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): October 16, 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. A copy of the presentation is filed as Exhibit 99.01 hereto and incorporated herein by reference. The Company also updated its TNX-1500 and TNX-601 (tianeptine hemioxalate extended-release tablets) product candidate presentations, which it intends to place on its website and which may contain nonpublic information. Copies of the presentations are filed as Exhibits 99.02 and 99.03 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, 99.02 and 99.03 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 October 2023
99.02	TNX-1500 Product Presentation
99.03	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: October 16, 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; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 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

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

CNS-Focused Biopharma with Preclinical to Commercial Stage Products

Robust Development Pipeline
Topline data for three late-stage CNS programs expected by end of 2023

Internal Facilities
For R&D and clinical-scale manufacturing

Marketed Products
For the treatment of acute migraine

Strategic Partnerships
With world-class academic & research organizations to bring innovative therapeutics to market faster

Late-Stage Clinical Portfolio

Molecule*	Indication	Phase 1	Phase 2	Phase 3	NDA Submission
TNX-102 SL Cyclobenzaprine Protectic® Sublingual Tablets	Fibromyalgia (FM)	*Phase 3 Topline Results Expected 4Q'23 (Late December)*			
	FM-Type Long COVID	*Phase 2 Topline Results Reported 3Q'23*			
TNX-601 ER Tianeptine Hemioxalate Extended-Release Tablets	Major Depressive Disorder	*Phase 2 Topline Results Expected 4Q'23 (Early November)*			
TNX-1900 Intranasal Potentiated Oxytocin with Magnesium	Chronic Migraine	*Phase 2 Topline Results Expected 4Q'23 (Early December)*			
TNX-1300 Cocaine Esterase	Cocaine Intoxication	*Phase 2 Study Start Expected 4Q'23*			

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

TONIX PHARMACEUTICALS

Two Marketed Proprietary Migraine Drugs
Non-oral Formulations of Sumatriptan

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

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

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

Acquired from Upsher-Smith Laboratories which has managed care contracts covering ~200 M lives

- Contract includes a transition period during which Tonix expects to secure its own contracts

Retail Product Sales for the 12 months ended December 31st 2022

- Retail sales: ~$23 M (Zembrace ~$19.6 M and Tosymra ~$3.5 M)[4]

Tonix is prepared to meet potential increased demand for Tosymra following GSK's planned discontinuation of Imitrex® (sumatriptan) nasal spray after January 2024

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

Tonix has contracted to acquire the Zembrace, SymTouch and Tosymra trademarks. Intravail is a registered trademark of Aegis Therapeutics, LLC, a wholly owned subsidiary of Neurelis, Inc.

Zembrace and Tosymra Bypass the GI Tract

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

- GI absorption may be inconsistent in migraineurs due to gastric stasis (also called "gastroparesis")[1-4]
- Nausea and vomiting are symptoms of migraine[5] which can complicate oral treatment

Existing intranasal products

- Imitrex® nasal spray (sumatriptan)
- Migranal® (dihydroergotamine) nasal spray – developed by Novartis, sold by Bausch Health

New intranasal products bringing attention to non-oral route

- Pfizer's Zavzpret® (zavegepant), FDA approved in March, 2023[1] is the first intranasal gepant
- Impel NeuroPharma's Trudhesa® (dihydroergotamine) FDA approved 2021[2]

[1]Pfizer Press Release March 10, 2023. – https://www.pfizer.com/news/press-release/press-release-detail/pfizers-zavzprettm-zavegepant-migraine-nasal-spray
[2]Impel Press Release September 3, 2021 - https://impelpharma.com/2021/09/03/impel-neuropharma-announces-u-s-fda-approval-of-trudhesa-dihydroergotamine-mesylate-nasal-spray-for-the-acute-treatment-of-migraine/

Upcoming Expected Topline Results

Fourth Quarter

2023

TNX-601 ER for Depression

Topline Results Expected – early November

Phase 2 Potential Pivotal Study

TNX-1900 for Chronic Migraine

Topline Results Expected – early December

Phase 2 Proof-of-Concept Study

TNX-102 SL for Fibromyalgia

Topline Results Expected – late December

Phase 3 Potential NDA Enabling Study

TONIX PHARMACEUTICALS

TNX-102 SL

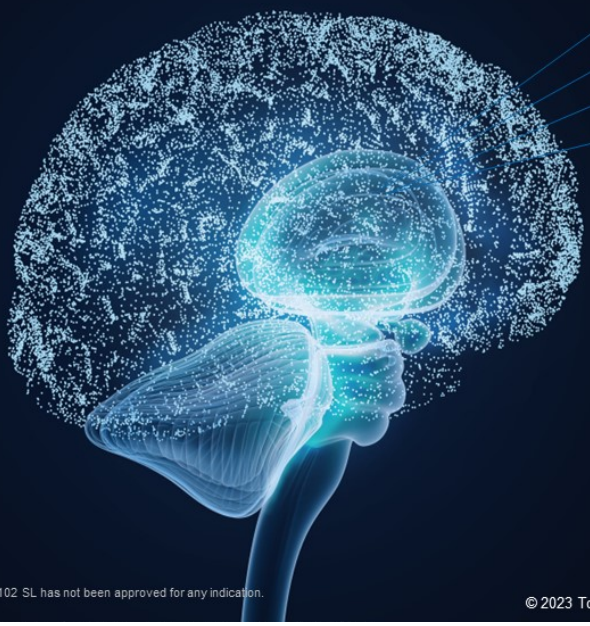
Cyclobenzaprine (Protectic®)

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

TONIX PHARMACEUTICALS

Unique MOA Facilitates Restorative Sleep: Centrally Acting Analgesic

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



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

Key Differentiators

Relative to Oral Cyclobenzaprine

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

Relative to Standard of Care

- Potential for better tolerability while maintaining efficacy
- Not scheduled nor with recognized abuse potential

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

TONIX PHARMACEUTICALS

About Fibromyalgia

*Fibromyalgia (FM) is a **chronic pain disorder** resulting from amplified sensory and pain signaling within the CNS. Symptoms include chronic widespread pain, **nonrestorative sleep**, fatigue, and cognitive dysfunction*

6-12 million adults

Fibromyalgia afflicts an estimated 6-12 million adults in the US, predominantly women[1]

Large unmet need:

- Patients struggle with daily activities, have impaired quality of life, and frequently are disabled
- Physicians and patients report common dissatisfaction with currently marketed products
  - Average patient has 20 physician office visits per year[2]

Current standard of care:

- FDA-approved products include Lyrica, Cymbalta, and Savella
- Fewer than half of those treated for fibromyalgia receive sustained benefit from the approved drugs[3]
  - Majority (60%) fail therapy due to lack of a response (25%) or poor tolerability (35%)[4]
  - Opioid usage is not uncommon

[1]American Chronic Pain Association (www.theacpa.org, 2019)
[2]Robinson et al, Pain Medicine 2013;14:1400
[3]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)
[4]Market research by Frost & Sullivan, commissioned by Tonix

Fibromyalgia Program Status

TNX-102 SL Cyclobenzaprine Protectic® Sublingual Tablets	**Fibromyalgia**	***Phase 3 Topline Results Expected 4Q'23 (Late December)***
	FM-Type Long COVID	*Phase 2 Topline Results Reported 3Q'23*

1) One **positive Phase 3 study (RELIEF) completed**[1]
2) Second Phase 3 study (RALLY) missed primary endpoint
   - Unexpected ~~~80%~~ increase in adverse event-related discontinuations in both drug and placebo arms, potentially due to recruiting during COVID-19
3) Confirmatory Phase 3 study (RESILIENT) **enrollment complete**

Next Steps: ***Potentially confirmatory topline results expected 4Q 2023 (Late December)***

*TNX-102 SL has not been approved for any indication.
[1]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", doi: 10.1002/acr.25142. Epub ahead of print. PMID: 37165930.

CNS PORTFOLIO

Phase 3 RESILIENT Study Design

RESILIENT Study

CNS PORTFOLIO

General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia
- U.S. sites only, ***completed enrollment of 457 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
- Threshold for potential NDA-enabling study is $p < 0.05$

Key Secondary Endpoints:

- Patient Global Impression of Change responder analysis
- Fibromyalgia Impact Questionnaire - Revised (FIQ-R) Symptom Domain score
- FIQ-R Function Domain score
- PROMIS Sleep Disturbance instrument
- PROMIS Fatigue instrument
- Weekly average of the daily diary assessment of sleep quality

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

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)

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About Fibromyalgia-Type Long COVID

Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after acute COVID-19 infection[1]

Many Long-COVID symptoms <u>overlap with core symptoms of fibromyalgia</u>

and are hallmarks of other chronic pain syndromes like myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

19% **Long COVID occurs in approximately 19% of recovered COVID-19 patients**[2]

40% **As many as 40% of Long COVID patients experience multi-site pain**[3,4]

[1]CDC - https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=Some%20people%20who%20have%20been,after%20acute%20COVID%2D19%20infection.
[2]CDC Press Release, June 22, 2022 - https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm
[3]Harris, H, et al. Tonix data on file. 2022
[4]TriNetX Analytics

TONIX PHARMACEUTICALS

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, ***completed enrollment of 63 patients***

Primary Endpoint:

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

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

Placebo once-daily at bedtime

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

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

14 weeks

Next Steps: *End of Phase 2 Meeting with FDA 1Q 2024*

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Phase 2 PREVAIL Topline Results[1]

CNS PORTFOLIO

Did not meet the primary endpoint of multi-site pain reduction at Week 14

However, findings fulfill the objectives of proof-of-concept study, supporting the decision to advance the program based on a proposed primary endpoint using the PROMIS Fatigue scale

- TNX-102 SL showed robust effect size in improving fatigue and consistent activity across secondary measures of sleep quality, cognitive function, disability and Patient Global Impression of Change (PGIC)
- Was generally well tolerated with an adverse event (AE) profile comparable to prior studies with TNX-102 SL:
  - AE-related discontinuations were similar in drug and placebo arms
  - No new safety signals were observed

Fatigue is the signature symptom of Long COVID and has been identified as the dominant symptom contributing to disability[2]

- We observed numerical improvement in the PROMIS fatigue score (in RELIEF p=0.007 MMRM and in RALLY p=0.007 MMRM) in both prior Phase 3 studies of TNX-102 SL in fibromyalgia,
- We believe the results of PREVAIL, together with extensive data from studies in other chronic conditions[3-5], makes PROMIS Fatigue a solid candidate for the primary endpoint of future Long COVID registrational studies

[1]Tonix Press Release, September 5, 2023 - https://bit.ly/3Z6FQHQ
[2]Walker S, *et al. BMJ Open* 2023;13:e069217. doi:10.1136/bmjopen-2022-069217
[3]Cook, K.F., et al. 2016. *Journal of Clinical Epidemiology*, 73, 89- 102
[4]Cella, D., et al. 2016. *Journal of Clinical Epidemiology*, 73, 128–134
[5]Lai, J.S., et al. 2011. *Archives of Physical Medicine and Rehabilitation*, 92(10 Supplement), S20-S27.

TONIX PHARMACEUTICALS

TNX-601 ER

Tianeptine Hemioxalate Extended-Release Tablets

An innovative approach to treating depression

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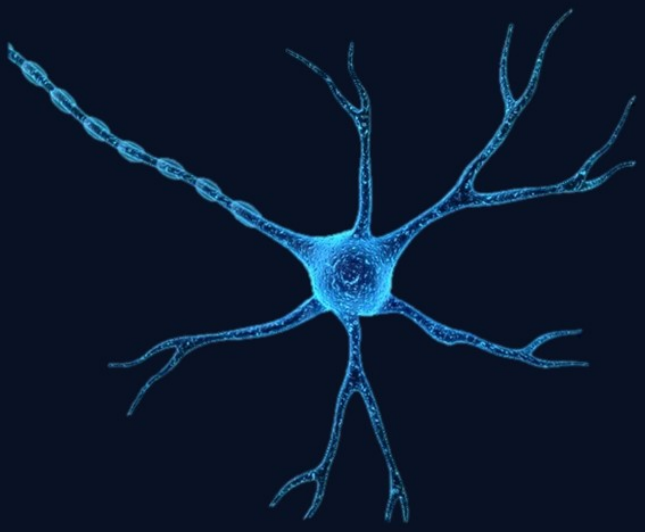
Improved Formulation of Tianeptine Promotes Neuroplasticity

Unique mechanism of action – beyond neurotransmitter modulation



Key Differentiators

Relative to tianeptine immediate release available ex-US

- Once daily dosing

Relative to traditional antidepressants

- Tianeptine sodium IR has similar efficacy but less weight gain or sexual side effects than traditional antidepressants
- Tianeptine's side effects are described in labeling in countries in which it is marketed[1]

[1]Summary of product characteristics (SmPC), European Medicines Agency, Stablon®.

