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

FORM 8-K

CURRENT REPORT

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

Date of report (date of earliest event reported): June 5, 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.

On June 5, 2023, the Company announced the presentation of data detailing the mechanism of action and pharmacokinetics of the Company's TNX-601 ER (tianeptine hemioxalate extended release) and TNX-4300 (estianeptine) product candidates. A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. Copies of the presentation and poster which present the data are furnished hereto as Exhibits 99.02 and 99.03, respectively, and incorporated herein by reference.

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

Item 8.01. Other Events.

On June 5, 2023, the Company announced the presentation of data detailing the mechanism of action and pharmacokinetics of TNX-601 ER (tianeptine hemioxalate extended release) and TNX-4300 (estianeptine) at the American Society of Clinical Psychopharmacology. TNX-601 ER is being tested in a potentially pivotal Phase 2 trial for the treatment of major depressive disorder ("MDD") for which results of a preplanned interim analysis are expected in the fourth quarter of 2023. TNX-4300 is in preclinical development for mood disorders, Alzheimer's disease and Parkinson's disease. The active ingredient of both products is the *(S)*-isomer of tianeptine, which activates PPAR-β/δ, restores neuroplasticity in neuronal tissue culture and lacks μ-opioid liability. In contrast, the *(R)*-isomer of tianeptine lacks PPAR-β/δ activity and is an agonist at the μ-opioid receptor.

The findings demonstrate how the pharmacokinetics of oral TNX-601 ER in humans differ from intraperitoneal (*i.p.*) tianeptine in mice. In humans, after an oral dose of TNX-601 ER the half-life of tianeptine in the blood is approximately five to seven hours. In contrast, in mice after an *i.p.* dose of tianeptine the half-life of tianeptine in the blood has been reported to be less than approximately 30 minutes, and the behavioral effects appear dominated by the longer-lasting MC5 metabolite, which maintains μ-opioid receptor activity. The data also demonstrate that the *(R)*-isomer of tianeptine is responsible for the decrease in immobility in the mouse forced swim test after *i.p.* administration, which is consistent with previous reports that the effect of tianeptine on the forced swim test is a μ-opioid receptor-dependent phenomenon. The Company believes these findings support the interpretation that the parent tianeptine and specifically, the *(S)*-isomer of tianeptine, exert antidepressant effects in humans by interacting with PPAR-β/δ and PPAR-γ. The Company plans to test single isomer TNX-4300 at a dose equivalent to 50% of the racemic dose, which is expected to provide equivalent exposure of *(S)*-

tianeptine as racemic tianeptine. Subsequently, the Company intends to test higher doses of *(S)*-tianeptine, as TNX-4300 lacks μ-opioid receptor activity, but such studies will require additional non-clinical studies.

Forward- Looking Statements

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

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

Item 9.01. Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release of the Company, June 5, 2023
99.02	TNX 601 ER & TNX-4300: Major Depressive Disorder
99.03	A Randomized Placebo-Controlled Multicenter Trial of Monotherapy with TNX-601 ER (Tianeptine Hemioxalate Extended-Release Tables) for Major Depressive Disorder
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

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

TONIX PHARMACEUTICALS HOLDING CORP.

Date: June 5, 2023

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

Exhibit 99.01

Tonix Pharmaceuticals Announces Presentation of Data Supporting Development of Racemic and Single *(S)*-Isomer Tianeptine, Plastogen Anti-Depressants, at the American Society of Clinical Psychopharmacology Meeting

Tianeptine's Mechanism of Restoring Neuroplasticity and Neurogenesis by Dual PPAR-β/δ and PPAR-γ Agonism Supports Development as a First-in-Class Oral Therapy for Psychiatric and Neurodegenerative Diseases

Racemic Tianeptine, or TNX-601 ER, is Enrolling in a Potentially Pivotal Phase 2 Study for the Treatment of Major Depressive Disorder; Results from Interim Analysis Expected Fourth Quarter 2023

Single (S)-Isomer of Tianeptine, or TNX-4300, is Free from μ-Opioid Receptor Activity Associated with the (R)-Isomer

TNX-4300 is in Preclinical Development for Depression, Bipolar Disorder, Alzheimer's Disease and Parkinson's Disease

CHATHAM, N.J., June 5, 2023 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced the presentation of data detailing the mechanism of action and pharmacokinetics of TNX-601 ER (tianeptine hemioxalate extended release) and TNX-4300 (estianeptine) at the American Society of Clinical Psychopharmacology (ASCP) meeting in Miami, Fla. TNX-601 ER is being tested in a potentially pivotal Phase 2 trial for the treatment of major depressive disorder (MDD) for which results of a preplanned interim analysis are expected in the fourth quarter of 2023. TNX-4300 is in preclinical development for mood disorders, Alzheimer's disease and Parkinson's disease. The active ingredient of both products is the *(S)*-isomer of tianeptine.[1] The *(S)*-isomer of tianeptine activates PPAR-β/δ, restores neuroplasticity in neuronal tissue culture and lacks μ-opioid liability. In contrast, the *(R)*-isomer of tianeptine lacks PPAR-β/δ activity and is an agonist at the μ-opioid receptor. The poster presentation is available on Tonix's website: www.tonixpharma.com.

Tonix recently announced that the plastogen anti-depressant tianeptine, a drug marketed outside the U.S. for more than 30 years, acts on nuclear PPAR-β/δ and PPAR-γ in neurons and glia to restore neuronal connectivity in depression.[2] The understanding that tianeptine bypasses the synapse and acts on the nucleus to exert its effects on restoring neuroplasticity and neurogenesis has direct applicability in a number of neurodegenerative diseases in which neuronal connections are atrophying.[2] The newly reported mechanism also provides clarity on why tianeptine is not associated with sexual dysfunction, weight gain or several other treatment-limiting toxicities, which are associated with the antidepressants currently marketed in the U.S. for long-term use.

"Restoring atrophied neuronal connections in psychiatric and neurodegenerative diseases has the potential to achieve better and more durable outcomes," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "The tianeptine marketed outside the U.S. for treating depression is a 1:1 racemic mixture of two mirror image isomers. Our team of scientists isolated and characterized the *(S)*-isomer of tianeptine, which is free from μ-opioid receptor activity and is now under development as TNX-4300 for treating psychiatric and neurodegenerative diseases. The *(S)*-isomer of tianeptine is responsible for tianeptine's activity on PPAR-β/δ and restoring neuroplasticity and neurogenesis, while the *(R)*-isomer is responsible for any off-target activity on the μ-opioid receptor."

