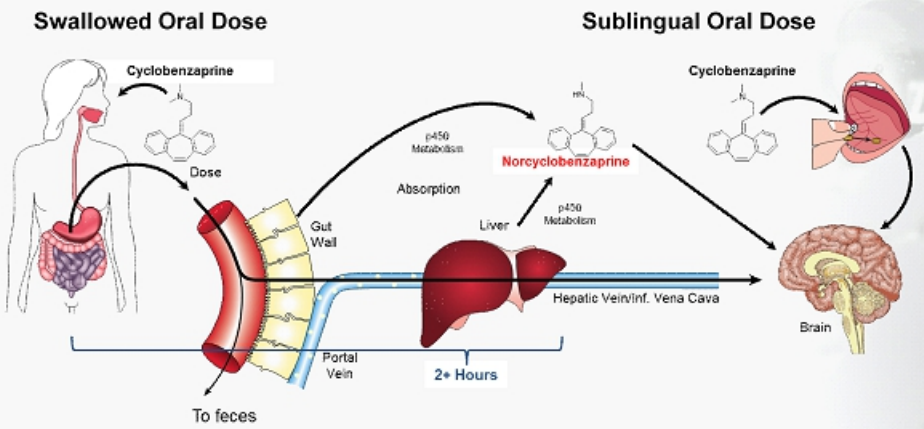
TNX-102 SL Sublingual Administration*

Transmucosal absorption avoids first pass hepatic metabolism



*U.S. Patent issued May 2, 2017

TNX-102 SL: Phase 3 RESILIENT Study Design

General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia
- U.S. sites only, expected to enroll approximately 470 patients

Primary Endpoint:

- Daily diary pain severity score change from baseline to Week 14 (TNX-102 SL vs. placebo)
  - Weekly averages of the daily numerical rating scale scores

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

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

Placebo once-daily at bedtime

14 weeks

ClinicalTrials.gov Identifier: NCT05273749
A Phase 3 Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily in Patients With Fibromyalgia (RESILIENT)

TNX-102 SL*: Fibromyalgia-Type Long COVID (PASC)
Cyclobenzaprine Protectic® Sublingual Tablets

PROFILE

- Occurs in approximately 13% of recovered COVID-19 patients[1]
- As many as 40% of Long COVID patients experience multi-site pain, a hallmark of fibromyalgia[2,3]
- Symptoms of Long COVID, like multi-site pain, fatigue and insomnia, are the hallmarks of chronic pain syndromes like fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- In August 2022, the HHS released the National Research Action Plan on Long COVID[4] which endorses the connection between Long COVID and chronic fatigue syndrome

DEVELOPMENT PROGRAM

Market Entry: Fibromyalgia-Type Long COVID (PASC)

Additional Indications: Fibromyalgia, PTSD, Agitation in Alzheimer's, Alcohol Use Disorder

Status: Phase 2 study PREVAIL has completed enrollment of 60 patients

Next Steps: Topline results expected 3Q 2023

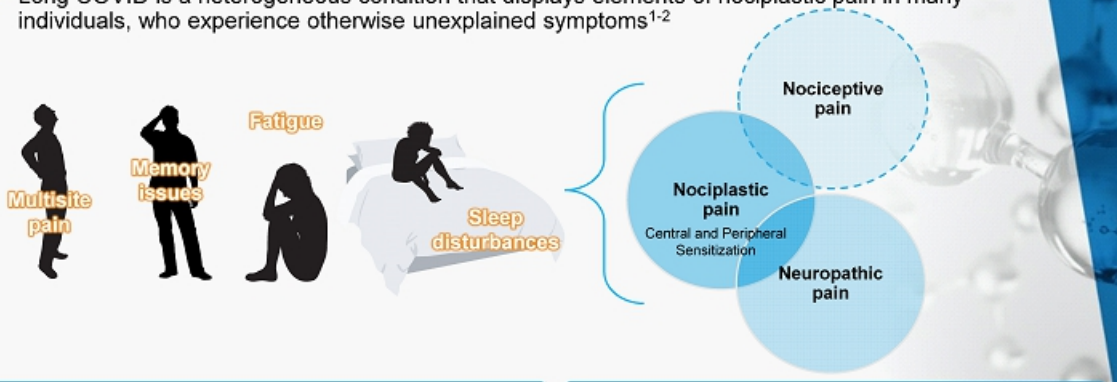
Patents Issued

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

[1]September 1, 2022- CDC - https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
[2]Harris, H, et al. Tonix data on file. 2022
[3]TriNetX Analytics
[4]Department of Health and Human Services, Office of the Assistant Secretary for Health. 2022. National Research Action Plan on Long COVID.

Fibromyalgia-Type Long COVID

- Long COVID is a heterogeneous condition that displays elements of nociplastic pain in many individuals, who experience otherwise unexplained symptoms[1-2]



Symptoms (multi-site pain, fatigue, sleep disorders and cognitive dysfunction) overlap with the key symptoms of fibromyalgia

Nociplastic pain[3]: (*new term for "Central and Peripheral Sensitization"*) Pain that arises from altered nociception despite no clear evidence of tissue damage, or for disease or lesion of the somatosensory system causing the pain

[1]Bierle et al., 2021. *J Prim Care Community Health.* 12:21501327211030826
[2]Moghimi et al., 2021. *Curr Neurol Neurosci Rep.* 21(9):44
[3]Trouvin et al., 2019. *Best Pract Res Clin Rheumatol.* 33(3):101415

TNX-102 SL: Phase 2 PREVAIL Study Design

PREVAIL Study

CNS PORTFOLIO

Study characteristics:

- Randomized, double-blind, placebo-controlled study of TNX-102 SL in fibromyalgia-type Long COVID
- U.S. sites only, has enrolled approximately 60 patients

Primary Endpoint:

- Daily diary pain severity score change from baseline to Week 14 (TNX-102 SL vs. placebo)
  - Weekly averages of the daily numerical rating scale scores

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

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

Placebo once-daily at bedtime

ClinicalTrials.gov Identifier: NCT05472090
"A Phase 2 Study to Evaluate the Efficacy and Safety of TNX-102 SL in Patients With Multi-Site Pain Associated With Post-Acute Sequelae of SARS-CoV-2 Infection (PREVAIL)"

14 weeks

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TNX-601 ER*: Depression
Tianeptine Hemioxalate Extended-Release Tablets (39.4 mg)

CNS PORTFOLIO

PROFILE

- A novel, oral, extended-release once-daily tablet
- Treatment effect of tianeptine sodium immediate release *t.i.d.* in depression is well-established
- Tianeptine restores neuroplasticity in animal models
- Indirectly modulates the glutamatergic system
- Does not interact with AMPA, NMDA or kainate receptors[1]

Differentiators:

Relative to tianeptine IR available ex-US:

- Once daily dosing

Relative to traditional antidepressants:

- Unique mechanism of action – beyond neurotransmitter modulation
- Tianeptine sodium IR has similar efficacy but fewer side effects than traditional antidepressants

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Disorder From Corticosteroids, Alzheimer's Disease[2]

Status: Phase 2 MDD study UPLIFT is currently enrolling

Next Steps: Interim analysis results on first 50% of sample expected 4Q 2023

*TNX-601 ER has not been approved for any indication.