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

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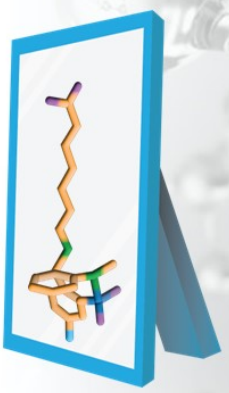
Tianeptine Composed of Two Isomers

Racemic tianeptine (TNX-601):
- Approved in Europe and ex-US
- 1:1 mixture of 2 mirrorr-image isomers[1,2]
- Weak μ-opioid receptor agonism[2]

***(S)*-Tianeptine (TNX-4300):**
- No opioid liability[3]
- New mechanism of action for treating depression

(S)-tianeptine

***(R)*-Tianeptine:**
- Opioid liability[3]
- Weak μ-opioid receptor agonism[4]



(R)-tianeptine

[1]Stablon. Summary of product characteristics. Les Laboratoires Servier Industrie; 2014.
[2]PubChem. Accessed November 10, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Tianeptine
[3]Sullivan G et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
[4]Rat Novel Object Recognition Test

About Major Depressive Disorder

*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].*

47 million **Depression afflicts nearly 47 million adults in the US (18.4% of population)**

Current standard of care:
- SSRIs are currently the most prescribed class of antidepressants

Large unmet need:
- Only about 50% of patients with MDD respond to initial SSRI treatment, and only 35-40% of those patients achieve full remission[2]
- Antidepressant treatments often continue for years, and the ***side effect profiles of the monoaminergic antidepressants are intolerable to many***

[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]Rush et al., 2004. *Control Clin Trials*. 25(1):119-42.
[3]CDC -https://www.cdc.gov/mmwr/volumes/72/wr/mm7224a1.htm?s_cid=mm7224a1_w

TNX-601 ER - Phase 2 UPLIFT* Study Design

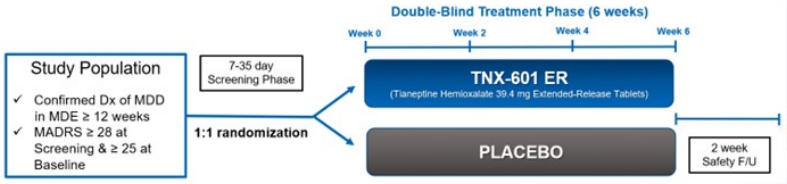
UPLIFT Study

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
- U.S. sites only, ***completed enrollment of 132 patients***
  - Clinical phase completed – announced October 16, 2023[1]

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6
- Threshold for achieving positive proof-of-concept study is effect size (ES) > 0.20
- Threshold for positive pivotal study is p-value < 0.05



Next Steps: *Topline results expected 4Q 2023 (Early November)*

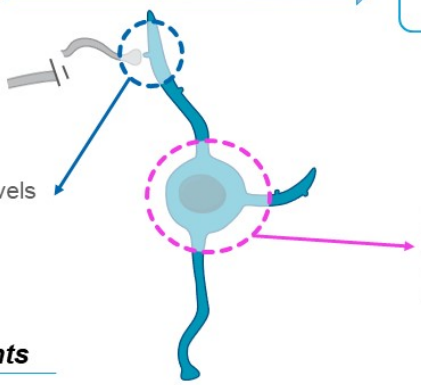
*ClinicalTrials.gov Identifier: NCT05686408
Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number
[1]Tonix Press Release, October 16 2023: https://ir.tonixpharma.com/news-events/press-releases/detail/1430/tonix-pharmaceuticals-completes-clinical-stage-of-phase-2

TONIX PHARMACEUTICALS

While Monoaminergic Antidepressants Work at the Synapse, *(S)*-Tianeptine "Cuts in Line" to More Directly Affect Neuroplasticity[1]

Decreased connectivity and neuroplasticity

Restored connectivity and neuroplasticity



Traditional classes of antidepressants work by modulating neurotransmitter levels and activity in the synapse, leading to downstream antidepressant effects

(S)-Tianeptine (TNX-4300) acts directly on nuclear receptors, bypassing the synapse and directly affecting neuroplasticity

Beyond Traditional Antidepressants

- Tianeptine shares neuroplasticity-promoting mechanism with psychedelics
  - Psychedelics may promote neuroplasticity both by directly binding to BDNF receptor TrkB, and by increasing BDNF gene expression[2,3]
  - Tianeptine may promote neuroplasticity by upregulating BDNF gene expression through activation of PPAR-β/δ[4,5]
- No opioid liability

[1]Sullivan G et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
BDNF=brain-derived neurotrophic factor.

[2]de Vos CMH, et al. *Front Psychiatry*. 2021;12:724606
[3]Moliner R, et al. *Nat Neurosci*. 2023;26(6):1032-1041
[4]Ji MJ, et al. *Int J Neuropsychopharmacol*. 2015;19(1):pyv083
[5]Seo MK, et al. *Psychopharmacology (Berl)*. 2016;233(13):2617-2627

TONIX PHARMACEUTICALS

TNX-1900 and TNX-2900

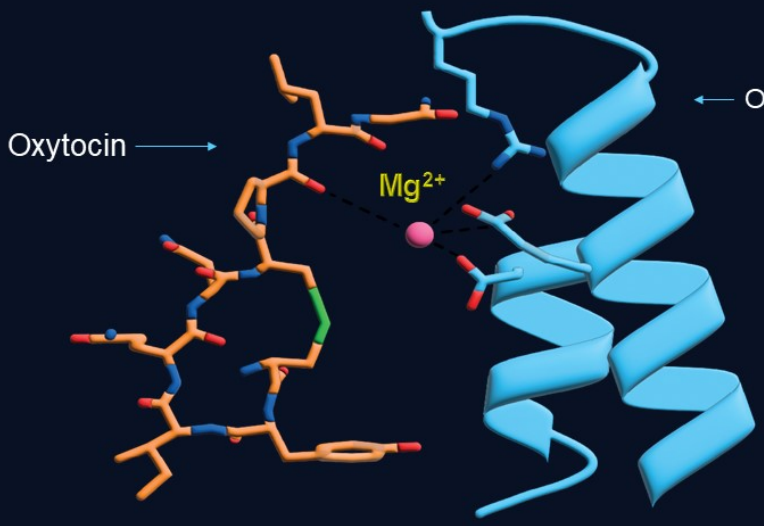
Intranasal Potentiated Oxytocin with Magnesium

A novel, non-CGRP antagonist approach to treatment

TONIX PHARMACEUTICALS

Novel Formulation of Intranasal Oxytocin (OT) Potentiated with Magnesium

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



Key Differentiators

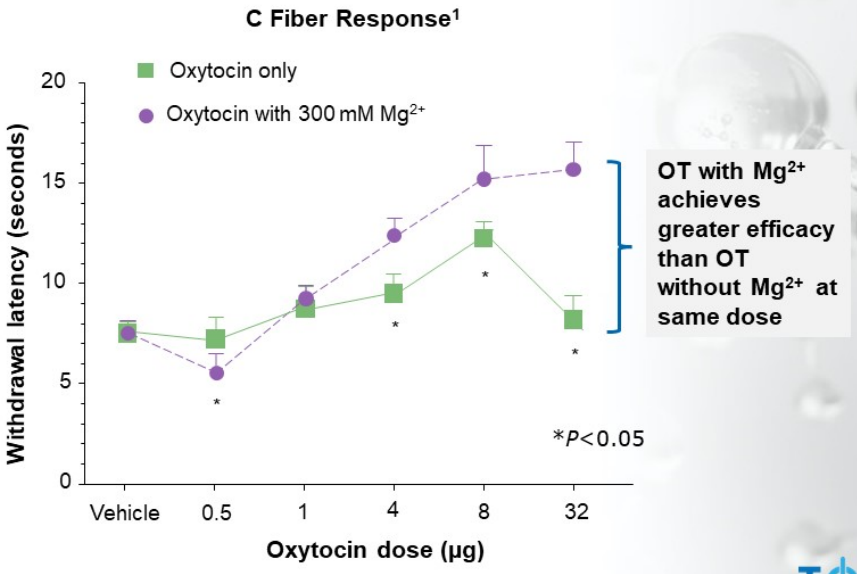
- Targeted intranasal delivery
  - Low systemic exposure
- Blocks release of CGRP from trigeminal ganglia neurons
  - CGRP is a key peptide in the pathogenesis of migraine

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

TONIX PHARMACEUTICALS

Oxytocin Effects – Addressing the "Inverted U" Dose Response
Addition of Mg^{2+} Augments Oxytocin-Induced Analgesia in Animal Model

- A ***nonlinear dose response*** decreases efficacy at higher doses
- Addition of ***Mg^{2+} rescues the efficacy*** of oxytocin at high doses



[1]Adapted from: Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.

About Chronic Migraine

*Chronic migraine involves frequent (>15 days per month) or long-lasting episodes of headaches and migraines over the course of at least 3 months. Migraines can occur with or without an aura and are often **debilitating for patients.***

3-7 ***million adults***

Chronic migraine afflicts 3-7 million adults in the US[1]

Current standard of care:
- Anti-CGRP antibodies and Botox® (onabotulinumtoxinA) are specifically approved to prevent headaches in chronic migraine
- Nurtec® (Rimegepant), a gepant, is approved for both prevention of migraine and acute treatment

Large unmet need:
- Anti-CGRP antibodies and oral gepants involve systemic exposure
- Long term safety concerns with prolonged systemic blockade of CGRP receptor[2]

[1]Natoli et al., Global prevalence of chronic migraine: a systematic review, Cephalagia, 2010, 30:599-609
[2]Robbins, At Stake: The Possible Long-Term Side Effects of CGRP Antagonists, https://www.practicalpainmanagement.com/pain/headache/stake-possible-long-term-side-effects-cgrp-antagonists, accessed November 8, 2020.

TNX-1900: Phase 2 PREVENTION Study Design

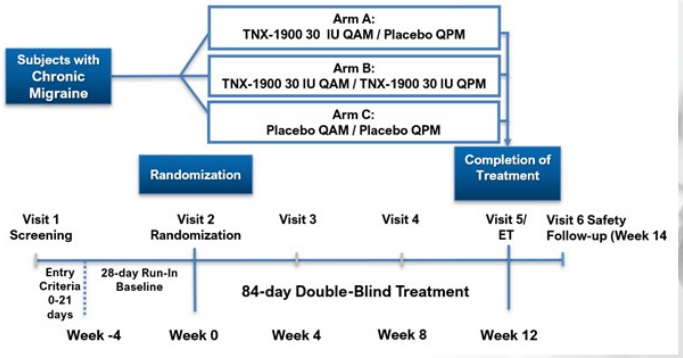
PREVENTION Study

General study characteristics:

- Randomized, double-blind, placebo-controlled study (three arms– two treatment regimens and one placebo) in chronic migraine
- U.S. sites only, ***completed enrollment with 88 patients***

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)
- Threshold for achieving positive proof-of-concept is Effect Size (ES) > 0.2

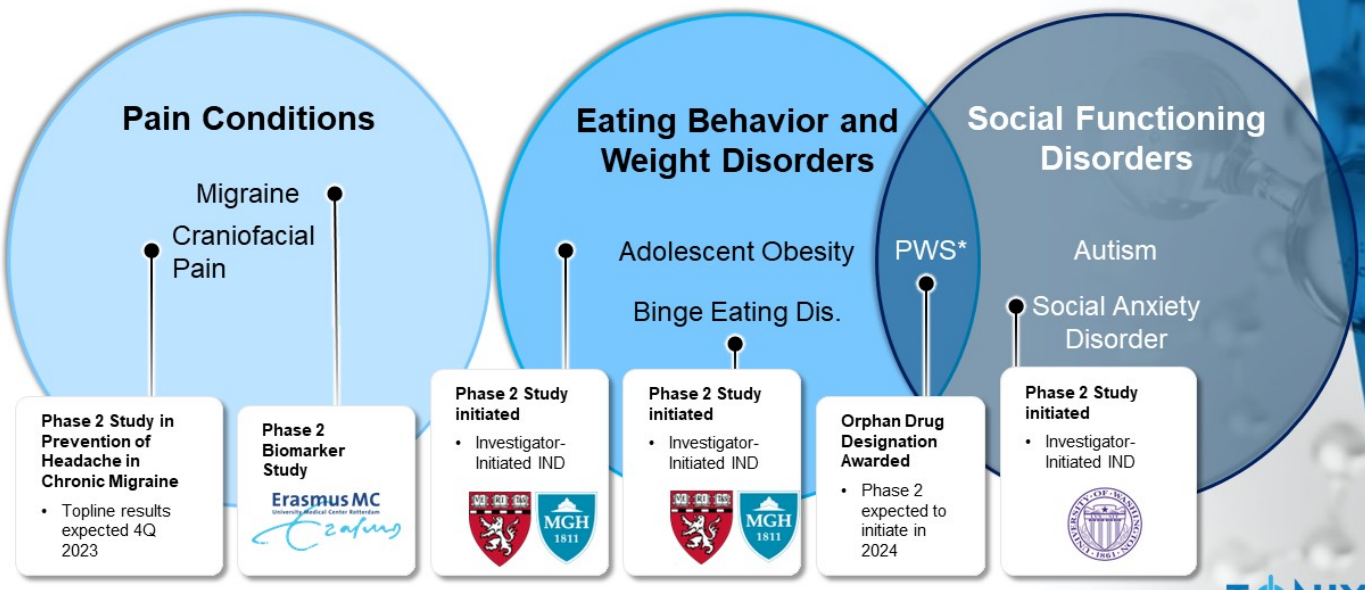


ClinicalTrials.gov Identifier: NCT05679908
A Study to Evaluate the Efficacy and Safety of TNX-1900 in Patients With Chronic Migraine (PREVENTION)

Next Steps: ***Topline results expected 4Q 2023 (Early December)***

TONIX PHARMACEUTICALS

Potential Applications of TNX-1900 & TNX-2900: Investigator Led Studies



*Prader-Willi Syndrome

TONIX PHARMACEUTICALS

About Prader-Willi Syndrome

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

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

Current standard of care:

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

Large unmet need:

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

Tonix has been granted FDA Orphan Drug Designation

[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

TNX-1300

Cocaine Esterase

Fast acting antidote for life threatening cocaine intoxication

Recombinant Protein Rapidly Degrades Cocaine in the Bloodstream

Drops plasma exposure by 90% in 2 minutes

FDA Breakthrough Therapy Designation

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

Key Differentiators

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

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

TONIX PHARMACEUTICALS

About Cocaine Intoxication

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

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

Current standard of care:

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

Large unmet need:

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

CNS PORTFOLIO

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

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

TONIX PHARMACEUTICALS

TNX-1500

Anti-CD40L Monoclonal Antibody

Next Generation mAb preserves efficacy without risk of thrombosis

Next Generation anti-CD40L mAb

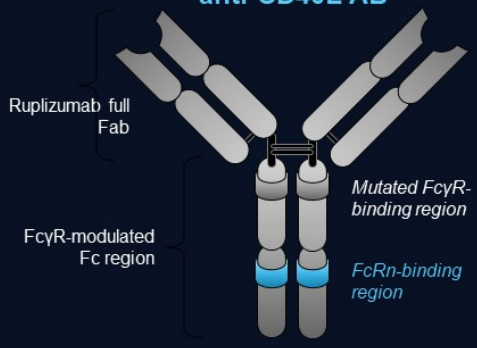
Re-engineered to better modulate the binding of FcγR and mitigate risk of thrombosis

Key Differentiators

Expected to deliver efficacy without compromising safety

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

Selectively Modified anti-CD40L AB



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

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

TONIX PHARMACEUTICALS

TNX-1500 Strategy and Status

IMMUNOLOGY PORTFOLIO

1 Proposed Initial Indication: Prevention of Allograft Rejection

Status: Phase 1 currently enrolling

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

Next Steps: Initiate Phase 2 study in Kidney Transplant Recipients

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

- Potential to reduce GvHD

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

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

Peer reviewed articles:

Two articles have recently published in the *American Journal of Transplantation* that demonstrate TNX-1500 prolongs non-human primate renal and heart allograft survival.[1,2]

[1]Lassiter, G., et al. (2023). TNX-1500, a crystallizable fragment–modified anti-CD154 antibody, prolongs non-human primate renal allograft survival. *American Journal of Transplantation*. April 3, 2023. https://doi.org/10.1016/j.ajt.2023.03.022
[2]Miura, S., et al. (2023) TNX-1500, a crystallizable fragment–modified anti-CD154 antibody, prolongs non-human primate cardiac allograft survival. *American Journal of Transplantation*. April 6, 2023. https://doi.org/10.1016/j.ajt.2023.03.025

TONIX PHARMACEUTICALS

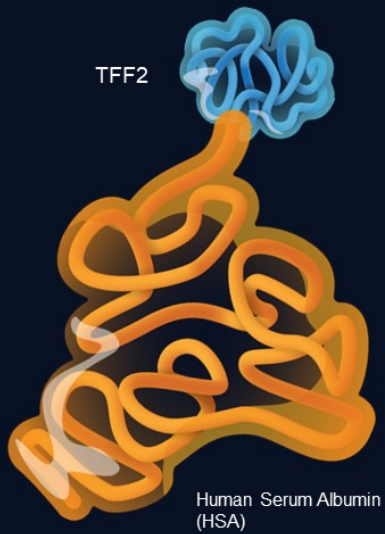
TNX-1700

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

Targeting the toxic tumor micro-environment

Fighting Cancer by Targeting the Tumor Micro-Environment

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



Key Differentiators

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

Preclinical Evidence

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

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

[1]Daugherty, B. et al. March 6, 2023 Keystone Poster. https://bit.ly/48nlRHM

About Gastric and Colorectal Cancer

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

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

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

Current standard of care:

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

Large unmet need:

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

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

TONIX PHARMACEUTICALS

Internal Development & Manufacturing Capabilities

R&D Center (RDC): Frederick, MD

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

Advanced Development Center (ADC): North Dartmouth, MA

- Development and clinical scale manufacturing of biologics
- ~45,000 square feet, BSL-2

INFECTIOUS DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

Broad-Spectrum Antiviral Discovery Programs

Host-directed antiviral discovery programs

CD45 targeted therapeutics

- Small molecule therapeutics that reduce endogenous levels of CD45, a protein tyrosine phosphatase
- Reduction in CD45 protects against many viruses including the Ebola virus

Cathepsin inhibitors

- Small molecule therapeutics that inhibit ***essential cathepsins*** which are required by viruses such as coronaviruses and filoviruses to infect cells
- Activity as monotherapy and in combination with other antivirals

Virus-directed antivirals discovery program

Viral glycan-targeted engineered biologics

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

INFECTIOUS DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

TNX-801

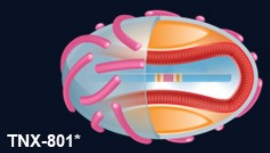
Live Virus Vaccine

Live virus vaccine platform with multitude of potential applications

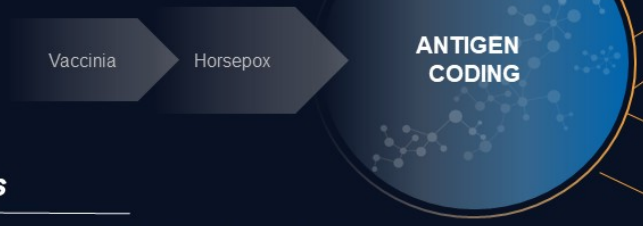
TONIX PHARMACEUTICALS

Recombinant Pox Vaccine (RPV) Platform Using Live Virus Technology

Cloned version of horsepox[1] purified from cell culture



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



Key Differentiators

Live virus vaccines are the most established vaccine technology

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

Economical to manufacture at scale

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

Standard refrigeration for shipping and storage

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

TONIX PHARMACEUTICALS

Key Development Partners

TNX-1500: ALLOGRAFT REJECTION

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

TNX-1900: MIGRAINE & OTHER INDICATIONS

STANFORD UNIVERSITY

UNIVERSITÉ DE GENÈVE

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

TNX-1300: COCAINE INTOXICATION
TNX-1700: GASTRIC AND COLORECTAL CANCERS

COLUMBIA UNIVERSITY

TNX-801: SMALLPOX AND MONKEYPOX VACCINE

UNIVERSITY OF ALBERTA

SR SOUTHERN RESEARCH

TNX-2900: PRADER-WILLI SYNDROME

InsermTransfert

CHU de Toulouse

Aix*Marseille université

TONIX PHARMACEUTICALS

Management Team

Seth Lederman, MD
Co-Founder, CEO & Chairman

TARGENT | Fusilev (levoleucovorin) for injection | 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

Summary of Upcoming Milestones

4th Quarter 2023 Clinical Trial Initiations

- **Phase 2 study of TNX-1300 for the treatment of cocaine intoxication - expected**

4th Quarter 2023 Data Readouts

- **Phase 2 UPLIFT study of TNX-601 ER for major depressive disorder**
  - Affects approximately 47 M adults in the U.S (18.4% of population)[1]
- **Phase 2 PREVENTION study of TNX-1900 for chronic migraine**
  - Affects approximately 3-7 M adults in the U.S[2]
- **Phase 3 RESILIENT study of TNX-102 SL for fibromyalgia**
  - Affects approximately 6-12 M adults in the U.S[3]

[1]CDC - https://www.cdc.gov/mmwr/volumes/72/wr/mm7224a1.htm?s_cid=mm7224a1_w
[2]Natoli et al., Global prevalence of chronic migraine: a systematic review, Cephalagia, 2010, 30:599-609
[3]American Chronic Pain Association (www.theacpa.org, 2019)

THANK YOU

Zembrace® Important Safety Information (1 of 2)

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

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

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

Do not use Zembrace if you have:

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

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

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

Zembrace® Important Safety Information (2 of 2)

Zembrace may cause serious side effects including:

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

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

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

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

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

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

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

CNS PORTFOLIO

TONIX PHARMACEUTICALS

Tosymra® Important Safety Information (1 of 2)

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

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

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

Do not use Tosymra if you have:

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

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

CNS PORTFOLIO

TONIX PHARMACEUTICALS

Tosymra® Important Safety Information (2 of 2)

Tosymra may cause serious side effects including:

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

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

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

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

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

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

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

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

TONIX PHARMACEUTICALS

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 s 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.

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 and Bone Marrow Transplant Rejection

Status: Phase 1 study currently enrolling

- Collaborations ongoing with Mass General Hospital on heart and kidney transplantation in non-human primates
- Collaboration with Boston Children's on bone marrow transplantation in non-human primates

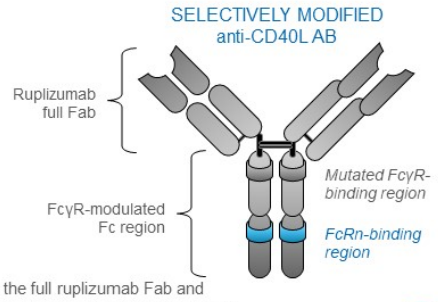
Next Steps: Initiate Phase 2 study in Kidney Transplant Recipients

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

TNX-1500 (α-CD40 Ligand)
Market Opportunity

IMMUNOLOGY PORTFOLIO

OPPORTUNITY

Organ transplant rejection drugs	Kidney transplants: 24,000/year/US[2]	Autoimmune Lupus: 1.5 M patients in US[4]	Autoimmune Disease
$4.7 billion[1]	**$5.54 billion[3]**	**1.87 billion[5]**	**$149.4 billion[6]**

[1]Global market as of 2018 (https://www.biospace.com/article/organ-transplant-rejection-medications-market-drug-companies-focus-on-improving-long-term-outcome-of-new-drugs/)
[2]Wang, Jeffrey H. and Hart, Allyson. *Kidney360* November 2021; 2(11) 1836-1839
[3]Global market as of 2020 (https://www.grandviewresearch.com/industry-analysis/transplantation-market)
[4]https://www.lupus.org/resources/lupus-facts-and-statistics
[5]Global market as of 2020 (https://www.globenewswire.com/news-release/2021/02/18/2177637/0/en/Global-Lupus-Therapeutics-Market-Is-Expected-to-Reach-USD-3-62-Billion-by-2028-Fior-Markets.html)
[6]Anticipated market size by 2025 (https://www.prnewswire.com/news-releases/the-global-autoimmune-disease-therapeutics-market-size-is-expected-to-reach-149-4-billion-by-2025--rising-at-a-market-growth-of-4-34-cagr-during-the-forecast-period-300902336.html)

TONIX PHARMACEUTICALS

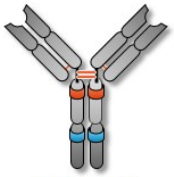
About CD40L (Also Called CD154)

- **CD40L is a transiently expressed T cell surface molecule and is also called CD154[1-4]**
  - Predominantly expressed by T cells and interacts with CD40 on B cells and macrophages
- **Mediates T cell helper function[1-4]**
  - Activates B cells for humoral (antibody-mediated) immune response
  - Activates macrophages and dendritic cells
  - Provides T cell help to activated CD8+ T cells
- **X-linked hyper-IgM syndrome is caused by a defective CD40L gene[5-6]**
  - Lack of T helper function with only IgM serum antibodies but no IgG or IgE because T cells are required for B cell isotype switching
  - If maintained on gamma globulin, patients are otherwise healthy
- **Member of the TNFα superfamily[4]**
  - TNFα and RANKL are other family members and are drug targets for approved products

[1]Lederman S, et al. *J Exp Med*. 1992;175(4):1091-1101.
[2]Lederman S, et al. *J Immunol*. 1992;149(12):3817-3826.
[3]Lederman S, et al. *J Immunol*. 1994;152(5):2163-2171.
[4]Covey LR, et al. *Mol Immunol*. 1994;31(6):471-484.
[5]Ramesh N, et al. *Int Immunol*. 1993;5(7):769-773.
[6]Callard RE, et al. *J Immunol*. 1994;153(7):3295-3306.

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

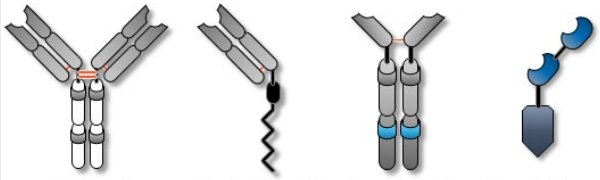
First-generation
anti-CD40L mAbs



Ruplizumab

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

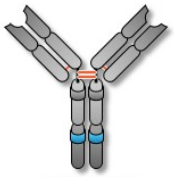
Second-generation
anti-CD40L proteins



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

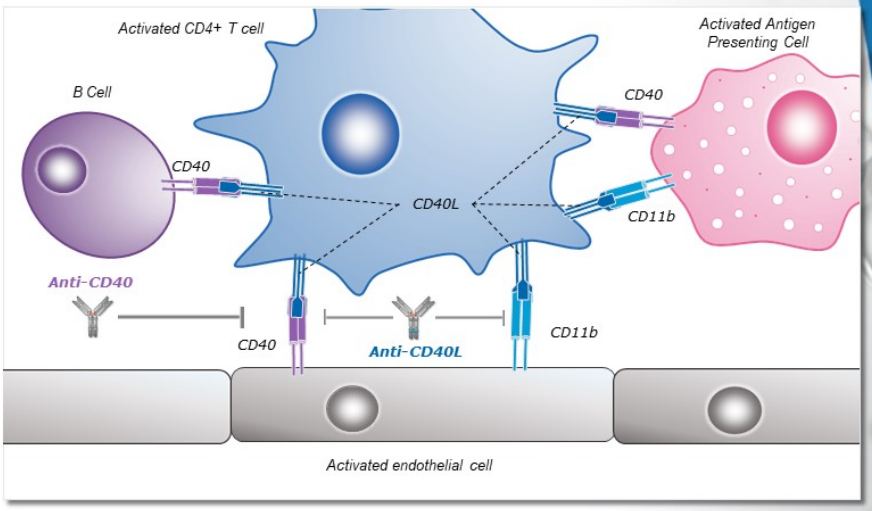
TNX-1500 is engineered to target CD40L therapeutically while reducing FcγRIIA binding and thereby lowering the potential for thrombosis.[1-9]

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

[1]Inwald DP, et al. *Circ Res*. 2003;92(9):1041-1048.
[2]Robles-Carrillo L, et al. *J Immunol*. 2010;185(3):1577-1583.
[3]Shock A, et al. *Arthritis Res Ther*. 2015;17(1):234.
[4]Xie JH, et al. *J Immunol*. 2014;192(9):4083-4092.
[5]Ferrant JL, et al. *Int Immunol*. 2004;16(11):1583-1594.
[6]Karnell JL, et al. *Sci Transl Med*. 2019;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 J, *Biocentury*; October 26, (2018).
[9]Company data.

CD40L is a Ligand for Both CD40 and CD11b

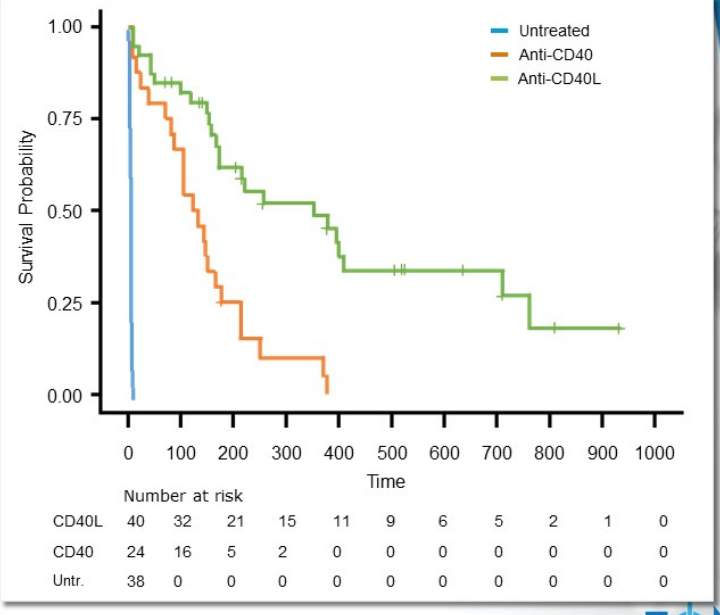
- Blocking interaction of CD40L and CD11b enhances efficacy of anti-CD40 treatment in prolonging allograft survival[1]
  - Anti-CD40 antibodies block CD40/CD40L binding, but do not affect CD11b/CD40L binding[1]
- Anti-CD40L antibodies may offer the advantage of blocking interaction with both CD40 and CD11b



[1]Liu D, et al. *Am J Transplant*. 2020;202216-2225.

CD40L inhibition offers decreased risk of graft rejection and increased survival vs CD40 inhibition[1]

- A meta-analysis of nonhuman primate studies compared anti-CD40 and anti-CD40L treatments for the prevention of renal transplant rejection
  - Both treatments increased probability of rejection-free survival compared to placebo
  - Anti-CD40L treatment resulted in a median survival of 352 days vs 131 days for anti-CD40 treatment (P=0.0001)

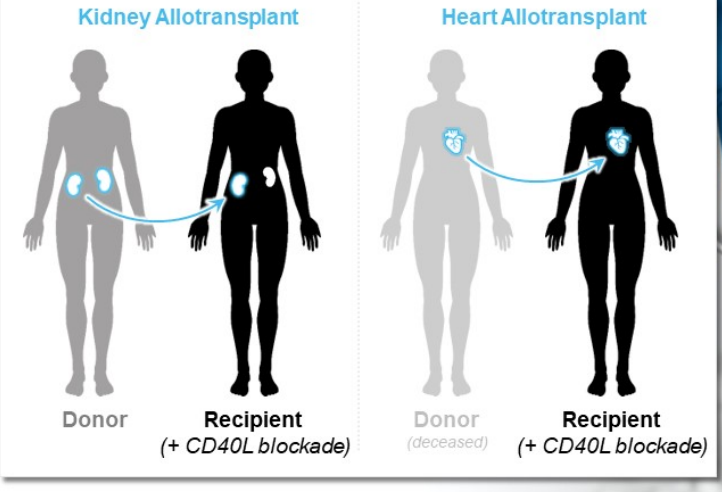


[1]Perrin S, et al. *Front Immunol*. 2022;13:861471.