The findings reported at the meeting show how the pharmacokinetics of oral TNX-601 ER in humans differ from intraperitoneal (*i.p.*) tianeptine in mice. In humans, after an oral dose of TNX-601 ER the half-life of tianeptine in the blood is approximately 5-7 hours. In contrast, in mice after an *i.p.* dose of tianeptine the half-life of tianeptine in the blood has been reported to be less than approximately 30 minutes and the behavioral effects appear dominated by the longer-lasting MC5 metabolite, which maintains μ-opioid receptor activity.[3] The data Tonix presented also show that the *(R)*-isomer of tianeptine is responsible for the decrease in immobility in the mouse forced swim test after *i.p.* administration, which is consistent with previous reports that the effect of tianeptine on the forced swim test is a μ-opioid receptor-dependent phenomenon.[3]

Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals, said, "From our clinical studies on volunteers, after oral dosing with TNX-601 ER, the extended pharmacokinetics of parent tianeptine is consistent with tianeptine exerting activity on PPAR-β/δ and resulting in neurorestorative effects. In contrast, after *i.p.* dosing of tianeptine in mice, the exposure of tianeptine is brief and the behavioral effects appear dominated by the MC5 metabolite.[3] While tianeptine's MC5 metabolite has been reported to maintain μ-opioid receptor activity[3], we found that MC5 metabolite lacks activity on either PPAR-β/δ or PPAR-γ in culture. Together, we believe these findings support the interpretation that the parent tianeptine and specifically, the *(S)*-isomer of tianeptine exert antidepressant effects in humans by interacting with PPAR-β/δ and PPAR-γ."

Dr. Sullivan continued, "Our ongoing work on racemic tianeptine in depression is expected to inform and potentially accelerate the development of TNX-4300. The dose of tianeptine for treating depression is well-established from racemic studies, so we plan to test single isomer TNX-4300 at a dose equivalent to 50% of the racemic dose, which is expected to provide equivalent exposure of *(S)*-tianeptine as racemic tianeptine. Subsequently, we plan to test higher doses of *(S)*-tianeptine, because TNX-4300 lacks μ-opioid receptor activity, but such studies will require additional non-clinical studies."

Key experiments were performed by scientists at Tonix's Research and Development Center (RDC) in Frederick, Maryland.

* TNX-601 and TNX-4300 are investigational new drugs and are not approved for any indication

[1] Tonix press release, May 23, 2023 https:// ir.tonixpharma.com/news-events/press-releases/detail/1392/tonix-pharmaceuticals-announces-the-isolation-and

[2] Tonix press release, May 17, 2023 https://ir.tonixpharma.com/news-events/press-releases/detail/1389/tonix-pharmaceuticals-announces-pharmacology-and-medicinal

[3] Samuels et al., *Neuropsychopharmacology*. 2017, 42(10):2052-2063

About Tianeptine

Racemic tianeptine sodium (amorphous) immediate release (dosed 3 times daily) was first marketed for depression in France in 1989 and has been available for decades in Europe, Russia, Asia, and Latin America for the treatment of depression. Tianeptine sodium has an established safety profile from decades of use in these jurisdictions. Currently no tianeptine-containing product is approved in the U.S. and no extended-release tianeptine product is approved in any jurisdiction. In animal models, tianeptine restores dendritic arborization of pyramidal neurons in the CA3 region of hippocampus and in the dentate gyrus region promotes new neuron formation and integration into hippocampal networks.[1] Tianeptine's enhancement of neuroplasticity in animal models of stress is believed to be mediated by activation of PPAR isoforms PPAR-β/δ and PPAR-γ, which makes its properties distinct from traditional monoaminergic antidepressants in the U.S. and contributes to its potential for clinical indications beyond MDD and stress disorders. Tianeptine and its MC5 metabolite are also weak mu-opioid receptor (MOR) agonists that present a potential abuse liability if illicitly misused in large

quantities (typically abused at 8-80 times the therapeutic dose on a daily basis).[2] In patients who were prescribed tianeptine for depression, the French Transparency Committee found an incidence of misuse of approximately 1 case per 1,000 patients treated[3] suggesting low abuse liability when used at the antidepressant dose in patients prescribed tianeptine for depression. Clinical trials have shown that cessation of a therapeutic course of tianeptine does not appear to result in dependence or withdrawal symptoms following 6-weeks[4-8], 3-months[9], or 12-months[10] of treatment. *(S)*-tianeptine mimics naturally occurring polyunsaturated fatty acid ligands in binding PPAR-β/δ and PPAR-γ. *(S)*-tianeptine's activation of nuclear PPAR-β/δ and PPAR-γ receptors appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity than current therapies. Its proposed mechanism as a plastogen is consistent with its clinical effects in promoting cognition in Alzheimer's disease and bipolar disorder [11,12] in addition to posttraumatic stress disorder (PTSD) and corticosteroid-induced cognitive dysfunction. The PPAR-β/δ target is validated by prior work on agonists treating animal models of neurodegenerative and autoimmune diseases of the central nervous system[13] and the concept that Alzheimer's can be considered a form of diabetes that affects the CNS, or type-III diabetes."[14]Tianeptine's reported pro-cognitive and anxiolytic effects as well as its ability to attenuate the neuropathological effects of excessive stress responses suggest that it may also be used to treat posttraumatic stress disorder (PTSD), and neurocognitive dysfunction associated with corticosteroid use.

[1] McEwen, B. S., et al. *Mol. Psychiatry* **2010**, *15* (3), 237–249.
[2] Lauhan, R., et al. *Psychosomatics* **2018**, *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, R., et al. *J. Clin. Psychiatry* **2018**, *79* (4)
[5] Bonierbale M, et al. *Curr Med Res Opin* **2003**, *19*(2):114-124.
[6] Guelfi, J. D., et al. *Neuropsychobiology* **1989**, *22* (1), 41–48.
[7] Invernizzi, G. et al., *Neuropsychobiology* **1994**, *30* (2–3), 85–93.
[8] Lepine, J. P., et al. *Hum. Psychopharmacol.* **2001**, *16* (3), 219–227.
[9] Guelfi, J. D. et al., *Neuropsychobiology* **1992**, *25* (3), 140–148.
[10] Lôo, H. et al., *Br. J. Psychiatry. Suppl.* **1992**, *15*, 61–65.
[11] García-Alberca JM, et al. *J Alzheimer's Dis* 2022, *88* (2), 707-720.
[12] Kauer-Sant'Anna M, et al. *J Psychopharmacol* 2019, *33* (4), 502-510.
[13] Kahremany S et al. *Br J Pharmacol* 2015, 172(3):754-70
[14] Nguyen et al., *Int J Mol Sci.* 2010, 21(9):3165

Tonix Pharmaceuticals Holding Corp.*

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing therapeutics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia with topline data expected in the fourth quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Enrollment in a Phase 2 study has been completed, and topline results are expected in the third quarter of 2023. TNX-1900 (intranasal potentiated oxytocin), in development for chronic migraine, is currently enrolling with topline data expected in the fourth quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets), a once-daily formulation being developed as a treatment for major depressive disorder (MDD), is also currently enrolling with interim data expected in the fourth quarter of 2023. TNX-4300 (estianeptine) is a small molecule oral therapeutic in preclinical development to treat MDD, Alzheimer's disease and Parkinson's disease. TNX-1300 (cocaine esterase) is a biologic designed to treat cocaine intoxication and has been granted Breakthrough Therapy designation by the FDA. A Phase 2 study of TNX-1300 is expected to be initiated in the third quarter of 2023. Tonix's rare disease portfolio includes TNX-2900 (intranasal potentiated oxytocin) for the treatment of Prader-Willi syndrome. TNX-2900 has been granted Orphan Drug designation by the FDA. Tonix's immunology portfolio includes biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the third quarter of 2023. Tonix's infectious disease pipeline includes TNX-801, a vaccine in development to prevent smallpox and mpox, for which a Phase 1 study is expected to be initiated in the second half of 2023. TNX-801 also serves as the live virus vaccine platform or recombinant pox vaccine platform for other infectious diseases. The infectious disease portfolio also includes TNX-3900 and TNX-4000, classes of broad-spectrum small molecule oral antivirals.