[1]AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA=N-methyl-D-aspartate
[2]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

TONIX PHARMACEUTICALS

TNX-601 ER - Phase 2 UPLIFT* Study Design

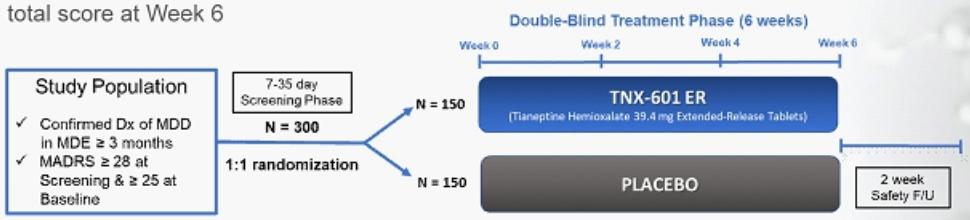
UPLIFT Study

General study characteristics:

- Randomized, double-blind, placebo-controlled study in Major Depressive Disorder to evaluate monotherapy with TNX-601 ER versus placebo
- Parallel design with two arms – treatment with tianeptine hemioxalate 39.4 mg or placebo
- ~30 U.S. sites only, expected to enroll approximately 300 patients
- One unblinded interim analysis based on 50% of randomized participants expected 4Q'23

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6



*ClinicalTrials.gov Identifier: NCT05686408

Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number

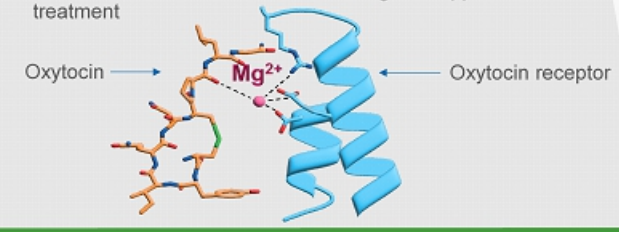
TONIX PHARMACEUTICALS

TNX-1900*: Migraine
Intranasal Potentiated Oxytocin (OT) with Magnesium

PROFILE

- Intranasal OT has potential utility in treating migraine[1]
- Magnesium is known to potentiate the binding of OT to its receptor[2,3]
- One billion individuals worldwide suffer from migraines

Differentiator: Novel non-CGRP antagonist approach to treatment



Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Chronic Migraine

Additional Indications: Acute Migraine, Craniofacial Pain, Insulin Resistance, Binge Eating Disorder

Status: Phase 2 study PREVENTION is currently enrolling[4]

Next Steps: Topline results expected 4Q 2023

Investigator initiated Phase 2 trial in obesity-associated binge eating disorder 2Q 2023

*TNX-1900 has not been approved for any indication. CGRP = calcitonin gene-related peptide.

[1]Tzabazis et al., 2017. *Headache*. 57 Suppl 2:64-75
[2]Antoni et al., 1989. *Biochem J*. 257(2):611-4
[3]Meyerowitz et al., 2022. *Nat Struct Mol Biol*. (3):274-281
[4]A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900

TONIX PHARMACEUTICALS

TNX-1900: Phase 2 PREVENTION Study Design

PREVENTION Study

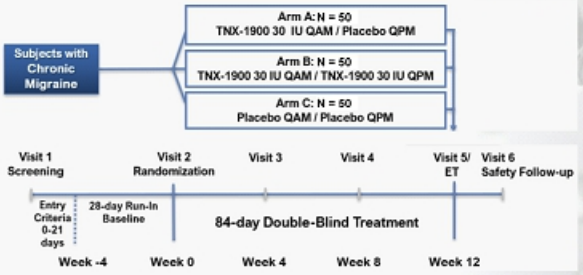
CNS PORTFOLIO

General study characteristics:

- Randomized, double-blind, placebo-controlled study (three arms– two treatment regimens and one placebo) in chronic migraine
- U.S. sites only, expected to enroll approximately 150 patients
- Topline results expected 4Q'23

Primary Endpoint:

- Mean change in the number of migraine headache days between the 28-day Run-In phase and the last 28-days of the Treatment phase (TNX-1900 vs. placebo)



ClinicalTrials.gov Identifier: NCT05679908
A Study to Evaluate the Efficacy and Safety of TNX-1900 in Patients With Chronic Migraine (PREVENTION)

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TNX-1300*: Cocaine Intoxication
Cocaine Esterase (CocE)

CNS PORTFOLIO

PROFILE

Cocaine is the main cause for drug-related ED visits[1]

CocE is a recombinant protein that degrades cocaine in the bloodstream

- Rapidly reverses physiologic effects of cocaine
- Drops plasma exposure by 90% in 2 minutes

Differentiators: Rapidly metabolizes cocaine in the bloodstream; no other product currently on the market for this indication

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Cocaine Intoxication

Status: Mid-Phase 2

Next Steps: Initiate new Phase 2 trial 3Q 2023

- Single-blind, placebo (+ usual care) controlled, randomized, potentially pivotal study
- Expected to enroll approximately 60 emergency department patients at sites in the US

FDA Breakthrough Therapy Designation

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

[1]Havakuk et al., 2017. *J Am Coll Cardiol.* 70:101-113.
ED = emergency department.