α-CD40L Treatment to Prevent Allograft Rejection

- Calcineurin inhibitors (CNIs), mainly tacrolimus, are the cornerstone of immunosuppressive therapy[1,2]
- However, CNIs cause irreversible and progressive deterioration of kidney function in all types of solid organ transplants[3,4]
- Costimulation blockade (anti-CD40L in particular) may be more effective at protecting allografts than CNIs[5]

Concept for Human-to-Human Allotransplantation[1,2]



[1]Enderby C, et al. *Am J Manag Care*. 2015;21(1 Suppl):s12-s23.
[2]Camilleri B, et al. *Exp Clin Transplant*. 2016;14(5):471-483.
[3]Naesens M, et al. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.
[4]Nankivell BJ, et al. *N Engl J Med*. 2003;349(24):2326-2333.
[5]Cooper DKC, et al. *Blood Purif*. 2018;45(1-3):254-259.

IMMUNOLOGY PORTFOLIO

TONIX PHARMACEUTICALS

Non-Human Primate Kidney Allo-Transplantation[1]
Dr. Tatsuo Kawai, Mass General Hospital

- **TNX-1500 monotherapy consistently prevents kidney transplant rejection**
  - Superior to results with conventional triple drug immunosuppressive regimen[2]
- **No thrombosis observed**
  - Thrombosis was observed with hu5c8 in prior studies
- **April 2023 Publication:**
  - Lassiter, G., et al. (2023). TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Renal Allograft Survival. *American Journal of Transplantation*.[1]

IMMUNOLOGY PORTFOLIO

[1]Lassiter, G., et al. (2023). TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Renal Allograft Survival. *American Journal of Transplantation*. April 7, 2023. https://doi.org/10.1016/j.ajt.2023.03.022 www.sciencedirect.com/science/article/pii/S1600613523003714
[2]Tacrolimus, MMF and steroids

TONIX PHARMACEUTICALS

Non-Human Primate Heart Heterotopic Allo-Transplantation[1]
Dr. Richard Pierson, Mass General Hospital

TNX-1500 monotherapy consistently prevents heart transplant rejection[1]

- Prolonged acceptance after cessation of therapy (in progress)

Similar activity to chimeric hu5c8[2] during treatment phase in prior studies

- No apparent loss of effector function with Fc-modified TNX-1500 mAb

April 2023 Publication:

- Miura, S., et al. (2023) TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Cardiac Allograft Survival. *American Journal of Transplantation*[1]

[1]Miura, S., et al. (2023) TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Cardiac Allograft Survival. *American Journal of Transplantation.* April 7, 2023. https://doi.org/10.1016/j.ajt.2023.03.025 www.sciencedirect.com/science/article/pii/S1600613523003969
[2]Mouse-human IgG1κ chimeric anti-CD154

Non-Human Primate Kidney Xenograft Transplantation
Dr. Tatsuo Kawai, Mass General Hospital

TNX-1500 therapy is part of a regiment to prevent rejection in kidney xenograft transplants

- Prolonged acceptance

October 11, 2023 - Publication and news coverage in *Nature*

- Anand, R.P., Layer, J.V., Heja, D. *et al.* Design and testing of a humanized porcine donor for xenotransplantation. *Nature* 622, 393–401 (2023). https://doi.org/10.1038/s41586-023-06594-4 Design and testing of a humanized porcine donor for xenotransplantation | Nature[1]
- Kozlov, M. Oct 11, 2023 News: "Monkey survives two years after gene-edited pig-kidney transplant" *Nature* : Monkey survives for two years after gene-edited pig kidney transplant (nature.com)
- Mohiuddin, M. Oct 11, 2023 *Nature*. News and Views. "Pig-to-primate organ transplants require genetic modifications of donor." News and Views. :Pig-to-primate organ transplants require genetic modifications of donor (nature.com)

[1]In Table 1, I see four TNX-1500 treated animals: M8220, M6421, M12621, M5722

Non-Human Primate Bone Marrow Transplantation
Dr. Leslie Kean[1], Boston Children's Hospital/Dana Farber

Studying TNX-1500 in combination with other drugs for preventing rejection and graft versus host disease (GvHD) in bone marrow transplant[2]

- Hematopoietic Stem Cell Transplantation (HCT) from unrelated donors is a component of the treatment protocol for several hematologic malignancies
- GvHD complicates treatment and limits the success of engraftment after HCT
- To be successful, the post-HCT indication requires prolonged engraftment.
- GvHD remains one of the most severe complications associated with HCT. For myeloablative MHC-haploidentical HCT, the risk of GvHD is substantial, and with the most severe form of acute GvHD, as many as half of patients can die from this disease. For these high-risk transplants, there is no fully effective GvHD prevention strategy.
- The primary objective of the preclinical research study is to study the activity of TNX-1500 administered prophylactically to modify GvHD progression in animals after HCT to support an Investigational New Drug (IND) application for human studies

Prof. Kean is a leader in the field of NHP bone marrow transplants

- Unique model of haplo-identical animals[3]

[1]The principal investigator is Leslie S. Kean M.D., Ph.D., Director, Stem Cell Transplantation Program, Division of Hematology/Oncology, Boston Children's Hospital, Department of Pediatric Oncology, Dana-Farber Cancer Institute and Robert A. Stranahan Professor of Pediatrics, Harvard Medical School.
[2]Tonix Press Release. Dec 5, 2022. https://ir.tonixpharma.com/news-events/press-releases/detail/1353/tonix-pharmaceuticals-announces-collaboration-with-boston
[3]Tkachev V, et al. 2017. *Sci Transl Med.*9(408):eaan3085. doi: 10.1126/scitranslmed.aan3085. PMID: 28931653; PMCID: PMC5681253.

α-CD40L Beyond Allografts: Autoimmunity

- Autoimmune diseases are also characterized by immune system activity that attacks "self," which can damage various parts of the body[1,2]
- First-generation anti-CD40L Abs showed evidence of efficacy in autoimmunity before trials were halted due to thromboembolic events[3]

*Not an exhaustive list of all autoimmune diseases or organ systems affected by autoimmune disease

Autoimmune Disease Targets[1,2,*]

Joints and Spine	Skin	Nervous System	Vasculature	Bowel
• Ankylosing spondylitis • Rheumatoid arthritis	• Psoriasis	• Guillain-Barre syndrome • Multiple sclerosis	• Vasculitis • ITP	• Ulcerative colitis • Crohn's disease

[1]Li P, et al. *Front Pharmacol.* 2017;8:460.
[2]WebMD. Accessed March 3, 2020. https://www.webmd.com/a-to-z-guides/autoimmune-diseases
[3]Tocoian A, et al. *Lupus.* 2015;24(10):1045-1056.

Anti-CD40L for Sjögren's Syndrome

- Sjögren's is a **life-long autoimmune condition**, where tear and salivary glands are initially affected
- In 2019, there were an estimated **2.26 million prevalent cases** of primary Sjögren's syndrome worldwide. Forecasted to increase to 2.52 million prevalent cases by 2028

Horizon (being acquired by Amgen) has announced two positive Phase 2 trials in Sjögren's Syndrome

September 12, 2022:

Horizon Therapeutics plc Announces Phase 2 Trial Evaluating Dazodalibep for the Treatment of Sjögren's Syndrome Meets Primary endpoint[1]

January 18, 2023

Horizon Therapeutics plc Announces Phase 2 Trial Evaluating Dazodalibep for the Treatment of Sjögren's Syndrome Meets Primary Endpoint in the Second Study Population; Only Phase 2 Trial to Meet Primary Endpoint in Both Patient Populations[2]

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

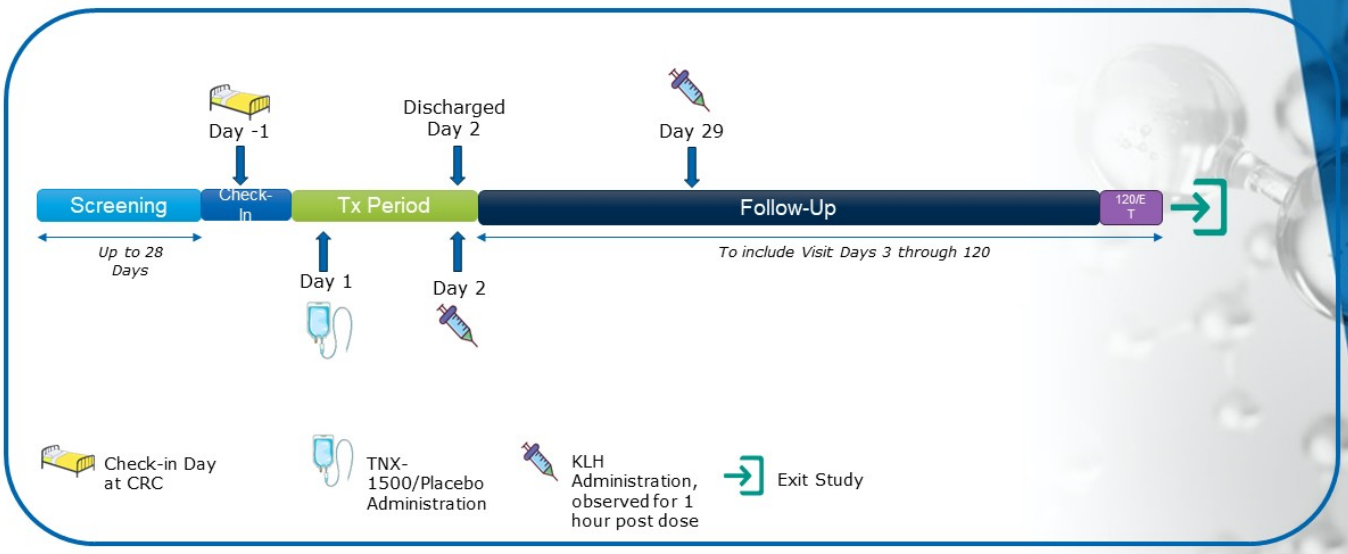
TNX-1500: Key Considerations

- TNX-1500 may be used in large markets that are not currently well served
- There is a long history of use of monoclonal antibodies
- Tonix has engineered a safer, potentially more efficacious molecule than previous anti-CD40L mAbs
- Intellectual property is in place (composition of matter)

Key milestones:

- Phase 1 study currently enrolling
- Autoimmune disorders – Planning INDs

Phase I Study Schematic



TNX-1500 Phase 1 Dosing

Cohort	Number of Subjects	Dose Level (IV)
Cohort 1	6 (4 active, 2 placebo)	3 mg/kg
Cohort 2	10 (8 active, 2 placebo)	10 mg/kg
Cohort 3	10 (8 active, 2 placebo)	30 mg/kg
Cohort 4	10 (8 active, 2 placebo)	60 mg/kg

Development and Regulatory Strategy

- **1st Indication – Kidney allotransplantation (human to human)**
  - Replacement for nephrotoxic CNI's (calcineurin inhibitors, *e.g.* Prograf® (tacrolimus)[1], Neoral® (cyclosporin)[2]
  - Similar development path to the successful development of BMS's Nulojix® (belatacept)[3], CTLA-4/Ig biologic
  - Clinical development may combine with Nulojix or Rapamune® (rapamycin/sirolimus)[4]

- **2nd Indication – Hematopoetic Cell Transplant (Bone Marrow Transplant)**
  - Potential to reduce GvHD

- **3rd Indication (and beyond) – Autoimmune disease (e.g., Multiple Sclerosis, Sjögen's Syndrome, Systemic Lupus Erythematosus)**
  - Autoimmune indications require large studies and represent large target markets

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050708s027,050709s021lbl.pdf
[2] http://www.novartis.us/sites/www.novartis.us/files/neoral.pdf
[3] https://packageinserts.bms.com/pi/pi_nulojix.pdf
[4] https://labeling.pfizer.com/showlabeling.aspx?id=139

TNFα Superfamily Members Are Targeted by mAbs

- CD40L is a member of the Tumor Necrosis Factor (TNFα) Superfamily[1]
- Other TNFα Superfamily members have proven to be effective targets for antagonist (blocking) mAbs[2]

anti-TNFα mAbs for the treatment of certain autoimmune conditions

- infliximab (Remicade®)
- adalimumab (Humira®)

TNFα antagonist receptor fusion protein

- etanercept (Enbrel®)

anti-RANKL (CD254) mAb for the treatment of osteoporosis, treatment-induced bone loss, metastases to bone, and giant cell tumor of bone

- denosumab (Prolia® or Xgeva®)

No mAb against CD40L has been licensed *anywhere* in the world

[1] Covey, L.R., et al. *Mol. Immunol.* 31:471-484. 1994. PMID: 7514269.
[2] Remicade® and Simponi® are trademarks of Janssen; Humira® is a trademark of AbbVie; Cimzia® is a trademark of UCB; Enbrel® is a trademark of Amgen; and Prolia® and Xgeva® are trademarks of Amgen.