**All of Tonix's product candidates are investigational new drugs or biologics and have not been approved for any indication.*

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

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; 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. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

Contacts

Jessica Morris (corporate)
Tonix Pharmaceuticals
investor.relations@tonixpharma.com
(862) 904-8182

Maddie Stabinski (media)
Russo Partners
Madeline.Stabinski@russopartnersllc.com

(212) 845-4273

Peter Vozzo (investors)
Westwicke/ICR
peter.vozzo@westwicke.com
(443) 213-0505

Exhibit 99.02

Cautionary Note on Forward-Looking Statements

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

TONIX PHARMACEUTICALS

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

Differentiators:
Relative to tianeptine IR available ex-US:
- Once daily dosing

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

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Disorder From Corticosteroids, Alzheimer's Disease[1]

Status: Phase 2 MDD study UPLIFT is currently enrolling

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

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

[1]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

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

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

TNX-601 ER - Phase 2 UPLIFT* Study Design

UPLIFT Study

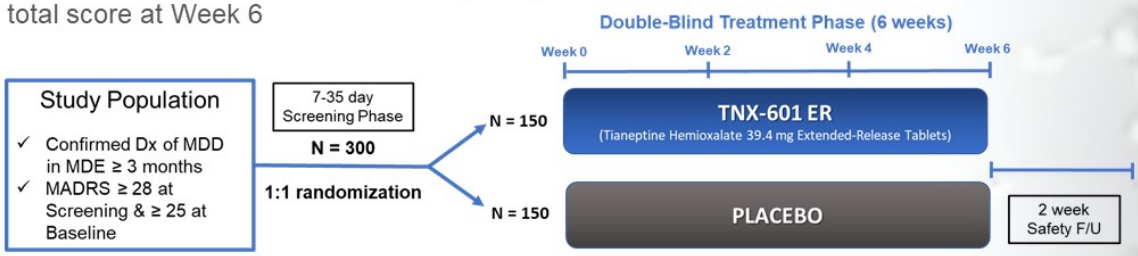
CNS PORTFOLIO

General study characteristics:

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

Primary Endpoint:

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



*ClinicalTrials.gov Identifier: NCT05686408

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

TONIX PHARMACEUTICALS

History of Tianeptine and TNX-601 ER

CNS PORTFOLIO

- 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.

TONIX PHARMACEUTICALS

Proposed MOA of Tianeptine

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

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

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

[1]Tartt et al., 2022. *Molecular Psychiatry* 27: 2689–2699.
[2]Plaisant et al.,2003. *Neuropharmacology* 44: 801–809.
[3]Slusarczyk et al., 2018. *Int J Mol Sci* 19: 1965.

TONIX PHARMACEUTICALS

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

TONIX PHARMACEUTICALS

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

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

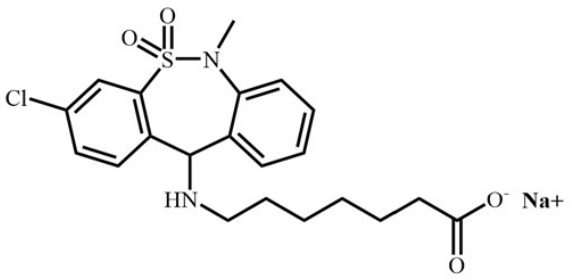
- Neurodegenerative disorders
  - Parkinson's (and associated conditions, e.g. depression and psychosis)[1]
  - Alzheimer's (and associated conditions, e.g. agitation, depression and psychosis)[2]
- ADHD[3]
- Stress disorders[4]
  - PTSD, Anxiety
- Aging/Neuroprotection[5,6]
  - Mild Cognitive Impairment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

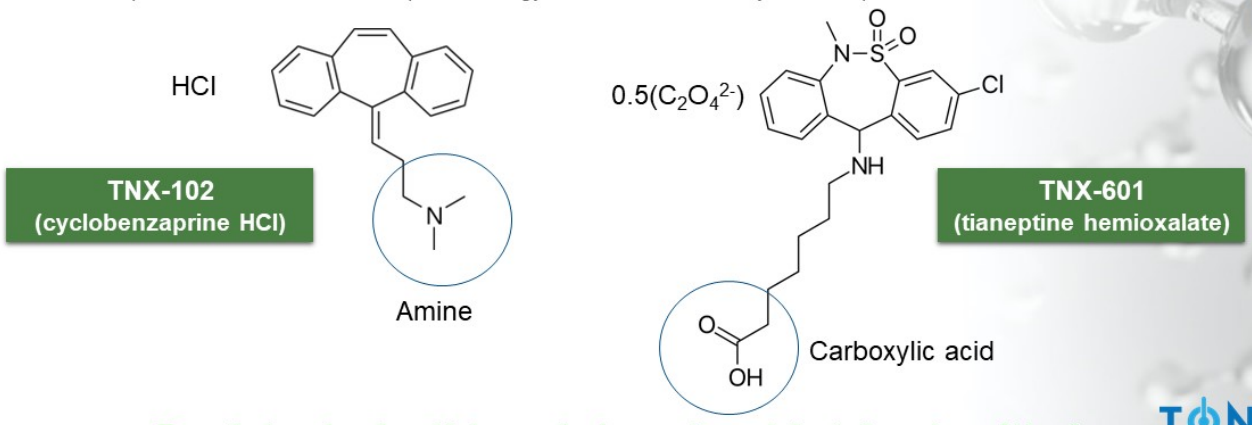


[3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(c,f)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt

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

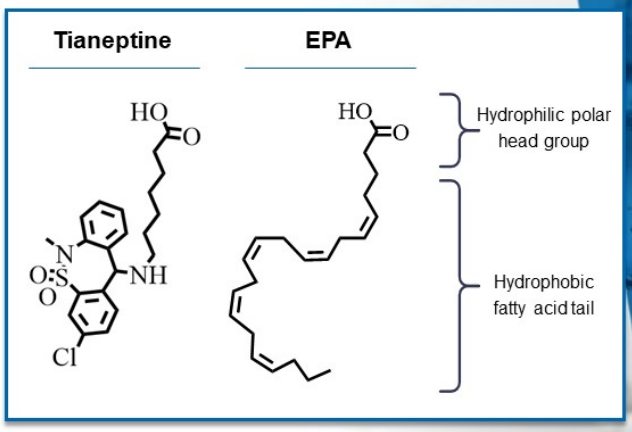
- Polar acidic "head" and hydrophobic fatty acid "tail"