TONIX PHARMACEUTICALS

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

TNX-2900*: Hyperphagia in Prader-Willi Syndrome
Intranasal Potentiated Oxytocin (OT) with Magnesium

PROFILE

Prader-Willi Syndrome is the most common genetic cause of life-threatening childhood obesity

- Rare disease occurring in 1 in 10,000 to 1 in 30,000 births

Differentiator: No approved therapeutic currently on the market for hyperphagia in PWS

Dangers of PWS Hyperphagia:

Unhealthy behaviors around food[1-4] → Consequences such as obesity, type 2 diabetes, cardiovascular disease[1-5] → Caretaker Burden[1-4]:

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Hyperphagia in Prader-Willi Syndrome

Additional Indications: Rare Hyperphagia Conditions

Status: Phase 2 ready

Next Steps: IND submission

FDA Orphan Drug Designation

*TNX-2900 is in the pre-IND stage of development and has not been approved for any indication.

RARE DISEASE PORTFOLIO

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

TONIX PHARMACEUTICALS

TNX-1500*

Next Generation α-CD40 Ligand (CD40L) Antibody

The CD40-CD40L pathway is a pivotal immune system modulator and a well-established and promising treatment target

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. Patents filed.

Prevention of Allograft Rejection

Status: Phase 1 ready

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

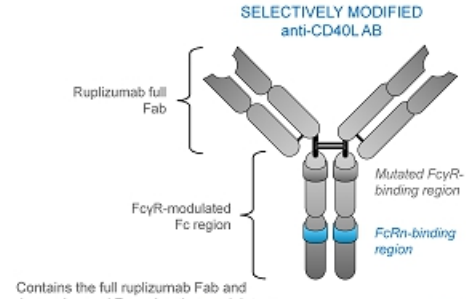
Next Steps: Initiate Phase 1 study 3Q 2023

Autoimmune Diseases

Status: Potential future indications include:

Sjögren's Syndrome, Systemic Lupus Erythematosus

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

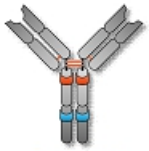


Contains the full ruplizumab Fab and the engineered Fc region that modulates FcγR-binding, while preserving FcRn function.

TONIX PHARMACEUTICALS

Third-Generation α-CD40L
Engineered to Decrease Risk of Thrombosis

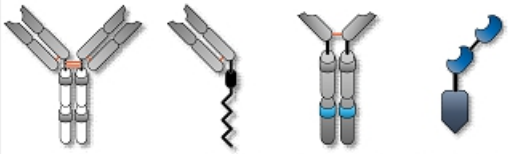
First-generation anti-CD40L mAbs



Ruplizumab

Constant fragment (Fc) domain interacted with FcγRIIA (CD32A), which suggested a mechanism for the increased risk of thrombosis.[1,2]

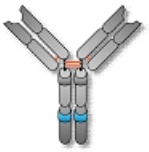
Second-generation anti-CD40L proteins



Aglycosyl Ruplizumab | *Dapirolizumab* | *Letolizumab* | *Dazodalibep*

Second-generation anti-CD40L proteins exhibited dramatically reduced binding to FcγRIIA[3-6] but had other issues, including decreased efficacy, shortened half-life, or engendering of anti-drug antibodies (ADAs).[7-9]

Third-generation anti-CD40L mAbs*



TNX-1500

TNX-1500 is engineered to target CD40L therapeutically while reducing FcγRIIA binding and thereby lowering the potential for thrombosis.[1-9]

*Sanofi's frexalimab (formerly SAR441344) and Eledon's tegoprubart (formerly AT-1501) also are Fc modified

[1]Inwald et al., 2003. *Circ Res.* 92(9):1041-1048
[2]Robles-Carrillo et al., 2010. *J Immunol.* 185(3):1577-1583
[3]Shock et al., 2015. *Arthritis Res Ther.* 17(1):234
[4]Xie et al., 2014. *J Immunol.* 192(9):4083-4092
[5]Ferrant et al., 2004. *Int Immunol.* 16(11):1583-1594
[6]Karnell et al., 2019. *Sci Transl Med.* 11(489):eaar6584
[7]ClinicalTrials.gov identifier: NCT02273960. Updated July 16, 2019. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/results/NCT02273960?view=results
[8]Waters, 2018. *Biocentury.*
[9]Company data

TONIX PHARMACEUTICALS

Other anti-CD40L Monoclonal Antibodies in Development

UCB (Co-developed with Biogen) – Systemic Lupus Erythematosus (SLE)
- Phase 3 Trial Currently Enrolling (NCT04294667)
  - Topline results expected 1H 2024[1]
- Dapirolizumab pegol (pegylated Fab)

Horizon (being acquired by Amgen) – Sjögren's Syndrome (SjS)
- Two Positive Phase 2 studies reported[2,3]
- Dazodalibep (tn03 fusion protein)

Sanofi – Sjögren's Syndrome (SjS), Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE)
- Phase 2 Trial Currently Enrolling in SjS (NCT04572841) and SLE (NCT05039840)
- Active Phase 2 Trial in Relapsing MS (NCT04879628)
- SAR441344 (Fc-modified)

Eledon – Amyotrophic Lateral Sclerosis (ALS) and 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)

Lundbeck and AprilBio – Neurology
- Phase 1 Trial Currently Enrolling in Healthy Adults (NCT05136053)
- APB-A1 or Lu AG22515 (HAS fusion protein)

[1]https://www.ucb.com/our-science/pipeline
[2]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating
[3]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-0

TONIX PHARMACEUTICALS

TNX-801*

Recombinant Pox Vaccine (RPV) Platform Using Live Virus Technology

Differentiators:

- **Live virus vaccines are the most established vaccine technology**
  - Starting with Edward Jenner's smallpox vaccine, the first vaccine, which eradicated smallpox
  - 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 shot administration
- **Standard refrigeration required for shipping and storage**

*TNX-801 is in the pre-IND stage of development and has not been approved for any indication. Patents filed.

[1]Noyce et al., 2018. *PLoS One*. 13(1):e0188453.