Recent mAb Transactions

2020 — October

Momenta acquired by Johnson & Johnson for $6.5B[1]

- Nipocalimab (M281) is a clinically validated anti-FcRn antibody with a rare pediatric disease designation from the US FDA
- J&J called nipocalimab "a pipeline in a product"

2021 — March - April

Kymab acquired by Sanofi for $1.1B[2]

- mAb anti-Ox40L for the treatment of autoimmune disease

Viela Bio acquired by Horizon for $3B[3]

- UPLIZNA® (inebilizumab-cdon) is an anti-CD19 (B-cell-depleting) antibody approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD), which is a rare and severe autoimmune disease
- VIB4920 anti-CD40L is Viela's second program

2022 — March

Sanofi and IGM Biosciences announce collaboration deal that could surpass $6B[4]

- The two companies will partner on immunoglobulin M (IgM) antibody agonists against three cancer targets and three immunology/inflammation targets

Merck announces plan to acquire Prometheus for $10.8B[5]

- Two mAbs targeting TNF family members:TL1A (PRA-023) and CD30L (PRA-052) for the treatment of inflammatory bowel disease and other autoimmune conditions

2023 — April - October

Horizon acquired by Amgen for $27.8B[6] – Lead Drugs:

- Krystexxa® (pegloticase) - Gout
- Tepezza® (teprotumumab) mAb anti-IGF-1R – Grave's Disease
- Dazodalibep (tn03 fusion protein) Anti-CD40L – Sjögren's Syndrome

Sanofi and Teva to co-develop anti-TL1A in $1.5B deal[7]

- Anti-TL1A mAb for inflammatory bowel disease

[1]Johnson & Johnson. October 1, 2020. Accessed June 3, 2021. https://www.jnj.com/johnson-johnson-completes-acquisition-of-momenta-pharmaceuticals-inc
[2]Sanofi. April 9, 2021. "Sanofi completes Kymab acquisition. www.sanofi.com/en/media-room/press-releases/2021/2021-04-09-05-00-00-2207173.
[3]Horizon. March 15, 2021. "Horizon Therapeutics plc completes acquisition of Viela Bio, Inc. https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-completes-acquisition-viela-bio-inc
[4]BioSpace. March 29, 2022. Accessed March 29, 2022. https://www.biospace.com/article/sanofi-and-igm-partner-on-oncology-and-immunology-in-deal-worth-more-than-6-billion/
[5]April 16, 2023. Merck. "Merck strengthens immunology pipeline with acquisition of Prometheus Biosciences" www.merck.com/news/merck-strengthens-immunology-pipeline-with-acquisition-of-prometheus-biosciences-inc/
[6]Endpoints News. October 6, 2023. "Amgen closes $28B Horizon acquisition a month after FTC battle ended." https://endpts.com/breaking-amgen-seals-28b-horizon-acquisition-a-month-after-ftc-battle-ended/
[7]BioSpace. October 4, 2023. "Sanofi, Teva Ink Potential $1.5B Deal Aimed at Blockbuster IBD Drug". https://www.biospace.com/article/sanofi-teva/

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 (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)
- Frexalimab, f.k.a.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

mAbs Represent 5 of Top 10 Products by 2023 Projected Sales

- Over 100 mAbs have been approved by the US FDA, and significant growth potential remains[1]
- Global mAb market is projected to grow from $179B in 2021 to $452B in 2028 at a CAGR of 14.1%[2]

TOP 10 DRUGS WORLDWIDE BASED ON 2023 PROJECTED SALES[3]

[1]Mullard A. May 5, 2021. Accessed February 24, 2022. (https://www.nature.com/articles/d41573-021-00079-7)
[2]Forbes Business Insights. August 2021. Accessed February 24, 2022.
[3]Matej Mikulic. Statista. Jan 18, 2023. Accessed January 24, 2023. (https://www.statista.com/statistics/973523/top-drugs-by-year-on-year-sales-increase/)

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TONIX PHARMACEUTICALS

TNX-1500 (α-CD40L mAb): Prophylaxis of Transplant Rejection
Potential Treatment for Autoimmune Conditions

Phase 1 Candidate

Targeted as a first-line monotherapy for autoimmunity and add-on therapy for preventing organ transplant rejection

- Distinct mechanism of action (MOA)—TNX-1500 blocks T cell helper function

New molecular entity, biologic

- US Patient Protection and Affordable Care Act provides 12 years of exclusivity for biologics

Patent applications directed to composition of matter

- Expected patent protection through 2039

Significant Unmet Need

Clinical evidence for anti-CD40L mAbs in the treatment of systemic lupus erythematosus (SLE), Sjögren's Syndrome (SjS), multiple sclerosis, allogeneic kidney transplant and bone marrow transplant

- Several studies have shown anti-CD40L to be active in the treatment of human SLE[1-3], SjS[4,5], and transplant rejection[6,7]

[1]Huang W, et al. *Arthritis Rheum*. 2002;46(6):1554-1562.
[2]Boumpas DT, et al. *Arthritis Rheum*. 2003;48(3):719-727.
[3]Grammer AC, et al. *J Clin Invest*. 2003;112(10):1506-1520.
[4]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating
[5]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-0
[6]Kawai T, et al. *Nat Med*. 2000;6(2):114.
[7]Koyama I, et al. *Transplantation*. 2004;77(3):460-462.

IMMUNOLOGY PORTFOLIO

TONIX PHARMACEUTICALS

THANK YOU

Exhibit 99.03

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

Upcoming Expected Topline Results

Fourth Quarter
2023

TNX-601 ER for Depression

Topline Results Expected – early November

Phase 2 Potential Pivotal Study

TNX-1900 for Chronic Migraine

Topline Results Expected – early December

Phase 2 Proof-of-Concept Study

TNX-102 SL for Fibromyalgia

Topline Results Expected – late December

Phase 3 Potential NDA Enabling Study

CNS PORTFOLIO

TNX-601 ER - Phase 2 UPLIFT* Study Design

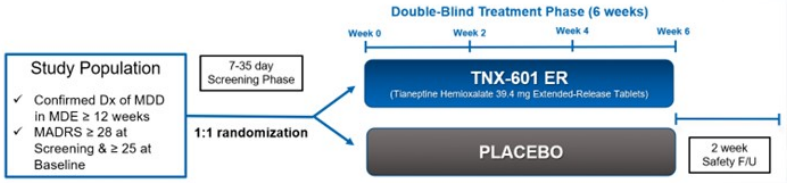
UPLIFT Study

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
- U.S. sites only, ***completed enrollment of 132 patients***
  - Clinical phase completed – announced October 16, 2023[1]

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6
- Threshold for achieving positive proof-of-concept study is effect size (ES) > 0.20
- Threshold for positive pivotal study is p-value < 0.05



Next Steps: *Topline results expected 4Q 2023 (Early November)*

*ClinicalTrials.gov Identifier: NCT05686408
Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number
[1]Tonix Press Release, October 16 2023: https://ir.tonixpharma.com/news-events/press-releases/detail/1430/tonix-pharmaceuticals-completes-clinical-stage-of-phase-2

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.)
- Hormonal aspects can significantly impact course and treatment (especially evident in post-partum depression)
- 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

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
- PPAR-β/δ and PPAR-γ agonist[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 less weight gain or sexual side effects than traditional antidepressants
- Tianeptine's side effects are described in labeling in countries in which it is marketed[2]

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Dysfunction From Corticosteroids, Alzheimer's Disease[3]

Status: Phase 2 MDD study UPLIFT enrollment complete. Clinical phase completed as of October 16, 2023

Next Steps:

Topline results expected early November 2023

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

[1]Sullivan G et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
[2]Summary of product characteristics (SmPC), European Medicines Agency, Stablon®, https://www.servier.com.ve/sites/default/files/spc-pil/spc-stablon.pdf accessed 9-25-23.
[3]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720
Abbreviations: IR, immediate release; *t.i.d.*, three times a day

TONIX PHARMACEUTICALS

TNX-601 ER - Pharmacokinetics and Formulation[1]

CNS PORTFOLIO

Table 1	TNX-601 ER 39.4 mg (fasted) N=12	TNX-601 ER 39.4 mg (fed) N=12	TNX-601 ER 39.4 mg (fasted) N=12	TNX-601 ER 39.4 mg (fed) N=12
Parameter (Mean*)	Tianeptine		Metabolite MC5	
AUC_{0-24} (ng.h/mL)	2040	1990	1220	1270
AUC_{0-last} (ng.h/mL)	2300	2060	1750	1700
$F_{rel}AUC_{0-last}$ (%)	89.22 [81.59, 97.56], p=0.043		97.02 [90.55, 103.96], p=0.45	
AUC_{0-inf} (ng.h/mL)	2360	2230	2030	1830
$F_{rel}AUC_{0-inf}$ (%)	92.81 [84.63, 101.77], p=0.17		93.57 [86.25, 101.51], p=0.17	
C_{max} (ng/mL)	230	321	76.3	102
$F_{rel}C_{max}$ (%)	139.70 [114.19, 170.91], p=0.013		134.19 [117.30, 153.51], p=0.002	
AUC_{extrap} (%)	1.944	1.691	6.821	6.198
T_{max} (h)[a]	3.500	5.000	8.042	8.000
$T_{1/2}$ (h)	6.874	5.050	11.306	11.175
Vz/F (L)	150	116	*ND	*ND

* Geometric means

Formulated with attention to potential abuse deterrent properties: lower solubility of hemioxalate salt (reduced extraction efficiency); microcrystalline cellulose as compression aid and compressed at >100 Newtons (difficulty crushing to fine particles for efficient insufflation or extraction); inclusion of high molecular weight gel-forming polymers (poor "syringe-ability"/injectability); and inclusion of fumed silica and magnesium stearate (nasal irritation with insufflation).

[1]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41

TONIX PHARMACEUTICALS

History of Tianeptine and TNX-601 ER

- 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.

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

LTP = Long term potentiation
LTD = Long term depression

[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: 1965.

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(6):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., 1996. *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's Off-target Activity

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

- Because of low affinity binding and agonist activity on μ-opioid receptor[1], 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
- Based on these μ–opioid data and interpretations,[1] 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

[1]Gassaway et al., 2014. *Transl Psychiatry*. 4(7):e411

Published μ-Opioid Receptor (MOR) Binding of *(R)*-Methadone and Certain Potential and Approved Antidepressant Agents

API	(R)-(-)-Methadone	(S)-(+)-Methadone	(±) Tianeptine	Dextromethorphan
Affinity to μ-opioid receptor, K_i (nM) (species)[1-4]	0.945 rat[1]	19.7 rat[1]	768 human[2]	1280 rat[1]
Program Name		REL-1017	TNX-601 ER	Auvelity®
Sponsor	-	Relmada	Tonix	Axsome
Indication	-	MDD	MDD	MDD
Antidepressant dose	N/A	25 or 50 mg/day	39.4 mg/day	90 mg[6]
Current dev. stage	-	Recruiting for Phase 3	Phase 2 topline expected early Nov	FDA Approved
Proposed MOA	N/A	NMDA receptor channel blocker[6]	PPAR-β/δ activator	NMDA-R antagonist SERT inhibitor

[1]Codd EE, et al. *J Pharmacol Exp Ther*. 1995 274(3):1263-70. PMID: 7562497.
[2]pdsp.unc.edu/databases/kidb.php
[3]Roth BL et al. *The Neuroscientist*, 6:252-262, 2000
[4]*Science Netwatch*, 28 January 2000; 287 (5453)
[5]Combination with bupropion HCl 105 mg; prescribed *b.i.d.*
[6]Fava M. et al., *Am JPsychiatry*. 2022 179(2):122-131. doi: 10.1176/appi.ajp.2021.21020197.

Prescription Tianeptine has Low Incidence of Abuse

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

- Tianeptine and its MC5 metabolite are weak 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].
- Post-marketing research in France showed that in patients who were prescribed tianeptine for depression, the incidence of misuse was approximately 1 case per 1,000 patients treated[3]
  - Suggests low abuse liability when used at the antidepressant dose
- Clinical trials have shown that abrupt cessation of a therapeutic course of tianeptine does not result in dependence or withdrawal symptoms following a treatment duration of:
  - 6-weeks[4-8]
  - 3-months[9]
  - 12-months[10]

[1]Gassaway et al., 2014. *Transl 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

Looking Forward: Additional Potential Indications for TNX-601 ER

Informed by clinical data and mechanistic insights

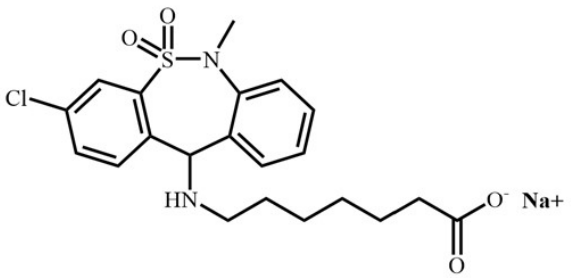
- Neurodegenerative disorders
  - Parkinson's (and associated conditions, e.g. depression and psychosis)[1]
  - Alzheimer's (and associated conditions, e.g. agitation, depression and psychosis)[2]
- ADHD[3]
- Stress disorders[4]
  - PTSD, Anxiety
- Aging/Neuroprotection[5,6]
  - Mild Cognitive Impairment
- 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

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

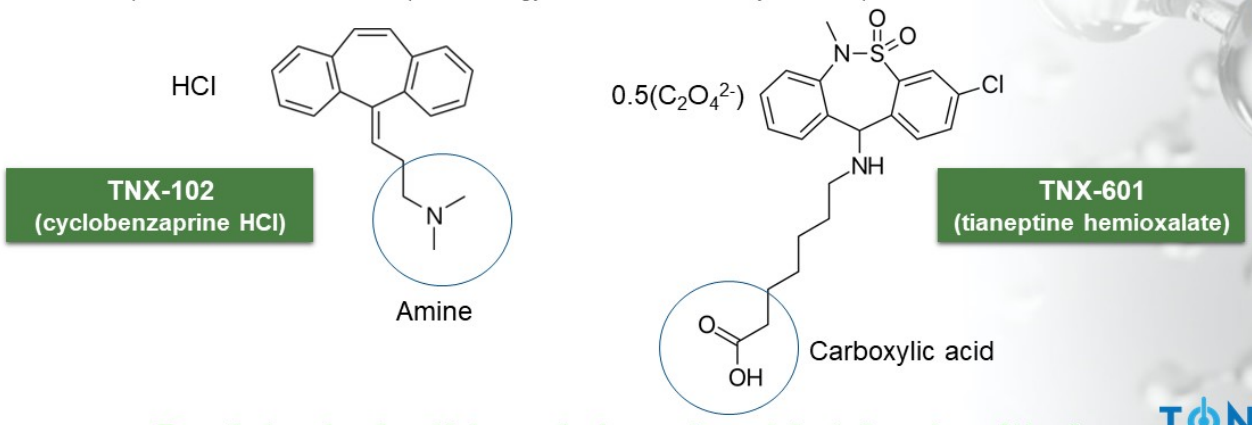


[3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(c,f)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt

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



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

Tianeptine is a Polyunsaturated Fatty Acid (PUFA) Analogue

PUFAs and PUFA-analogues

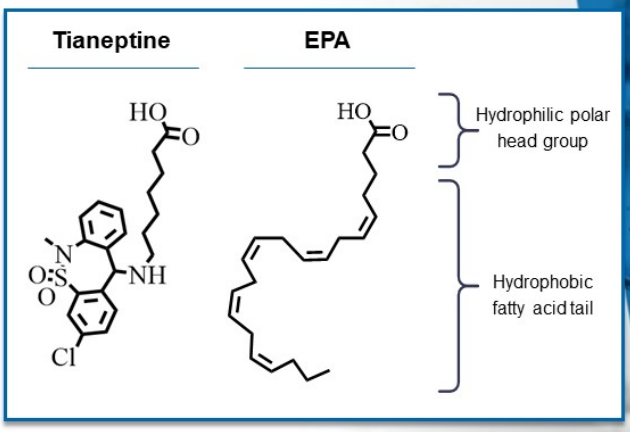
- Polar acidic "head" and hydrophobic fatty acid "tail"

Pharmacological modulation of PUFA signaling has therapeutic potential in multiple pathologies

- Act through the binding sites of endogenous FA metabolites on enzymes, transporters, and receptors
- Several PUFA analogues have been developed as drugs, including the ethyl ester of eicosapentaenoic Acid (EPA)[1] which is branded as Vascepa®

PUFAs and PUFA-analogues have distinctive ligand-target interactions with PUFA binding proteins

- PUFA binding sites share common chemical features: low affinity[2,3] and low off-rate
- Traditional PUFA selectivity has been limited



EC_{50} for EPA is ~3 µM

[1]EPA = eicosa-5Z, 8Z, 11Z, 14Z, 17Z-pentaenoic acid.
[2]Xu et al., 1999. *Mol Cell.* 3(3):397-403.
[3]Helmstädter et al., 2022. *Int J Mol Sci.* 23(17):10070.