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)

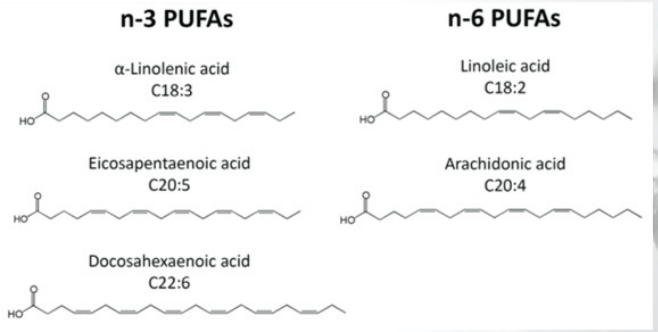
Eicosapentaenoic acid (EPA)[2]

- 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

TONIX PHARMACEUTICALS

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

CNS PORTFOLIO

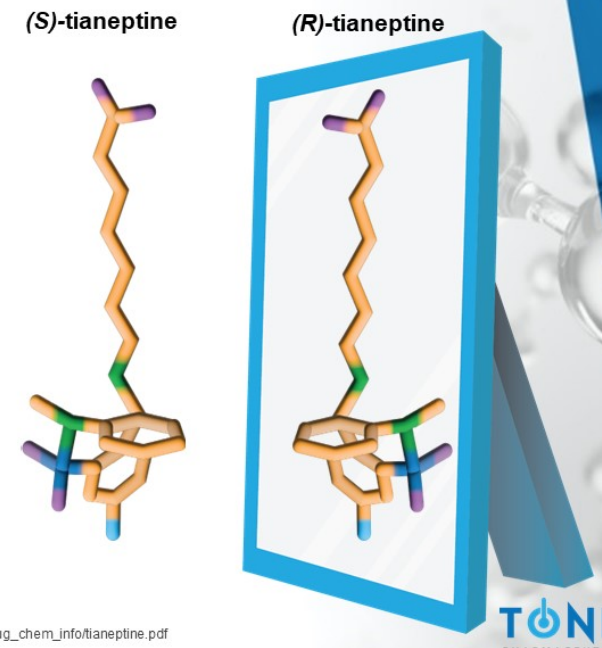
Racemic tianeptine:

- Approved in Europe and ex-US
- 1:1 mixture of 2 mirrorr-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 opiate liability

- Both *(S)*- and *(R)*-tianeptine are agonists of PPAR-γ
- New mechanism of action for treating depression

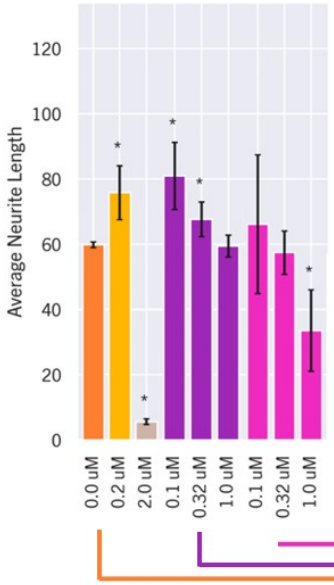
	Racemic-Tianeptine	*(S)*-Tianeptine TNX-4300	*(R)*-Tianeptine
μ-Opioid Receptor	+	-	+
PPAR-β/δ	+	+	-
PPAR-γ	+	+	+



[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

TONIX PHARMACEUTICALS

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

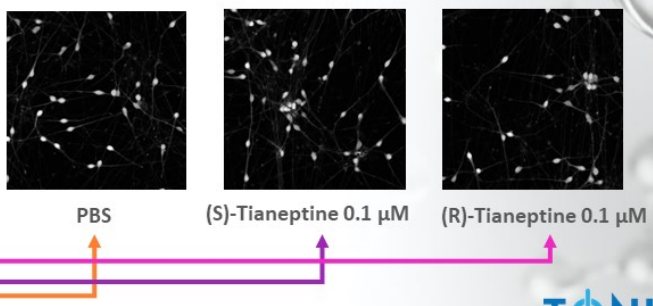


Neurite network dynamics tested in plated human iPSC-derived glutamatergic neurons

- 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]

PBS
Staurosporine
Vincristine
(S)-Tianeptine
(R)-Tianeptine

* p<0.05 relative to PBS control

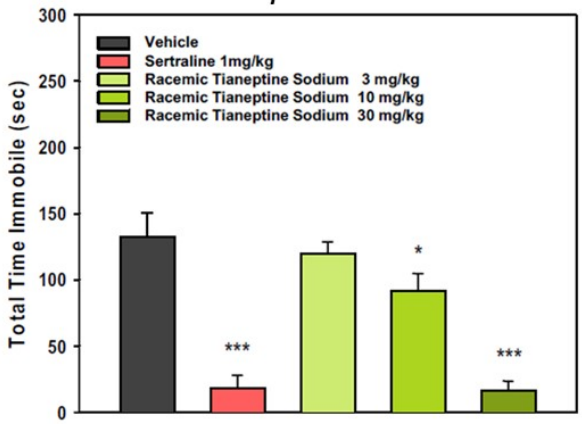


[1]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41
[2]McEwen BS, et al. *Mol Psychiatry*. 2010;15(3):237-249.

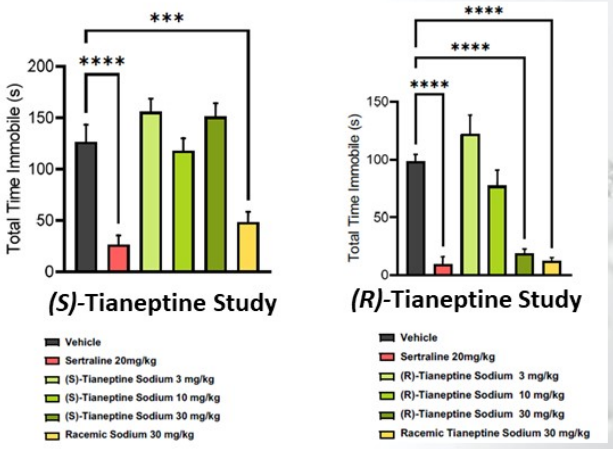
TONIX PHARMACEUTICALS

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

Racemic Tianeptine in FST



***p<0.001 and ****p<0.0001 compared to vehicle in both figures



(*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

TONIX PHARMACEUTICALS

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

	Racemic-Tianeptine	*(S)*-Tianeptine TNX-4300	*(R)*-Tianeptine
μ-Opioid Receptor	+	-	+
PPAR-β/δ	+	+	-
PPAR-α	-	-	-
PPAR-γ	+	+	+
FST	+	-	+
Neurite Outgrowth	No Data	+	-

FST – Forced Swim Test

CNS PORTFOLIO

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
  - 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[1]

Status: Pre-clinical

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

*TNX-4300 has not been approved for any indication.