Mpox and Smallpox Vaccine

Status: Preclinical

- TNX-801 is a cloned version of horsepox[1] (without any insert) purified from cell culture

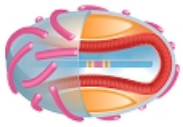
Next Steps: Initiate Phase 1 Trial 2H 2023

Vaccine for Future Emerging Infectious Diseases

Example: TNX-1850 for COVID-19

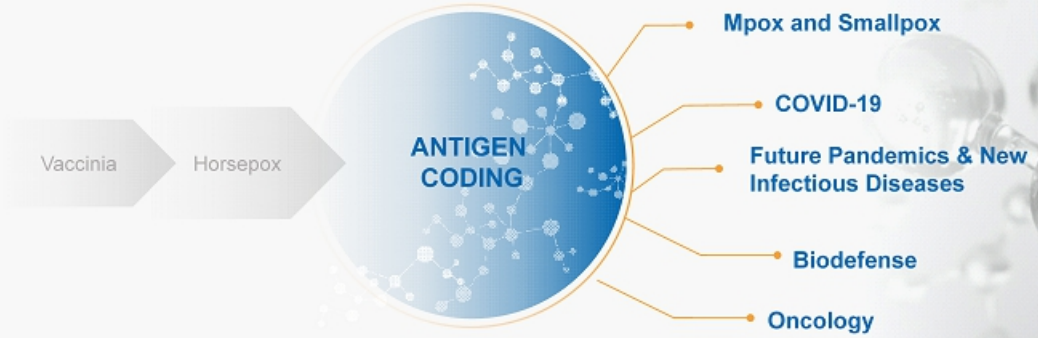
Status: Model System

TNX-801*
scHPXV (Horsepox)
212,811 bp



TONIX PHARMACEUTICALS

Live Virus Vaccine Platform: Recombinant Pox Vaccine (RPV)
Technology for Emerging Infectious Diseases and Oncolytics



RPV VECTOR BELIEVED SIMILAR TO EDWARD JENNER'S VACCINE[1-3]

Using Proven Science To Address Challenging Disease States, We Have Created A Programmable Technology Platform Aimed At Combating Future Threats To Public Health

[1]Shrick, 2017. *N Engl J Med* 377:1481-1492
[2]Esparza, 2020. *Vaccine*. 38(30): 4773–4779
[3]Brinkmann, 2020. *Genome Biol*. 21: 286

TONIX PHARMACEUTICALS

Internal Development & Manufacturing Capabilities

R&D Center (RDC) – Frederick, MD
- **Functions:**
  - Accelerated development of vaccines and antiviral drugs against COVID-19, its variants and other infectious diseases
  - Research advancing CNS and immunology drugs
- **Description:** ~48,000 square feet, BSL-2 with some areas designated BSL-3
- **Status:** Operational

Advanced Development Center (ADC) – North Dartmouth, MA
- **Function:** Development and clinical scale manufacturing of biologics
- **Description:** ~45,000 square feet, BSL-2
- **Status:** Operational

Commercial Manufacturing Center (CMC) – Hamilton, MT
- **Function**: Phase 3 and Commercial scale manufacturing of biologics
- **Description:** ~44-acre green field site, planned BSL-2
- **Status:** Planning for site enabling work in 2023

Architectural Rendering

TONIX PHARMACEUTICALS

Pipeline: Key Pre-Clinical Programs

Candidates*	Indication	Status/Next Milestone
TNX-1600[1]	Depression, PTSD and ADHD	Preclinical
TNX-1700[2]	Gastric and colorectal cancers	Preclinical
TNX-1850[3]	COVID-19 (horsepox-based live virus vaccine platform)	Preclinical
TNX-2300[4]	COVID-19 (bovine parainfluenza virus-based live virus vaccine)	Preclinical
TNX-3700[5]	COVID-19 (zinc nanoparticle mRNA technology)	Preclinical
TNX-3900	Filoviruses (broad spectrum antiviral)	Preclinical
TNX-4000	Filoviruses (broad spectrum antiviral)	Preclinical

[1]Acquired from TRImaran Pharma; license agreement with Wayne State University
[2]Recombinant trefoil factor 2 (rTFF2) based protein; licensed from Columbia University
[3]Live attenuated vaccine based on horsepox virus vector, expressed SARS-CoV-2 spike protein. TNX-1850 is based on the BA.2 variant spike protein.
[4]Live attenuated vaccine based on bovine parainfluenza (BPI) virus
[5]COVID vaccine based on mRNA in zinc nanoparticle (ZNP) formulation with CD40L molecular trigger

TNX-1700*: Gastric and Colorectal Cancers
Recombinant Trefoil Factor 2 (rTFF2-HSA) Fusion Protein

IMMUNOLOGY PORTFOLIO

Potential New Cancer Treatment

- TNX-1700 (rTFF2-HSA) has effects on cancer by altering the tumor micro-environment
- Mechanism of action: suppresses myeloid-derived suppressor cells and activates anti-cancer CD8+ T cells
- Potential synergy with anti-PD1 or anti-PD-L1 monoclonal antibodies (mAbs)

Preclinical Evidence for Inhibiting Growth of Cancer Cells

- In an MC38 mouse model of colorectal cancer, mTNX-1700 (murine TNX-1700) alone inhibited tumor growth by 50%, and combination therapy with anti-PD1 inhibited tumor growth by 87%[1]
- In an advanced mouse model of gastric cancer, mTNX-1700 combination therapy with anti-PD1 inhibited tumor growth by 78%[2]
- Mechanistically, the combination therapy reduced intratumoral MDSCs, profoundly increased tumor-infiltrating CD8+ T cells, and significantly reduced spontaneous metastasis[2]

Market Entry: Immuno-oncology, combination therapy with PD1 blockers for gastric and colorectal cancer

Status: Preclinical

Next Steps: Animal studies ongoing

Differentiator: No product yet identified consistently augments PD1 effects on cold tumors

Licensed from Columbia University

- Developing in partnership under sponsored research agreement

Patents Filed

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

[1]Daugherty, 2023. AACR Annual Meeting. https://www.tonixpharma.com/wp-content/uploads/2023/04/MDSC-Targeted-mTFF2-MSA-mTNX-1700-Suppresses-Tumor-Growth-and-Increases-Survival-in-Anti-PD-1-Treated-MC38-and-CT26.wt-Murine-Colorectal-Cancer-Models.pdf
[2]Qian, 2023. AACR Annual Meeting. https://www.tonixpharma.com/wp-content/uploads/2023/04/MDSC-targeted-TFF2-MSA-synergizes-with-PD-1-blockade-therapy-in-advanced-gastric-cancer-models.pdf

TONIX PHARMACEUTICALS

Preclinical Infectious Disease Therapeutics in Development

INFECTIOUS DISEASE PORTFOLIO

TNX-2300*: Live Virus Vaccine Based on Bovine Parainfluenza (BPI) Virus

Market Entry: COVID-19 Vaccine
Status: Preclinical
Next Steps: Animal studies with Kansas State University (KSU) to test the effect of co-expression of CD40-ligand to stimulate T cell immunity

TNX-3700*: Zinc Nanoparticle (ZNP) Formulation for mRNA Vaccines

Market Entry: Booster for COVID-19 Vaccines
Status: Preclinical
Next Steps: Research at KSU on CoV-2 spike based vaccine in tissue culture and animals; initiate animal studies in 1H 2023

TNX-3900*: Host-Directed Broad-Spectrum Antiviral

Market Entry: Coronaviruses and Filoviruses
Status: Preclinical
Next Steps: Further in-house development

TNX-4000*: Direct-Acting Broad-Spectrum Antiviral

Market Entry: Coronaviruses, Retroviruses, and Filoviruses
Status: Preclinical
Next Steps: Further in-house development

*TNX-2300, TNX-3700, TNX-3900 and TNX-4000 are in the pre-IND stage of development and have not been approved for any indication.