EPA and DHA are Examples of Polyunsaturated Fatty Acids (PUFAs)

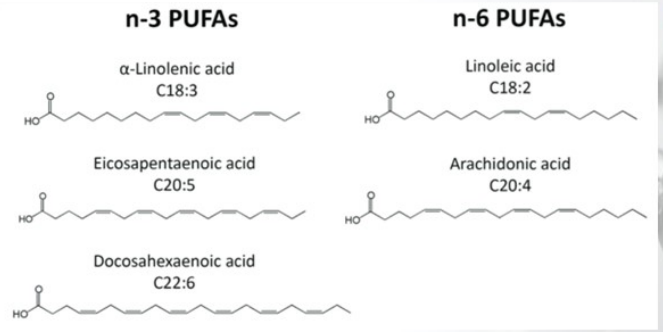
Eicosapentaenoic acid (EPA)[2]

- Essential PUFA – obtained from diet
- EPA is the active ingredient in Vascepa® (ethyl-ester EPA prodrug) which reduces heart attacks, stroke and death in statin-resistant hyper-triglyceridemia

Docosahexaenoic acid (DHA)[3]

- Primary structural component of the brain
- Most abundant omega-3 fatty acid in the brain and retina
- Comprises 40% of the PUFAs in the brain and 60% of the PUFAs in the retina

PUFAs[1]



EPA and DHA have activity in treating MDD[4,5]

- Activity shown in studies and meta-analyses, but insufficient randomized studies to be conclusive

[1]Bohannon et al., 2023. *bioRxiv* preprint
[2]Wikipedia: https://en.wikipedia.org/wiki/Eicosapentaenoic_acid
[3]Wikipedia: https://en.wikipedia.org/wiki/Docosahexaenoic_acid
[4]Liao et al., 2019. *Transl Psychiatry*. 9(1):190
[5]Wani et al., 2015. *Integr Med Res*. 4(3):132-141

TNX-601 ER – Racemic Tianeptine – Composed of Two Isomers

Racemic tianeptine:

- Approved in Europe and ex-US
- 1:1 mixture of 2 mirror-image isomers[1,2]
- Weak μ-opioid receptor agonism[2]
  - Risk of abuse or diversion for euphoric effects[3]

***(S)*-Tianeptine: PPAR-β/δ agonist, no opioid liability[4]**

- New mechanism of action for treating depression

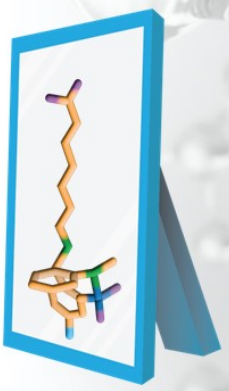
***(R)*-Tianeptine: opioid liability[4]**

- Weak μ-opioid receptor agonism[4]

	Racemic-Tianeptine	*(S)*-Tianeptine TNX-4300	*(R)*-Tianeptine
Activates PPAR-β/δ	+	+	-
Neuroplasticity	+	+	-
Novel Object Recognition Test[5]	+	+	-
μ-Opioid Receptor	+	-	+
Forced Swim Test[6]	+	-	+
Activates PPAR-γ	+	+	+

***(S)*-tianeptine**

***(R)*-tianeptine**

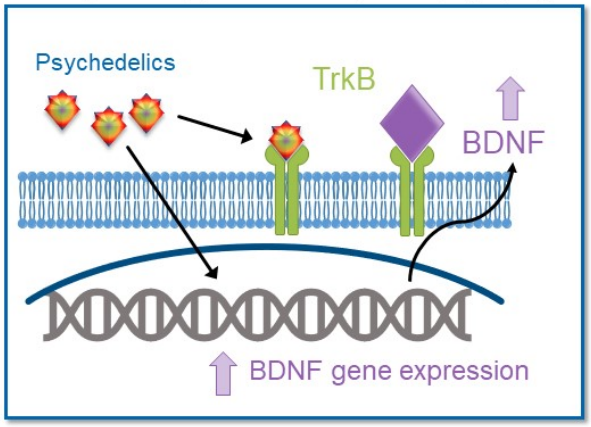


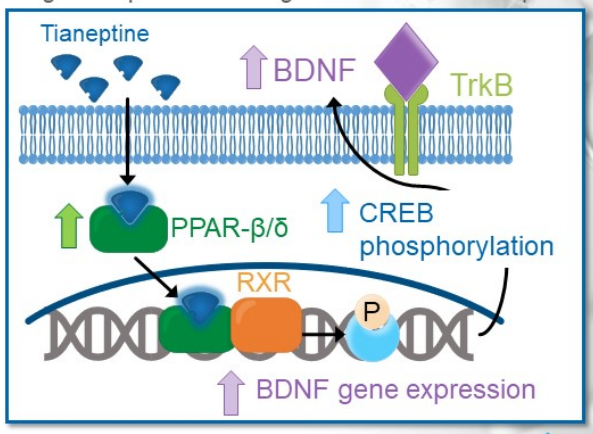
[1]Stablon. Summary of product characteristics. Les Laboratoires Servier Industrie; 2014.
[2]PubChem. Accessed November 10, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Tianeptine
[3]Drug Enforcement Administration. May 2019. Accessed November 11, 2022. https://www.deadiversion.usdoj.gov/drug_chem_info/tianeptine.pdf
[4]Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
[5]Rat Novel Object Recognition Test
[6]Mouse Porsolt Forced Swim Test

Tianeptine Shares a Neuroplasticity-Promoting Mechanism With Psychedelics

The neurotrophic growth factor BDNF plays a key role in the regulation of synaptic plasticity, and is diminished in populations suffering from anxiety and depression[1]

- Psychedelics may promote neuroplasticity both by directly binding to BDNF receptor TrkB, and by increasing BDNF gene expression[1,2]
- Tianeptine may promote neuroplasticity by upregulating BDNF gene expression through activation of PPAR-β/δ[3,4]

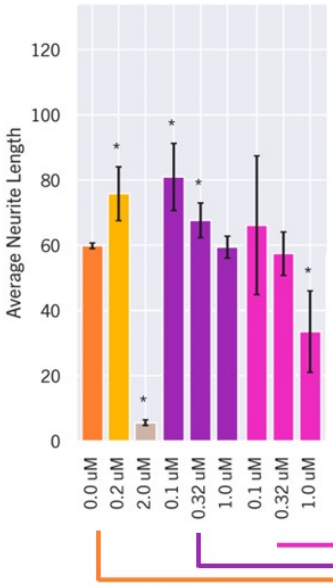




BDNF=brain-derived neurotrophic factor; CREB=cAMP response element binding protein; TrkB=tyrosine receptor kinase B

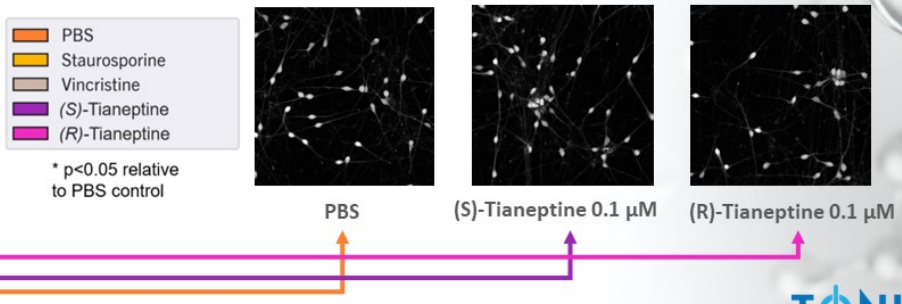
[1]de Vos CMH, et al. *Front Psychiatry*. 2021;12:724606
[2]Moliner R, et al. *Nat Neurosci*. 2023;26(6):1032-1041
[3]Ji MJ, et al. *Int J Neuropsychopharmacol*. 2015;19(1):pyv083
[4]Seo MK, et al. *Psychopharmacology (Berl)*. 2016;233(13):2617-2627

Treatment with 0.1 and 0.32 µM *(S)*-Tianeptine Significantly Increased Average Neurite Length[1]



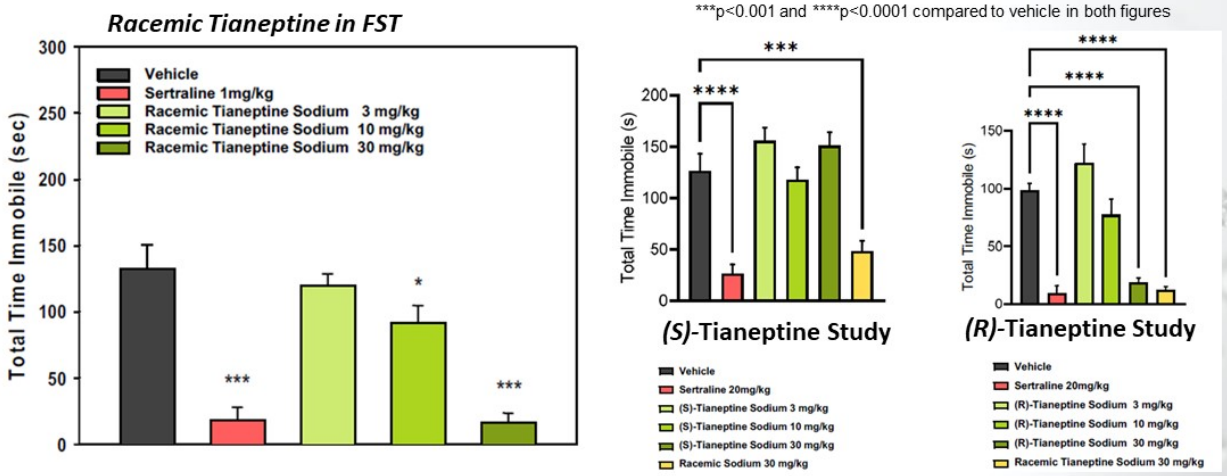
Neurite network dynamics tested in plated human iPSC-derived glutamatergic neurons

- Increase in average neurite length in culture for *(S)*-Tianeptine indicates plastogenic effects which are independent µ-opioid activity (µ-opioid activity only in *(R)*-isomer)
- Consistent with neuroregenerative effects of tianeptine on dendritic connectivity of glutamatergic neurons in hippocampus CA3 region, identified by McEwen & Coworkers[2]



[1]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41
[2]McEwen BS, et al. *Mol Psychiatry*. 2010;15(3):237-249.

(R)-Tianeptine, but not *(S)*-Tianeptine Reduces Immobility in Murine Forced Swim Test (FST)[1]



(*S*)-Tianeptine not active in FST, (*R*)-Tianeptine is active

Similar Acute Effects Reported by Samuels & Co-Workers[2]

- Samuels et al found no effect of tianeptine on FST activity in μ–opioid receptor KO mouse or in mice pretreated with opioid antagonists, indicating behavioral effect was μ–opioid mediated
- Their murine PK studies demonstrated tianeptine rapidly metabolized and nearly eliminated from murine plasma and brain after 1 hour (the time after tianeptine their FST was performed); whereas MC5 metabolite detectable for at least 8 hours
- Authors suggest MC5 is expected to play a major role in mediating the behavioral effects on FST in mice

[1]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41
[2]Samuels et al., 2017. *Neuropsychopharmacology*. 42(10):2052-2063

CNS PORTFOLIO

TONIX PHARMACEUTICALS

Summary of CNS Abilities: Tianeptine, (S)- & (R)-Isomers[1]

	Racemic-Tianeptine	*(S)*-Tianeptine TNX-4300	*(R)*-Tianeptine
PPAR-β/δ	+	+	-
Novel Object Recognition	+	+	-
Neurite Outgrowth	No Data	+	-
μ-Opioid Receptor	+	-	+
Forced Swim Test	+	-	+
PPAR-α	-	-	-
PPAR-γ	+	+	+

[1]Tonix data on file

CNS PORTFOLIO

TONIX PHARMACEUTICALS

TNX-4300*: Depression, Alzheimer's & Parkinson's diseases
Estianeptine (Single *(S)*-isomer of Tianeptine)

PROFILE

- Single isomer, oral treatment
- Proposed mechanism of action from lab studies indicates estianeptine is the active ingredient of TNX-601 ER[1]
  - PPAR-β/δ and PPAR-γ agonist
  - Free of μ-opioid receptor activity
- Estianeptine restores neuroplasticity in tissue culture

Differentiators:

Relative to racemic tianeptine IR or TNX-601 ER:

- Lack of opioid liability

Relative to traditional antidepressants:

- Unique mechanism of action – beyond neurotransmitter modulation
- Racemic 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: Pre-clinical

Next Steps: Potential for IND to be supported by pre-clinical and clinical data from TNX-601 (racemic tianeptine) development

*TNX-4300 is in the pre-IND stage of development and has not been approved for any indication

[1]Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
[2]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

PPAR-β/δ Targeted by Two Other Programs

- **Bezafibrate is a dual PPAR-β/δ / PPAR-γ agonist in a P-o-C trial for bipolar depression**[1,2]
  - Study underway at Mass General
  - PPARδ/δ and PPAR-γ co-activator 1α are targets validated by pre-clinical and clinical studies[3]
- **T3D-959 is a dual is a dual PPAR-β/δ / PPAR-γ agonist in development for Alzheimer's**[4-8]
  - T3D Therapeutics is developing it for Alzheimers after previous work (by DARA BioSciences as DB959 in Phase 1 trials for dyslipidemia and Type 2 diabetes)
  - Phase 1 and 2 studies reportedly encouraging[5-8]

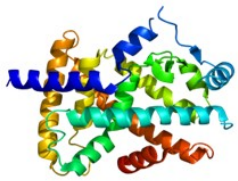
[1]Nierenberg, AA, Principal Investigator, Massachusetts General Hospital. "Bezafibrate Treatment for Bipolar Depression: A Proof of Concept Study." https://classic.clinicaltrials.gov/ct2/show/NCT02481245
[2]Tenenbaum A, et al. *Cardiovasc Diabetol.* 2005 4:14. doi: 10.1186/1475-2840-4-14. PMID: 16168052; PMCID: PMC1236941.
[3]Nierenberg AA, et al. *Biol Psychiatry.* 2018 83(9):761-769. doi: 10.1016/j.biopsych.2017.12.014. Epub 2018 Jan 10. PMID: 29502862.
[4]Chamberlain S, et al. *J Alzheimers Dis.* 2020;73(3):1085-1103. doi: 10.3233/JAD-190864. PMID: 31884472; PMCID: PMC7081093.
[5]Tong M, et al. *J Alzheimers Dis Parkinsonism.* 2016 6(3):238. doi: 10.4172/2161-0460.1000238. Epub 2016 Jun 3. PMID: 27525190; PMCID: PMC4979550.
[6]www.t3dtherapeutics.com/wp-content/uploads/2017/01/CTAD-Presentation-09-Dec-2016_website-posting.pdf
[7]www.t3dtherapeutics.com/2023/10/04/t3d-therapeutics-selected-to-present-topline-results-from-the-phase-2-pioneer-study-of-t3d-959-as-late-breaking-news-at-the-16th-clinical-trials-on-alzheimers-disease-conference-ctad/
[8]www.t3dtherapeutics.com/lead-product-candidate-t3d-959/