[1]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

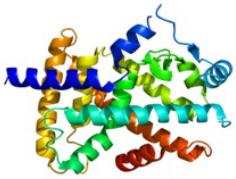
CNS PORTFOLIO

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

PPAR-α[1]

Expression
Liver, muscle, heart

Known roles
FA oxidation

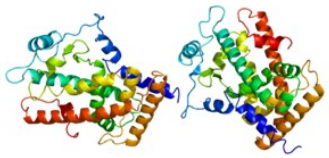


Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png

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

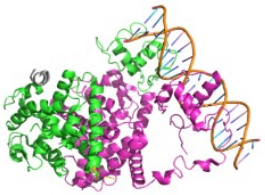


Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png

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

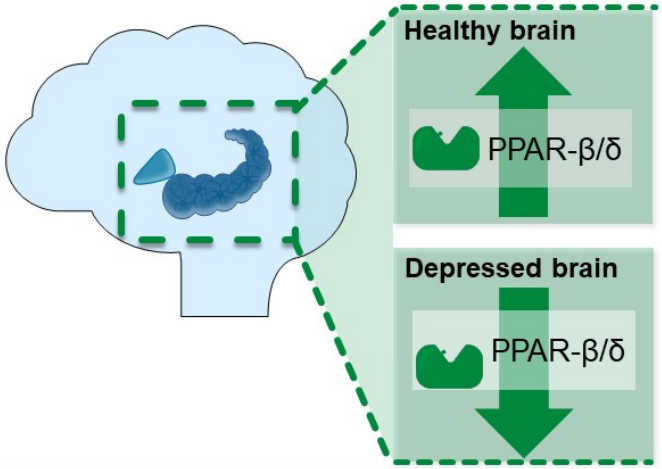
[1]Tyagi et al., 2011. *J Adv Pharm Technol Res.* 2(4):236-240
[2]D'Angelo et al., 2011. *J Cell Physiol.* 226(8):2170-2180

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

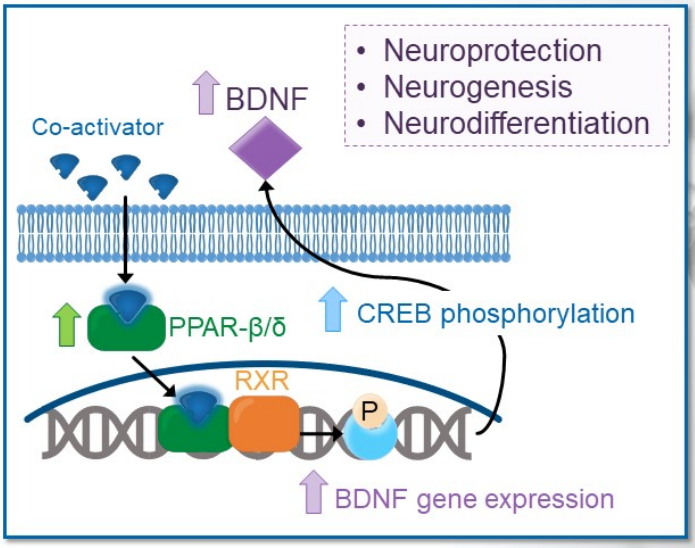
[1]Woods et al., 2003. *Brain Res.* 975(1-2):10-21
[2]Higashiyama et al., 2007. *Histochem Cell Biol.* 127(5):485-494
[3]Chen et al., 2019. *Int J Neuropsychopharmacol.* 22(6):372-382
[4]Liu et al., 2017. *Clin Exp Pharmacol Physiol.* 44(6):664-670

TONIX PHARMACEUTICALS

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

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

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



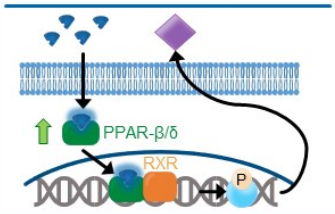
BDNF = brain-derived neurotrophic factor
CREB = cAMP response element binding protein
mBDNF = mature BDNF

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

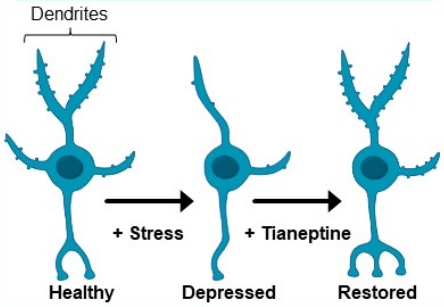
TONIX PHARMACEUTICALS

Tianeptine Helps Restore Stress-Related Hippocampal Remodeling

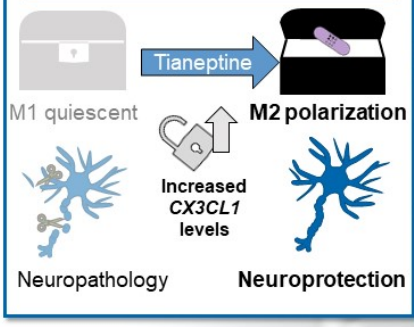
Tianeptine activation of PPAR-β/δ appears related to tianeptine's known effect on reducing inflammation and encouraging neuronal growth and development[1,2]



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



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

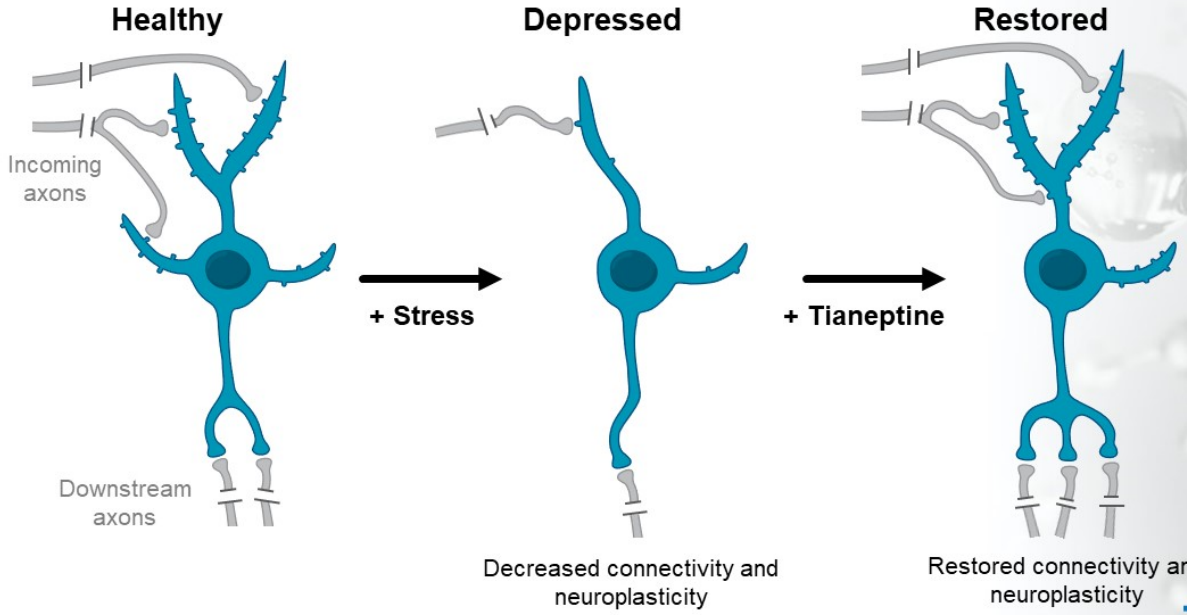


Tianeptine activation of PPAR-β/δ regulates the expression of genes that stimulate dendrite arborization and reduce proinflammatory microglia activation. By these activities, tianeptine is thought to treat depression at the neuroplastic and neurogenerative levels[1-4]