TONIX PHARMACEUTICALS


TONIX TEAM, NETWORK
AND FUTURE OUTLOOK
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Key Development Partners
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL
TNX-1500: ALLOGRAFT REJECTION
COLUMBIA UNIVERSITY
TNX-1300: COCAINE INTOXICATION
TNX-1700: GASTRIC AND COLORECTAL CANCERS
STANFORD UNIVERSITY
UNIVERSITÉ DE GENÈVE
TNX-1900: MIGRAINE & OTHER INDICATIONS
UNIVERSITY OF ALBERTA
SR SOUTHERN RESEARCH
TNX-801: SMALLPOX AND MONKEYPOX VACCINE
TNX-1850: COVID-19 VACCINE
InsermTransfert
CHU de Toulouse
Aix*Marseille université
TNX-2900: PRADER-WILLI SYNDROME
KANSAS STATE UNIVERSITY
TNX-3700: COVID-19 VACCINE (ZINC NANOPARTICLE mRNA TECHNOLOGY)
TNX-2300: BOVINE PARAINFLUEZNA VIRUS
TONIX PHARMACEUTICALS
36
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Management Team

Seth Lederman, MD
Co-Founder, CEO & Chairman

TARGENT Fusilev vela

Gregory Sullivan, MD
Chief Medical Officer

Columbia University Department of Psychiatry | New York State Psychiatric Institute

Bradley Saenger, CPA
Chief Financial Officer

Shire | VERTEX | Steward | pwc

Jessica Morris
Chief Operating Officer

Deutsche Bank | svb Silicon Valley Bank | American Capital

TONIX PHARMACEUTICALS

Milestones: Recently Completed and Upcoming

- ☑ 2nd Quarter 2022 Phase 3 RESILIENT study start of TNX-102 SL for the management of fibromyalgia
- ☑ 3rd Quarter 2022 Phase 2 PREVAIL study start of TNX-102 SL for the treatment of fibromyalgia-type Long COVID
- ☑ 1st Quarter 2023 Phase 2 PREVENTION study start of TNX-1900 for the treatment of migraine
- ☑ 1st Quarter 2023 Phase 2 UPLIFT study start of TNX-601 ER for major depressive disorder

Expected Data

- ☐ 3rd Quarter 2023 Topline results of Phase 2 PREVAIL study of TNX-102 SL for fibromyalgia-type Long COVID
- ☐ 4th Quarter 2023 Topline results of Phase 2 PREVENTION study of TNX-1900 for chronic migraine
- ☐ 4th Quarter 2023 Interim Analysis results of Phase 2 UPLIFT study of TNX-601 ER for major depressive disorder
- ☐ 4th Quarter 2023 Topline results of Phase 3 RESILIENT study of TNX-102 SL for fibromyalgia

Expected Clinical Trial Initiations

- ☐ 3rd Quarter 2023 Phase 1 study start of TNX-1500 for prevention of allograft rejection
- ☐ 3rd Quarter 2023 Phase 2 study start of TNX-1300 for the treatment of cocaine intoxication
- ☐ 2nd Half 2023 Phase 1 study start of TNX-801 for prevention of mpox and smallpox

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THANK YOU
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Exhibit 99.02

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; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

TONIX PHARMACEUTICALS

TNX-601 ER*: Depression
Tianeptine Hemioxalate Extended-Release Tablets (39.4 mg)

CNS PORTFOLIO

PROFILE

- A novel, oral, extended-release once-daily tablet
- Treatment effect of tianeptine sodium immediate release *t.i.d.* in depression is well-established
- Tianeptine restores neuroplasticity in animal models
- Indirectly modulates the glutamatergic system
- Does not interact with AMPA, NMDA or kainate receptors[1]

Differentiators:

Relative to tianeptine IR available ex-US:

- Once daily dosing

Relative to traditional antidepressants:

- Unique mechanism of action – beyond neurotransmitter modulation
- Tianeptine sodium IR has similar efficacy but fewer side effects than traditional antidepressants

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Disorder From Corticosteroids, Alzheimer's Disease[2]

Status: Phase 2 MDD study UPLIFT is currently enrolling

Next Steps: Interim analysis results on first 50% of sample expected 4Q 2023

*TNX-601 ER has not been approved for any indication.

[1]AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA=N-methyl-D-aspartate
[2]Garcia-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

TONIX PHARMACEUTICALS

TNX-601 ER - Phase 2 UPLIFT* Study Design

UPLIFT Study

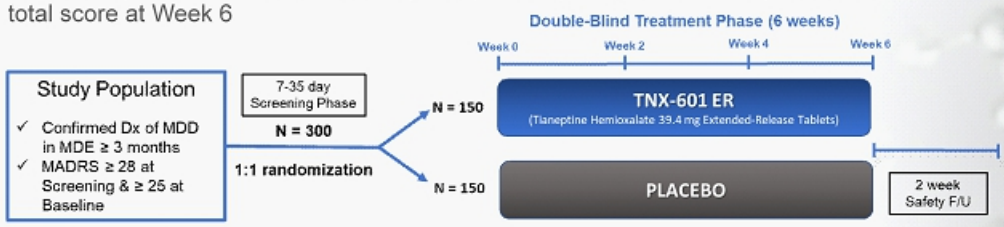
CNS PORTFOLIO

General study characteristics:

- Randomized, double-blind, placebo-controlled study in Major Depressive Disorder to evaluate monotherapy with TNX-601 ER versus placebo
- Parallel design with two arms – treatment with tianeptine hemioxalate 39.4 mg or placebo
- ~30 U.S. sites only, expected to enroll approximately 300 patients
- One unblinded interim analysis based on 50% of randomized participants expected 4Q'23