Peroxisome Proliferator Activated-Receptor (PPAR) Family: PPAR-β/δ

PPAR-α[1]

Expression
Liver, muscle, heart

Known roles
FA oxidation

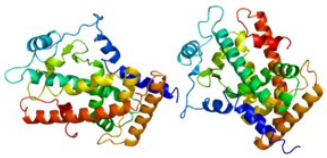


Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png

PPAR-β/δ[1,2]

Expression
Brain, skeletal muscle, adipose tissue, microglia, lungs, skin

Known roles
Promotes CNS neurotrophic factors and reduces expression of inflammatory mediators

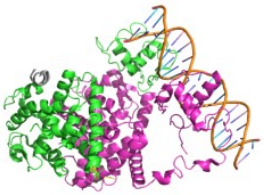


Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png

PPAR-γ[1]

Expression
Endothelial and smooth muscle cells

Known roles
Adipocyte differentiation regulation, FA storage, glucose metabolism



A2-33. Wikimedia Commons. March 14, 2012. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:PPARG.png

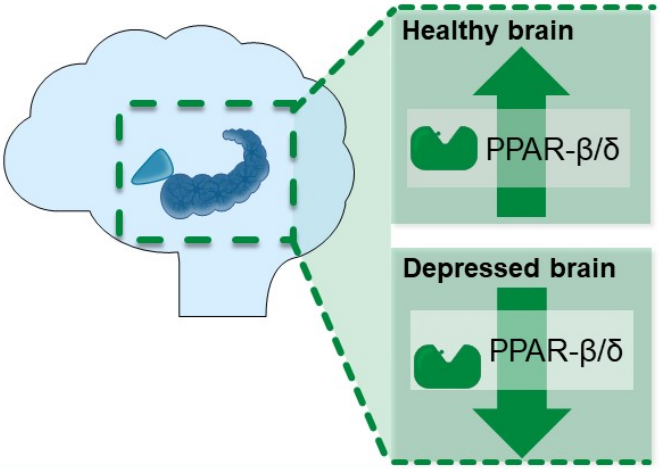
[1]Tyagi et al., 2011. *J Adv Pharm Technol Res.* 2(4):236-240
[2]D'Angelo et al., 2011. *J Cell Physiol.* 226(8):2170-2180

PPAR-β/δ Protects Against Pathology in CNS Animal Models

- **PPAR-β/δ normally protects against pathophysiological processes in the nervous system[1]**
  - PPAR-β/δ also plays roles in neuronal development and function
- **PPAR-β/δ-deficient mice exhibited abnormal neurophysiological processes**
  - Decreased myelination, augmented inflammatory reactions and low score in memory tests[2]
  - Tau (τ) hyperphosphorylation, astrogliosis and CNS inflammation[3]
  - Worse outcome after cerebral ischemia with defective antioxidant responses[4,5]
- **Selective PPAR-β/δ agonists improve outcome after:**
  - Experimental Autoimmune Encephalomyelitis[6]
  - Experimental cerebral ischemia[7]
  - Transgenic model of Alzheimer's[8]
  - Spinal cord trauma[9]
  - Ischemic stroke related vascular dysfunction[10]
  - Chemically induced Parkinson's[7,11]

[1]Kahremany et al., 2015. *Br J Pharmacol.* 172(3):754-70
[2]Peters et al., 2000. *Mol Cell Biol.* 20:5119–5128
[3]Barroso et al., 2013. *Biochim Biophys Acta.* 1832:1241–1248
[4]Arsenijevic D, et al. *J Cereb Blood Flow Metab.* 2006;26:433–445
[5]Pialat et al., 2007. *NMR Biomed.* 20:335–342
[6]Polak et al., 2005. *J Neuroimmunol.* 168:65–75
[7]Iwashita et al., 2007. *J Pharmacol Exp Ther.* 320:1087–1096
[8]Kalinin et al., 2009. *Curr Alzheimer Res.* 6:431–437
[9]Paterniti et al., 2010. *J Pharmacol Exp Ther.* 333:465–477
[10]Yin et al., 2010. *J Neurosci.* 30:6398–6408
[11]Martin et al., 2013. *Neuroscience.* 240:191–203

Peroxisome Proliferator-Activated Receptor Delta (PPAR-β/δ)



- In the brain, PPAR-β/δ is found at high levels in the hypothalamus and hippocampus[1,2]
- Chronic stress reduces PPAR-β/δ, whereas overexpression or activation of hippocampal PPAR-β/δ produces antidepressant-like effects[3,4]

PPAR-β/δ upregulation/activation is associated with the upregulation of neurotrophic growth factors, such as BDNF[1]

BDNF=brain-derived neurotrophic factor

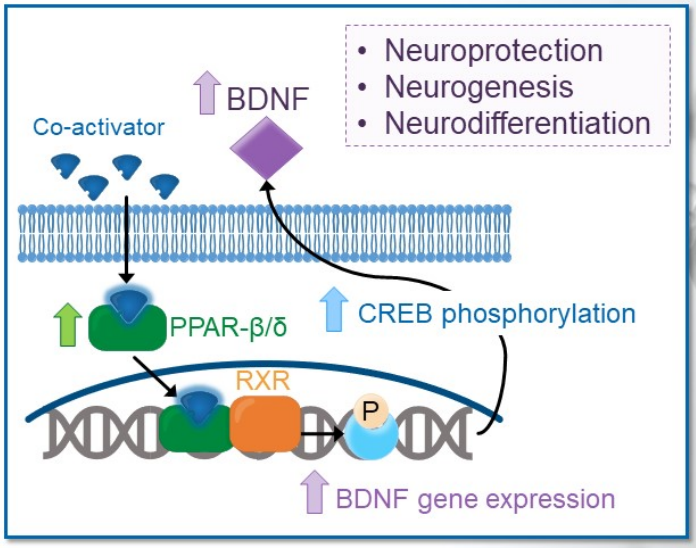
[1]Woods et al., 2003. *Brain Res.* 975(1-2):10-21
[2]Higashiyama et al., 2007. *Histochem Cell Biol.* 127(5):485-494
[3]Chen et al., 2019. *Int J Neuropsychopharmacol.* 22(6):372-382
[4]Liu et al., 2017. *Clin Exp Pharmacol Physiol.* 44(6):664-670

TONIX PHARMACEUTICALS

Peroxisome Proliferator-Activated Receptor Delta (PPAR-β/δ)

PPAR-β/δ upregulation or activators improve depressive symptoms by upregulating neurotrophic growth factors like BDNF[1]

- BDNF downregulation is correlated with decreased levels of CREB phosphorylation and mBDNF[1,2]
- PPAR-β/δ upregulation increased these levels[1]



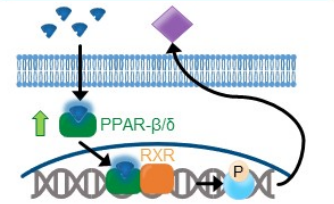
BDNF = brain-derived neurotrophic factor
CREB = cAMP response element binding protein
mBDNF = mature BDNF

[1]Ji et al., 2015. *Int J Neuropsychopharmacol.* 19(1):pyv083
[2]Liu et al., 2017. *Clin Exp Pharmacol Physiol.* 44(6):664-670

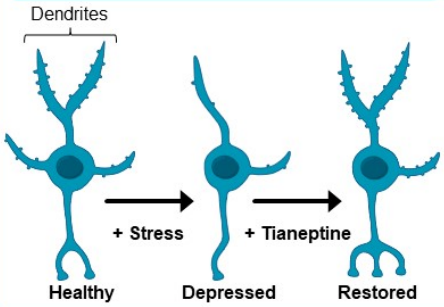
TONIX PHARMACEUTICALS

Tianeptine Helps Restore Stress-Related Hippocampal Remodeling

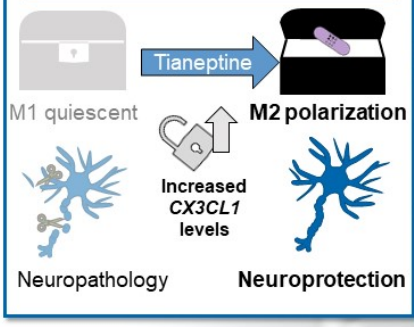
Tianeptine activation of PPAR-β/δ appears related to tianeptine's known effect on reducing inflammation and encouraging neuronal growth and development[1,2]



Tianeptine administration reversed stress-induced dendrite shrinkage in hippocampal CA3 dendrites[3]



Tianeptine normalizes *CX3CL1* levels and polarizes microglia to M2 activation[4]

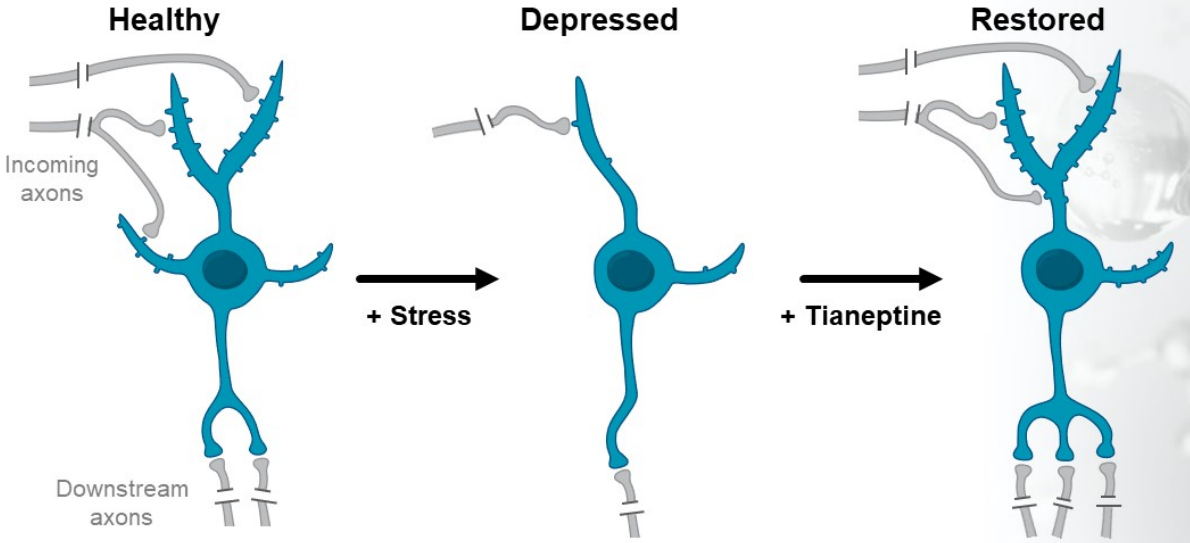


Tianeptine activation of PPAR-β/δ regulates the expression of genes that stimulate dendrite arborization and reduce proinflammatory microglia activation. By these activities, tianeptine is thought to treat depression at the neuroplastic and neurogenerative levels[1-4]

[1]Ji et al., 2015. *Int J Neuropsychopharmacol*. 19(1):pyv083
[2]Liu et al., 2017. *Clin Exp Pharmacol Physiol*. 44(6):664-670
[3]Magariños et al., 1999. *Eur J Pharmacol*. 371(2-3):113-122
[4]Trojan et al., 2017. *Front Pharmacol*. 8:779

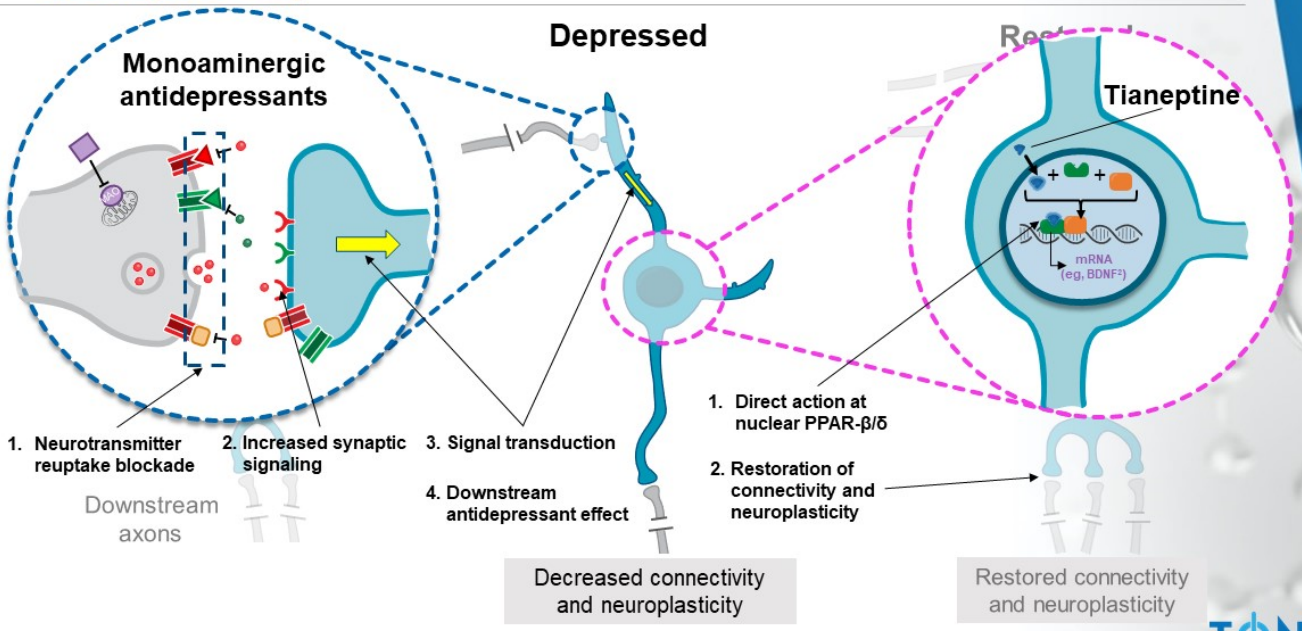
TONIX PHARMACEUTICALS

Tianeptine Restores Neuronal Connectivity and Neuroplasticity in Animal Models



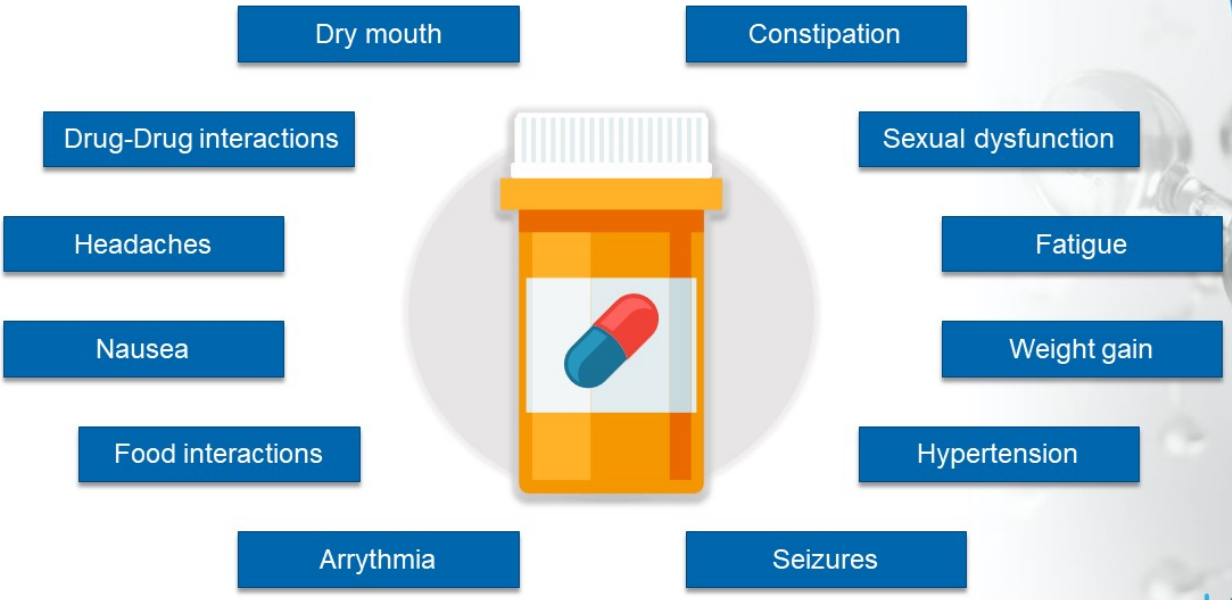
TONIX PHARMACEUTICALS

While Monoaminergic Antidepressants Work at the Synapse, *(S)*-Tianeptine "Cuts in Line" to More Directly Affect Neuroplasticity[1]



[1]Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. https://bit.ly/42o3jnV
[2]BDNF=brain-derived neurotrophic factor.