[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

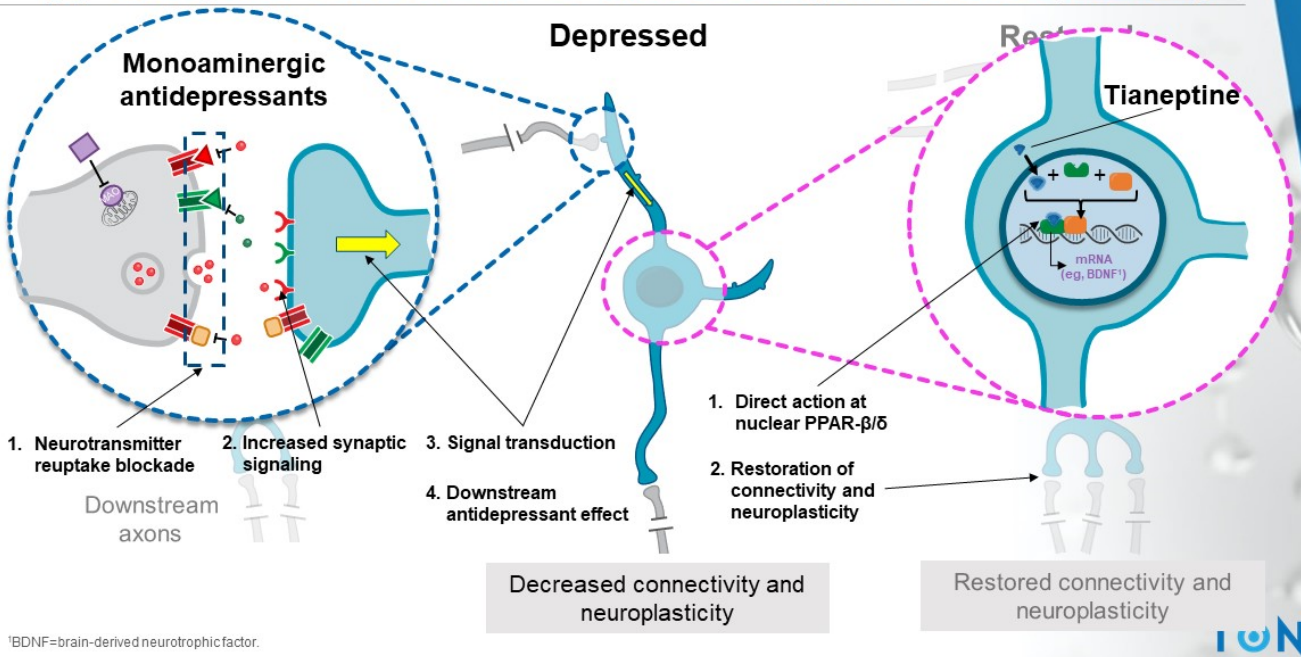
TONIX PHARMACEUTICALS

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



†BDNF=brain-derived neurotrophic factor.

Potential Side Effects of Monoaminergic Antidepressants Related to Neurotransmitter Modulation

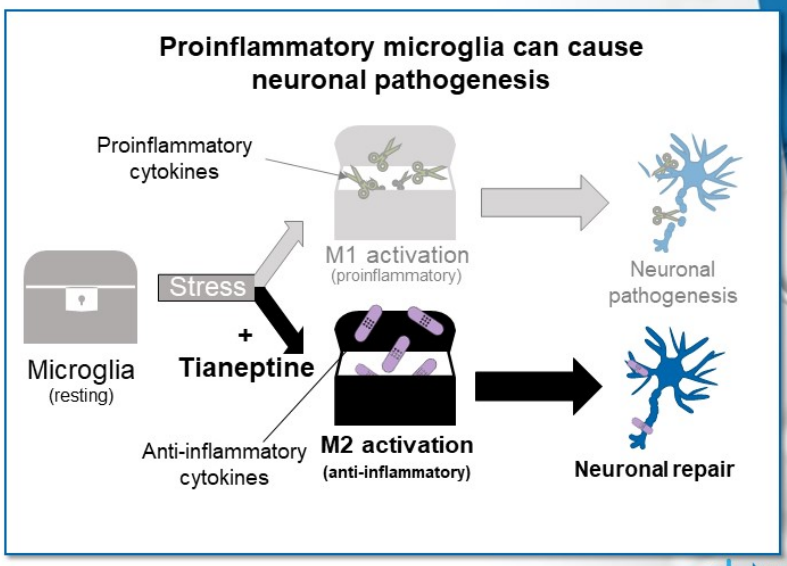
- Dry mouth
- Constipation
- Drug-Drug interactions
- Sexual dysfunction
- Headaches
- Fatigue
- Nausea
- Weight gain
- Food interactions
- Hypertension
- Arrythmia
- Seizures

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]



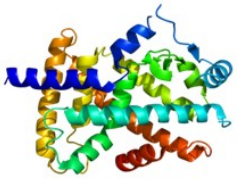
[1]Wang et al., 2022. *J Neuroinflammation*. 19(1):132
[2]Pawelec et al., 2020. *Cells*. 9(10):2277
[3]Trojan et al., 2017. *Front Pharmacol*. 8:779

PPAR Family Members: PPAR-γ

PPAR-α[1]

Expression
Liver, muscle, heart

Known roles
FA oxidation

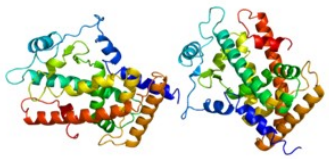


Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png

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

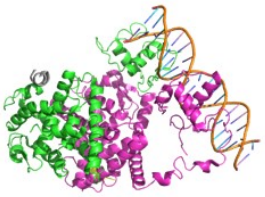


Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png

PPAR-γ[1]

Expression
Endothelial and smooth muscle cells

Known roles
Adipocyte differentiation regulation, FA storage, glucose metabolism



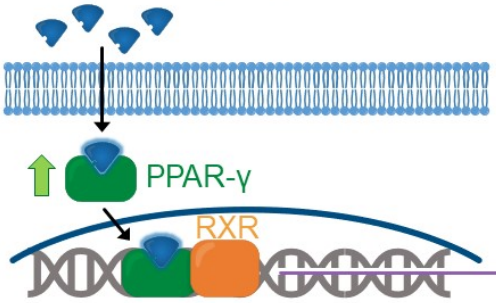
A2-33. Wikimedia Commons. March 14, 2012. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:PPARG.png