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6



*ClinicalTrials.gov Identifier: NCT05686408

Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number

TONIX PHARMACEUTICALS

Major Depressive Disorder (MDD)

Epidemiology and Characteristics of Depression

- Major depressive disorder (MDD) is a leading cause of disability worldwide, with 21 million adults in the US alone experiencing a depressive episode in 2020[1]
- Lifetime prevalence of 16%, and associated with important psychological suffering, as well as elevated rates of suicide and worse prognosis of comorbid medical conditions[2,3]
- Highly comorbid with other psychiatric disorders, e.g., anxiety disorders, substance use disorders, as well as medical conditions, e.g., cardiovascular disease, metabolic syndromes, respiratory diseases, various deficiencies, infections, collagen disorders, endocrine diseases, etc.
- Occurs in women at three times the rate in men
- Hormonal aspects can significantly impact course and treatment (especially evident in post-partum depression)
- Increased incidence during COVID-19 pandemic in all age groups and both sexes
- Most treatment guidelines support use of antidepressants in moderate to severe MDD

[1]Substance Abuse and Mental Health Services Administration (SAMHSA). 2020. Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health.
[2]Kupfer et al., 2012. *The Lancet*. 379, 1045–1055
[3]Otte et al., 2016. *Nat. Rev. Dis. Primer*. 2:16065

High Unmet Need for New Classes of Antidepressants

- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, regarded as the largest antidepressant trial ever conducted, indicated approximately 30% of depressed patients fail to achieve remission, even after multiple treatment attempts[1,2]
- SSRIs are currently the most prescribed class of antidepressants, **yet only about 50% of patients with MDD respond to initial SSRI treatment**, and only 35-40% of those patients achieve full remission[1]
- Antidepressant treatments often continue for years, and the side effect profiles of the monoaminergic antidepressants are intolerable to many
- There is a high unmet need for new classes of antidepressants with **different mechanisms of action**

[1]Rush et al., 2006. *Am J Psychiatry*. 163:1905–1917
[2]Rush et al., 2004. *Control Clin Trials*. 25(1):119-42

About TNX-601 ER

Targeted therapy for Major Depressive Disorder

- Tianeptine sodium (amorphous) immediate release (IR) tablets have been available in Europe and many countries in Asia and Latin America for the treatment of MDD since it was first marketed in France in 1989
- Due to its short half-life, tianeptine sodium IR is taken three times daily, which is challenging for patient adherence
- Currently, there is no tianeptine-containing product approved in the U.S. and no extended-release tianeptine product approved anywhere in the world
- Tonix discovered a novel hemioxalate salt of tianeptine that may provide improved stability, consistency, and manufacturability compared to known salt forms of tianeptine
- TNX-601 ER is taken once daily, increasing patient adherence and is thereby anticipated to improve the overall effectiveness of treatment compared to that of tianeptine sodium IR

Clinical Trials of Tianeptine Sodium

Placebo-controlled and comparative trials in depression

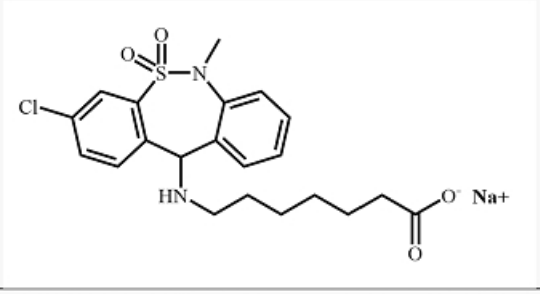
- Antidepressant efficacy confirmed in multicenter double-blind, placebo-controlled, randomized trials[1,2]
- Enriched enrollment randomized withdrawal design trial of long-term (16.5 months) treatment demonstrated reduction of MDD relapse and recurrence by 2- to 3-fold compared to placebo[3]
- Head-to-head comparisons showing equivalent efficacy of tianeptine with:
  - TCAs
    - Imipramine[1]
    - Amitriptyline[4,5,6]
  - SSRIs
    - Fluoxetine[4,7]
    - Sertraline[8]
    - Paroxetine[9,10,11]
    - Escitalopram[12]
  - Mianserin[13]
- Rigorous meta-analysis[14,15] of studies comparing tianeptine to SSRIs concluded tianeptine at least as effective as SSRIs, and trend noted for better overall acceptability profile in treatment of depressed patients

[1]Cassono et al., 1996. *Eur Psychiatry*.11(5):254-9
[2]Costa e Silva et al., 1997. *Neuropsychobiology*. 35(1):24-9
[3]Dalery et al., 2001. *Hum Psychopharmacol*.16(S1):S39-S47
[4]Lôo et al., 1999. *Neuropsychobiology*.19(2):79-85
[5]Guelfi et al., 1989. *Neuropsychobiology*. 22(1):41-8
[6]Invernizzi et al., 1994. *Neuropsychobiology*. 30(2-3):85-93
[7]Novotny et al., 2002. *Hum Psychopharmacol*. 17(8):299-303
[8]Szádóczky et al., 2002. *Encephale*. 28(4):343-9
[9]Lepine et al., 2001. *Hum Psychopharmacol*. 16(3):219-227
[10]Waintraub et al., 2002. *CNS Drugs*. 16(1):65-75
[11]Nickel et al., 2003. *J Clin Psychopharmacol*. 23(2):155-68
[12]Emsley et al., 2018. J Clin Psychiatry. 79(4):17m11741
[13]Brion et al., 1998. *Presse Med*. 25(9):461-8
[14]Kasper et al., 2002. *Eur Psychiatry*. 17 Suppl 3:331-40
[15]Olié et al., 2003. *Encephale*. 29(4 Pt 1):322-8

Tianeptine Sodium

First marketed in France over thirty years ago

- Tianeptine discovered and patented by French Society of Medical Research in 1960s
- Tianeptine first marketed in 1989 for the treatment of major depression by French pharmaceutical company Servier Laboratories under the trade name Stablon®
- Currently marketed in over 60 countries in Europe, Asia, and South America



[3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(c,f)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt (racemic)