Potential Side Effects of Monoaminergic Antidepressants Related to Neurotransmitter Modulation

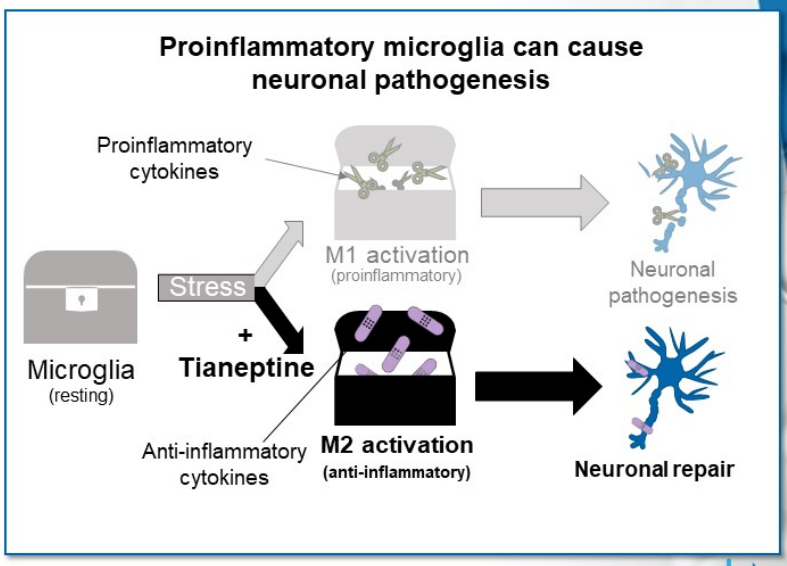


Gelenberg et al., 2010. *Am J Psychiatry*.167(suppl):1-152

Tianeptine Acts on Microglia in the Hippocampus to Facilitate Neuronal Remodeling Under Stress

Microglia and neurogenesis

- Microglia are immune effector cells[1]
- Under normal conditions, microglia regulate synaptic transmission, prune neuronal synapses, and assist in the formation of neural circuits[1,2]
- When homeostasis is disrupted, microglia may activate and release proinflammatory cytokines and inhibit normal neuronal growth[1,2]
- Tianeptine acts on microglia to bias response towards M2 activation by normalizing *CX3CL1* levels[3]



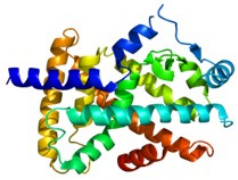
[1]Wang et al., 2022. *J Neuroinflammation*. 19(1):132
[2]Pawelec et al., 2020. *Cells*. 9(10):2277
[3]Trojan et al., 2017. *Front Pharmacol*. 8:779

PPAR Family Members: PPAR-γ

PPAR-α[1]

Expression
Liver, muscle, heart

Known roles
FA oxidation

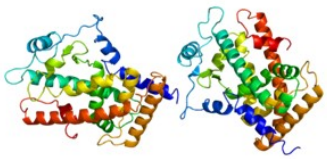


Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png

PPAR-β/δ[1,2]

Expression
Brain, skeletal muscle, adipose tissue, microglia, lungs, skin

Known roles
Promotes CNS neurotrophic factors and reduces expression of inflammatory mediators

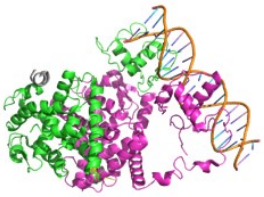


Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png

PPAR-γ[1]

Expression
Endothelial and smooth muscle cells

Known roles
Adipocyte differentiation regulation, FA storage, glucose metabolism

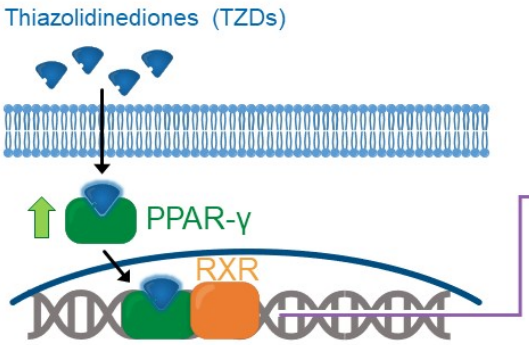


A2-33. Wikimedia Commons. March 14, 2012. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:PPARG.png

[1]Tyagi et al., 2011. *J Adv Pharm Technol Res*. 2(4):236-240
[2]D'Angelo et al., 2011. *J Cell Physiol*. 226(8):2170-2180

PPAR-γ Restores Glucose-Sensing Ability in Type 2 Diabetes

Diabetes defines a group of diseases whose common trait is high blood sugar levels, which can result in damage to neurons, kidneys, eyes, and blood vessels



Glucose metabolism
- Insulin receptor substrate 1 (IRS-1)
- Insulin receptor substrate 2 (IRS-2)
- P85 subunit of PI3K
- CAP

Restore glucose-sensing ability

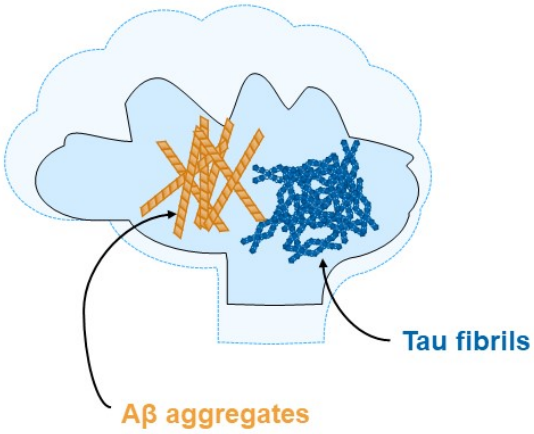
In type 2 diabetes, the agonist class of TZDs has been shown to restore glucose-sensing ability (decrease insulin resistance) and trigger activation of insulin-responsive genes

CAP=catabolite activator protein
PI3K=phosphatidylinositol 3-kinase

Kim et al., 2004. *Diabetologia.* 47(12):2215-2225

Diabetes Is a Risk Factor for Neurodegenerative Diseases Like Alzheimer's Disease (AD)[1-3]

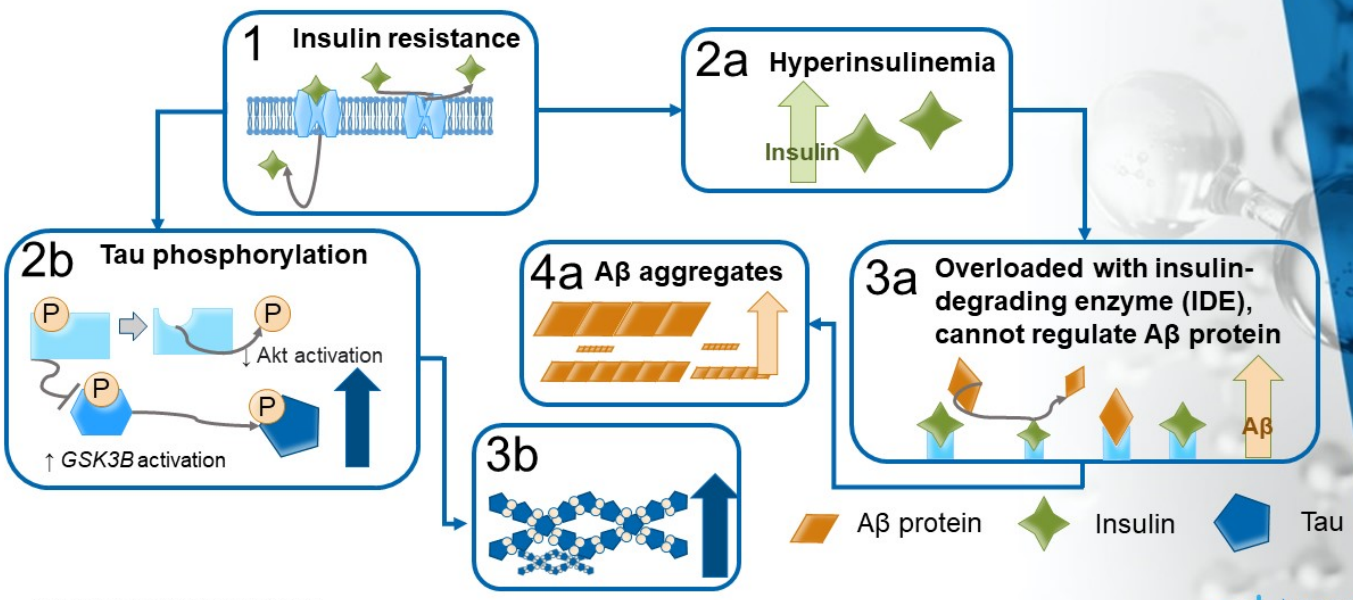
AD is a neurodegenerative disease characterized by brain cell death largely attributed to amyloid plaques and neurofibrillary tangles



While type 2 diabetes has long been considered a risk factor for AD, type 3 diabetes is a newly recognized category of diabetes centered around **insulin resistance within the brain**

[1]Nguyen et al., 2010. *Int J Mol Sci.* 21(9):3165
[2]Kandimalla et al., 2017. *Biochim Biophys Acta Mol Basis Dis.* 1863(5):1078-1089
[3]Pugazhenthi et al., 2017. *Biochim Biophys Acta Mol Basis Dis.* 1863(5):1037-1045

The Relationship Between Type 3 Diabetes and Alzheimer's[1-4]



[1]Nguyen et al., 2010. *Int J Mol Sci*. 21(9):3165
[2]Kandimalla et al., 2017. *Biochim Biophys Acta Mol Basis Dis*. 1863(5):1078-1089
[3]Pugazhenthi et al., 2017. *Biochim Biophys Acta Mol Basis Dis*. 1863(5):1037-1045
[4]Lechin, F et al. 2009. *The Open Neuroendocrinology Journal 2*, 10-19

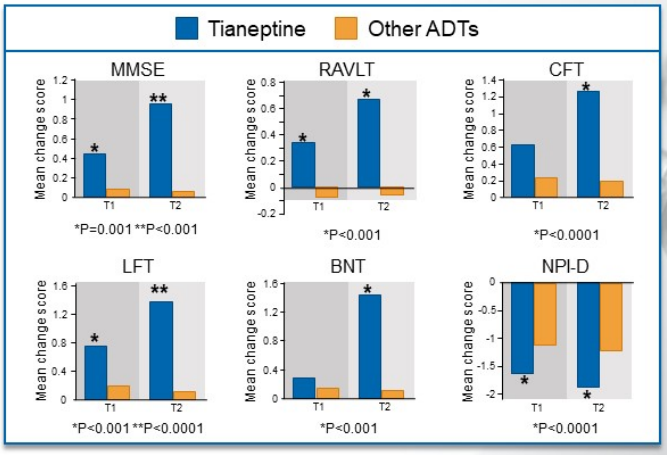
TONIX PHARMACEUTICALS

Tianeptine Has Pro-cognitive Effects in Alzheimer's and Bipolar

After 12 months, patients with AD on tianeptine demonstrated improvements on most cognitive measurements[1]

Significant results from the linear mixed models for cognition and depression performances

- MMSE: Mini-Mental State Examination
- RAVLT: Rey Auditory Verbal Learning Test
- CFT: Category Fluency Test
- LFT: Letter Fluency Test
- BNT: Boston Naming Test
- NPI-D: Neuropsychiatric Inventory Depression subscale
- T0=baseline, T1=follow-up 6 months, T2=follow-up 12 months



An additional study showed that after 24 weeks on tianeptine, patients with bipolar disorder performed better on the Wechsler Adult Intelligence Scale subtest, with improvements on most cognitive measurements[2]

[1]García-Alberca et al., 2022. *J Alzheimers Dis*. 88(2):707-720
[2]Kauer-Sant'Anna et al., 2019. *J Psychopharmacol*. 33(4):502-510

TONIX PHARMACEUTICALS

Observations that Relate Tianeptine's Action to PPAR Activation

Tianeptine is an agonist at PPAR-β/δ and PPAR-γ

- Tianeptine selectively activates PPAR-β/δ and PPAR-γ, but not PPAR-α[1]
  - Regulates PPAR-β/δ and PPAR-γ driven transcription
  - Tianeptine metabolite MC5 does not activate PPAR-β/δ or PPAR-γ
- Tianeptine's neuroplastic effects on cultured neurons correlate with PPAR-β/δ and PPAR-γ agonism[1]
  - TNX-4300 (estianeptine) is a new chemical entity, that activates PPAR-β/δ and PPAR-γ and restores neuroplasticity in cultured neurons
- Company plans to submit data supporting tianeptine's mechanism of action to upcoming scientific conferences and for publication

[1]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41

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[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[4,5]
  - 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
  - Some μ–opioid receptor agonists have a signal in the FST[6-8], which complicates the interpretation of tianeptine effects
- In 2023, using medicinal chemistry and pharmacology, scientists at Tonix found no connection between tianeptine's neuroplastic effects on cultured neurons and its weak μ–opioid receptor agonism[9]
  - TNX-4300 (estianeptine) restores neuroplasticity in cultured neurons and is free from μ–opioid receptor activity[9]

[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
[6]Szumiec L, et al. *Behav Brain Res*. 2023. 3:114466.
[7]Zomkowski AD, et al., *Neurosci Lett*. 2005. 381(3):279-83.
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