[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

Thiazolidinediones (TZDs)



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

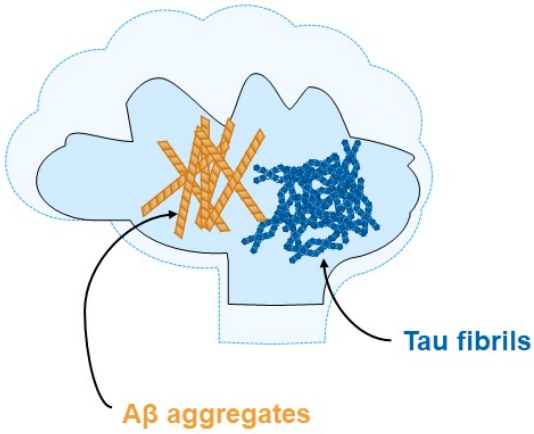
CAP=catabolite activator protein
PI3K=phosphatidylinositol 3-kinase

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

TONIX PHARMACEUTICALS

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

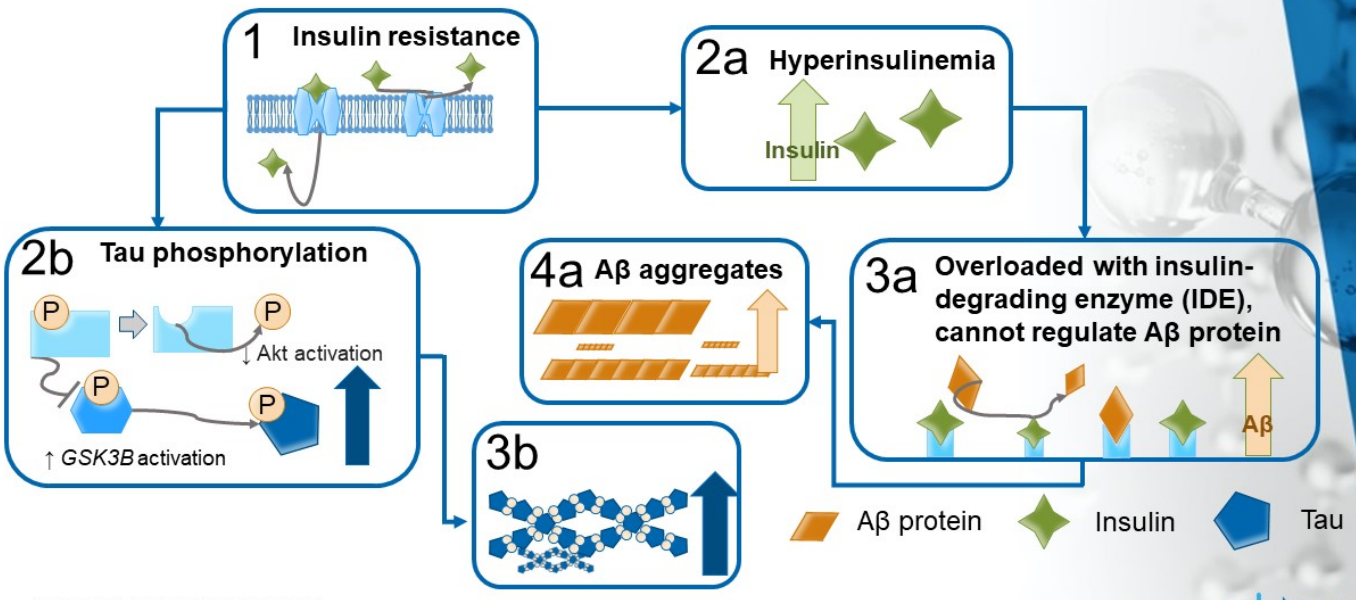


While type 2 diabetes has long been considered a risk factor for AD, type 3 diabetes is a newly recognized category of diabetes centered around **insulin resistance within the brain**

[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

TONIX PHARMACEUTICALS

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



[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

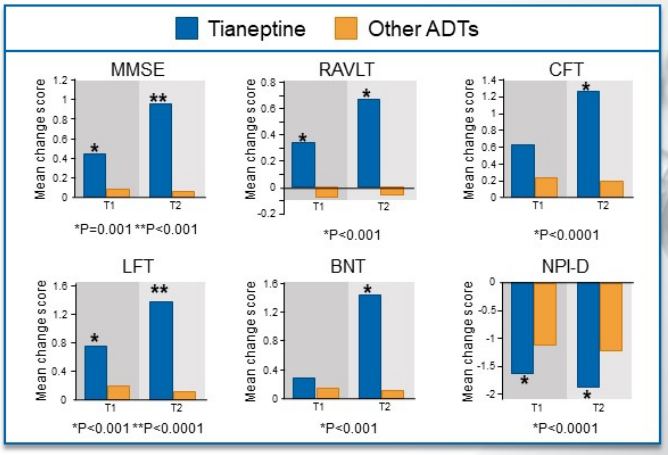
TONIX PHARMACEUTICALS

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.
[8]Falcon E, et al. *Psychopharmacology (Berl)*. 2015 232(5):907-15.
[9]Tonix poster presented at ASCP 2023 Annual Meeting, Miami FL, May 30-June 2, Poster T41


THANK YOU
© 2023 Tonix Pharmaceuticals Holding Corp.

Exhibit 99.03

A Randomized Placebo-Controlled Multicenter Trial of Monotherapy with TNX-601 ER* (Tianeptine Hemioxalate Extended-Release Tablets) for Treatment of Major Depressive Disorder (MDD)

T41

Gregory M Sullivan[a], Ashild Peters, David Hsu, Darryl Rideout, Tim Roush, Bruce Daugherty, Perry Peters, Seth Lederman

Tonix Pharmaceuticals Inc

[a] Presenter

* TNX-601 ER is an investigational new drug and has not been approved for any indication

INTRODUCTION

In the US in 2020, ~21 million adults experienced at least 1 major depressive episode (MDE). Despite an array of antidepressants, mostly targeting monoaminergic (MA) neurotransmitters, only ~20% achieve remission. Importantly, MA antidepressants have intolerable side effects for many, including sexual dysfunction, agitation, insomnia with daytime sedation, weight gain, and mild cognitive impairment.

Tianeptine is a unique non-MA antidepressant used across Europe, Asia, and Latin America, first marketed in France in 1989. There are over 30 years of studies demonstrating that tianeptine's efficacy is comparable to both the SSRIs and TCAs. Tianeptine also appears to be much more tolerable than MA antidepressants, without significant sexual side effects, adverse effects on sleep, or weight gain. Other unique advantages of tianeptine include anxiolysis without sedation, and pro-cognitive effects.