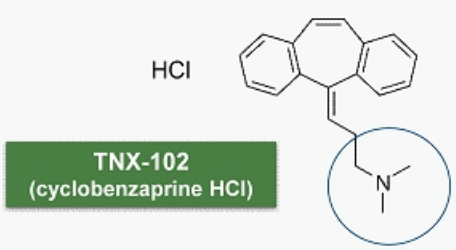
CNS PORTFOLIO

TONIX PHARMACEUTICALS

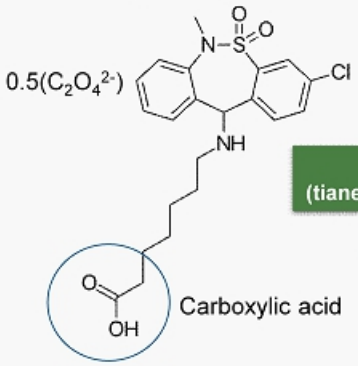
Structural Comparison: Tricyclic and TNX-601

Cyclobenzaprine and tianeptine share structural similarities with classic tricyclic antidepressants (TCAs) and to each other, but each has unique pharmacological profile

- Tricyclic nucleus, but 7-carbon straight chain fatty acid side chain terminates with a carboxylic acid
  - Tianeptine's side chain terminates in a carboxylic acid
  - Tianeptine's side chain results in a pharmacology that is distinct from tricyclic antidepressants



TNX-102
(cyclobenzaprine HCl)



TNX-601
(tianeptine hemioxalate)

Tianeptine's carboxylic acid changes its pharmacology relative to the amines of tricyclics

CNS PORTFOLIO

TONIX PHARMACEUTICALS

Proposed Mechanism of Action (MOA)

Effects on Neuroplasticity & Neurogenesis

- The proposed MOA of TNX-601 ER is **distinct from traditional monoaminergic antidepressants** in the U.S.
  - *"It is now recognized that monoamine deficits are only part of the story and are not sufficient on their own to explain the mechanism of action of antidepressants"*[1]
- MDD may be associated with an impairment of neuroplasticity and cellular resilience, and antidepressant medications may act by normalizing this impairment[2-4]
- In animal studies involving severe stress exposure, TNX-601 ER has a unique MOA that **restores brain neuroplasticity** by exerting biological effects on neurons and glial cells that increase arborization of dendrites in critical hippocampal circuitry[1]
- In animal models, tianeptine also **reverses stress-induced impairments** in synaptic glutamate neurotransmission, and it **restores hippocampal neurogenesis**[1]

[1]McEwen et al., 2010. *Mol. Psychiatry.*15(3). 237–249.
[2]Duman et al., 1999. *Biol Psychiatry.* 46: 1181–1191.
[3]Manji et al., 2001. *Psychopharmacol Bull.* 35: 5–49.
[4]Pittenger et al., 2008. *Neuropsychopharmacology.* 33: 88–109.

Proposed MOA of Tianeptine

Distinct compared to other antidepressants currently marketed in the U.S.

- In Table[1] (right), it is illustrated how downstream effects of AD actions on neuroplasticity, including enhanced neurogenesis, contribute to improvements in *both mood and cognitive function*
- Tianeptine additionally has neuroprotective effects against hypoxia and deleterious effects of inflammatory cytokines in cortex and white matter[2]
- Tianeptine additionally has partially protective effects on the changes in microglia viability/death evoked by lipopolysaccharide[3]
- And >30 years of real-world experience with tianeptine for depression ex-US support its unique aspects, heretofore unavailable in US

	Untreated Depression	Treated Depression
Behavior	↓Memory ↑Rumination ↑Negative Affect	↑Memory ↓Negative Affect
Network	↑Hippocampal-Amygdala connectivity during negative emotional recall ↓Hippocampal-Amygdala connectivity at rest	↓Hippocampal-Prefrontal cortex connectivity at rest
Neurons	↓Neurogenesis ↓Pyramidal Cells ↓Granule Neurons ↓Dendrites	↑Neurogenesis ↑Dendrites ↑Granule Neurons
Synapses	↓AMPA Receptors ↓Spine Density ↓LTP ↑LTD ↓Spine Complexity	↑LTP ↑Spine Density ↓LTD ↑Spine Complexity
Molecules (BDNF, mTOR)	↓BDNF ↑Glutamate ↓mTOR	↑BDNF ↑Glutamate

[1]Tartt et al., 2022. *Molecular Psychiatry* 27: 2689–2699.
[2]Plaisant et al.,2003. *Neuropharmacology* 44: 801–809.
[3]Slusarczyk et al., 2018. *Int J Mol Sci* 19: 1955.

Observations that Relate Tianeptine's Action to μ-Opioid Receptors

Tianeptine is a weak μ-opiate receptor agonist

- In 2014, tianeptine was reported to be a weak μ–opioid agonist by Javitch & Sames at Columbia[1]
  - K_i = 383 nM and EC_{50} = 194 nM[1]
  - Others have found even lower binding and activity, e.g., K_i = 768 nM[2] or EC_{50} >3 uM[3]
- In 2017, tianeptine's μ–opioid activity was implicated as central to its mechanism of treating depression by Hen, Javitch & Sames at Columbia[4,5]
  - Observations: *e.g.*, The effect of tianeptine at 30 mg/kg on the Porsolt Forced Swim Test (FST) was decreased by naloxone treatment or in knock-out mice lacking the μ–opioid receptor
  - Tonix interpretation: While Samuels *et al*. provided information on the effects of high doses of tianeptine in murine analgesic models, the presented FST studies *did not* conclusively show the antidepressant effect of tianeptine at the therapeutic dose in humans requires μ-opioid receptor agonism

[1]Gassaway et al., 2014. *Transl Psychiatry*. 4(7):e411
[2]BL Roth PDSP K$_i$ database; https://pdsp.unc.edu/databases
[3]Vandeputte et al., 2020. *Arch Toxicol*. 94(11):3819-3830
[4]Samuels et al., 2017. *Neuropsychopharmacology*. 42(10):2052-2063
[5]Han et al., 2022. *Neuropsychopharmacology*. 47(7):1387-1397

Tianeptine's off-target activity

Illicit or unregulated introduction of the drug substance to the United States

- Based on these μ–opioid data and interpretations, unregulated tianeptine entered the US
  - As a research chemical - *not for human use*
  - As an ingredient in food supplements sold over the counter
  - Without any submitted data or regulatory status, promoted as a "smart drug" (nootropic) sold over the internet
- Because of low affinity binding and agonist activity on μ-opioid receptor, there is the potential abuse liability of tianeptine drug substance when available in large quantities by
  - People seeking a μ-opioid "high"
  - People self-managing withdrawal effects from opioids

Prescription Tianeptine has Low Incidence of Abuse in France

Low activity at μ-opioid receptor is associated with low misuse of prescription oral tianeptine

- Tianeptine and its MC5 metabolite are weak mu-opioid (μ-opioid) receptor (MOR) agonists[1] that present a potential abuse liability if illicitly misused in large quantities (typically abused at 8-80 times the therapeutic dose on a daily basis[2]).
- In patients who were prescribed tianeptine for depression, the French Transparency Committee found a low incidence of misuse
  - Approximately 1 case per 1,000 patients treated[3] suggesting low abuse liability when used at the antidepressant dose in patients prescribed tianeptine for depression.
- Clinical trials have shown that abrupt cessation of a therapeutic course of tianeptine does not appear to result in dependence or withdrawal symptoms following treatment for:
  - 6-weeks[4-8]
  - 3-months[9]
  - 12-months[10]

[1]Gassaway et al., 2014. *Trans! Psychiatry.* 4(7):e411
[2]Lauhan et al., 2018. *Psychosomatics.* 59(6), 547–53.
[3]Haute Authorite de Sante. Transparency Committee Opinion. Stablon 12.5 Mg, Coated Tablet, Re-Assessment of Actual Benefit at the Request of the Transparency Committee. December 5, 2012.
[4]Emsley et al., 2018. *J. Clin. Psychiatry. 79* (4)
[5]Bonierbale et al., 2003. *Curr Med Res Opin.* 19(2):114-124
[6]Guelfi et al., 1989. *Neuropsychobiology.* 22 (1), 41–48
[7]Invernizzi et al., 1994. *Neuropsychobiology.* 30 (2–3), 85–93
[8]Lepine et al., 2001. *Hum. Psychopharmacol.* 16 (3), 219–227
[9]Guelfi et al., 1992. *Neuropsychobiology.* 25 (3), 140–148.
[10]Lôo et al., 1992. *Br. J. Psychiatry. Suppl.* No. 15, 61–65.

TNX-601 ER Drug product

TNX-601 ER formulated with attention to FDA-guided potential abuse deterrent properties*

- The *only* abuse-deterrent properties approved for the labels of certain marketed opioids are extended-release formulations with physiochemical barriers +/- aversive components to abuse
- TNX-601 ER was formulated with attention to these potentially abuse deterrent properties:
  - Active ingredient, tianeptine oxalate less soluble than sodium salt, reducing extraction efficiency in solvents such as water and alcohol
  - Microcrystalline cellulose is a compression aid that results in extremely hard tablets, reducing ability to crush to fine particulate matter for insufflation or efficient extraction, pressed at >100 Newtons
  - Inclusion of high molecular weight gel-forming polymers also adversely affects the "syringe-ability" and injectability of the drug product
  - Inclusion of hydrophilic fumed silica as well as magnesium stearate may cause nasal irritation if insufflated; in high doses, orally ingested magnesium stearate may cause GI hyperactivity and irritation
  - All potentially serve to make TNX-601 ER a **non-optimal source of tianeptine for high dose abuse**

*https://www.fda.gov/drugs/information-drug-class/final-guidance-evaluation-and-labeling-abuse-deterrent-opioids

Summary: TNX-601 ER vs. Other Antidepressants

- Given tianeptine's unique metabolic pathway, which is independent of the hepatic P450 system, it is anticipated that, like tianeptine sodium, TNX-601 ER will have a reduced risk of drug-drug interactions compared to most antidepressants
- Unique mechanism of action (MOA) compared to available antidepressants in the U.S.
- The efficacy of tianeptine sodium IR is comparable to both selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressants[1,2] while being associated with a low incidence of sexual dysfunction compared with either of those classes[3], and **no associated derangement of sleep architecture, sedative effects, weight gain, or cognitive impairment[1]**
- Once-daily dosing regimen compared to tianeptine sodium IR at three times a day

[1]Wagstaff et al., 2001. *CNS Drugs*. 15(3), 231–259
[2]Kasper et al., 2002. *Eur Psychiatry*. 17 (Suppl 3), 331-340
[3]Bonierbale et al., 2003. *Curr Med Res Opin*. 19(2):114-124

About TNX-601 ER

Targeted therapy for Major Depressive Disorder with convenience of once-daily dosing

- Tianeptine sodium (amorphous) immediate release (IR) tablets have been available in Europe and many countries in Asia and Latin America for the treatment of MDD since it was first marketed in France in 1989. Due to its short half-life, tianeptine sodium IR is taken three times daily, which is challenging for patient adherence.
- Currently, there is no tianeptine-containing product approved in the U.S. and no extended-release tianeptine product approved anywhere in the world. Tonix discovered a novel hemioxalate salt of tianeptine that may provide improved stability, consistency, and manufacturability compared to known salt forms of tianeptine.
- TNX-601 ER is taken once daily, increasing patient adherence and is thereby anticipated to improve the overall effectiveness of treatment compared to that of tianeptine sodium IR.

Potential Indications for TNX-601 ER

Informed by clinical data and mechanistic insights

- Neurodegenerative disorders
  - Parkinson's (and associated conditions, e.g. depression and psychosis)[1]
  - Alzheimer's (and associated conditions, e.g. agitation, depression and psychosis)[2]
- ADHD[3]
- Stress disorders[4]
  - PTSD, Anxiety
- Aging/Neuroprotection[5,6]
  - Mild Cognitive Impairment
- Asthma[7]
- Overlapping chronic pain syndromes
  - Fibromyalgia[8]
  - Irritable bowel syndrome
- Addiction
  - Opiate use disorder[9]
  - Alcohol use disorder

[1]Levin, 2007. *Neurosci Behav Physiol.* 37(4):419-24
[2]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720
[3]Niederhofer et al., 2004. *Neuropsychobiology.* 49(3): 130-3.
[4]Krystal et al., 2009. *Drug Discov Today.* 14(13-14):690-697
[5]Yoo et al., 2015. *J Affect Disord.* 185:24-30.6
[6]Saiz-Ruiz et al., 1998. Prog. Neuro-Psychopharmacol. & Bio. Psychiat. 22(2): 319-329
[7]Lechin et al., 2004. *Methods Find Exp Clin Pharmacol.* 26(9): 697–701
[8]"ISRCTN16400909 – Tianeptine for the treatment of fibromyalgia: a prospective double-blind, randomised, single-centre, placebo-controlled, parallel group study". Controlled-trials.com. Archived from the original on 21 July 2010. Retrieved 13 August 2010
[9]Chu et al., 2010. *Behav Pharmacol.* 21(5-6):523-9

TONIX PHARMACEUTICALS

THANK YOU