Until recently, the mechanism of action was elusive and distinctive, lacking direct effects on CNS receptors and transporters. The predominant hypothesis of its mechanism of action in depression has been that it indirectly modulates the glutamatergic system, thereby reversing the adverse effects of stress on hippocampal function, stimulating new interneural connections, and restoring neuroplasticity through synaptogenesis.[1] Subsequently, it has been discovered that the enhancement of these connections is also a common therapeutic principle for traditional antidepressants, which modulate neuroplasticity indirectly by modulating synaptic neurotransmitters.

Tianeptine and its main metabolite MC5 are also weak μ-opioid receptor agonists, presenting an abuse liability if illicitly misused in large quantities (typically 8-80X therapeutic dose daily[2]). Prescribed for depression, incidence of misuse is approximately 0.1%,[3] suggesting low abuse liability when used as antidepressant under clinical care.

A novel once-daily extended-release formulation of tianeptine hemioxalate, TNX-601 ER, is being developed by Tonix Pharmaceuticals under an investigational new drug (IND) in the US. A randomized, placebo-controlled, multicenter Phase 2 trial for the treatment of major depressive disorder (MDD) is currently enrolling across about 30 US sites. The methods of this trial will be presented, and the enrollment status updated. Additionally, several critical new findings from discovery and nonclinical work will be presented which clarify tianeptine's unique molecular mechanism of action in treatment of depression.

[1]McEwen BS, et al. Mol Psychiatry. 2010;15(3):237-249. [2]Lauhan R, et al. Psychosomatics. 2018;59(6). 547-553. [3]Haute Authorite de Sante; Transparency Committee Opinion 5 Dec 2012.

Pharmacokinetics and Formulation

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	
$AUC_{0\text{-}24}$ (ng·h/mL)	2040	1990	1220	1270
$AUC_{0\text{-}last}$ (ng·h/mL)	2300	2060	1750	1700
F_{rel} $AUC_{0\text{-}last}$ (%)	89.22 [81.59, 97.56], p=0.043		97.02 [90.55, 103.96], p=0.45	
$AUC_{0\text{-}inf}$ (ng·h/mL)	2360	2230	2030	1830
F_{rel} $AUC_{0\text{-}inf}$ (%)	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)*	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

AUC: area under the curve; C_{max}: max. observed conc. (MOC); F_{rel}: relative bioavailability; T_{max}: time of MOC; $T_{1/2}$: apparent elimination half-life; Vz/F: apparent volume of distribution (for plasma tianeptine only); *ND, no data

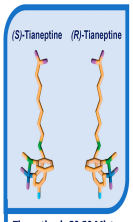
TNX-601 ER was formulated with attention to potential abuse deterrent properties: lower solubility of hemioxalate salt (reduced extraction efficiency); microcrystalline cellulose as compression aid and compressed at >100 Newtons (difficulty crushing to fine particles for efficient insufflation or extraction); and inclusion of high molecular weight gel-forming polymers (poor "syringe-ability"/injectability).

Mechanism of Action of Racemic Tianeptine in Depression and Potential of Single Isomer, TNX-4300#, in Psychiatric and Neurodegenerative Conditions

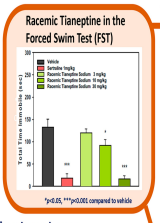
CNS Activities: Tianeptine, *(S)-* & *(R)*-Isomers

	Racemic- Tianeptine	*(S)-* Tianeptine TNX-4300	*(R)-* Tianeptine
μ-Opioid Receptor	+	-	+
PPAR-β/δ	+	+	-
PPAR-α	-	-	-
PPAR-γ	+	+	+
FST	+	-	+
Neurite Outgrowth	ND	+	-

ND, no data



Tianeptine is 50:50 Mixture of Mirror Image Isomers



Tianeptine Reduces Immobility in Murine Forced Swim Test

Similar Acute Effects Reported by Samuels & Co-Workers, 2017^

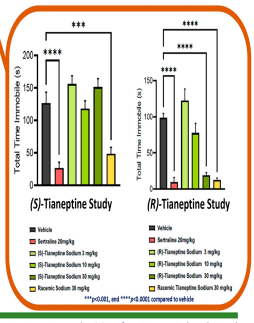
- Samuels et al found no effect of tianeptine on FST activity in μ–opioid receptor KO mouse or in mice pretreated with opioid antagonists, indicating behavioral effect was μ–opioid mediated
- Their murine PK studies demonstrated tianeptine rapidly metabolized and nearly eliminated from murine plasma 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

^Samuels BA, et al. Neuropsychopharmacology. 2017;42(10):2052-2063

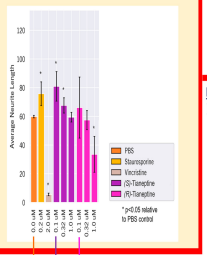
μ-Opioid Activity Studies of Tianeptine and its Pure *(S)-* and *(R)*-Isomers

- The >99.9% pure Tianeptine *(S)*-Isomer shows ***no activity*** in μ-opioid receptor agonism (β-arrestin and cAMP) studies
- In contrast, Tianeptine *(R)*-isomer has β-arrestin recruitment EC_{50}=1.873 μM and cAMP inhibition EC_{50}=0.044 μM
- Tianeptine *(S)*-Isomer in development by Tonix, TNX-4300 (estianeptine) for psychiatric and neurodegenerative conditions

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



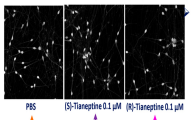
Treatment with 0.1 and 0.32 μM *(S)*-Tianeptine Significantly Increased Average Neurite Length



(S)-Tianeptine Significantly Increases Neurite Length in Culture

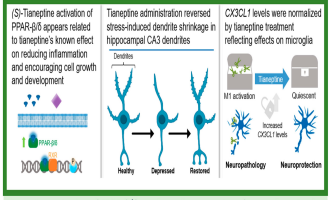
Neurite network dynamics tested in plated human iPSC-derived glutamatergic neurons

- 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

Tianeptine Restores Neuroplasticity After Stressor-Induced Atrophy



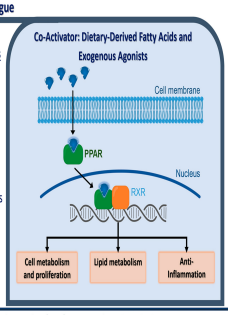
Tianeptine activation of PPAR-β/δ regulates the expression of genes that stimulate dendrite arborization and reduce proinflammatory microglia activation. By these activities, tianeptine is thought to treat depression at the neuroplastic and neurogenerative levels[1-4]

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

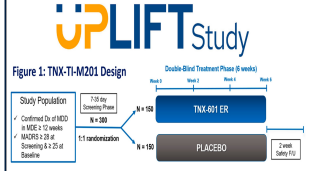
Tianeptine is a Polyunsaturated Fatty Acid (PUFA) Analogue

PUFAs and Analogues: Distinct Ligand-Target Interactions with PUFA Binding Proteins

- Peroxisome proliferator-activated receptors (PPARs) are members of the ligand-activated transcription factors of nuclear receptors
- Three isotypes: PPAR-α, PPAR-β/δ, and PPAR-γ
- Regulate important cellular metabolic and proliferative functions, lipid metabolism and anti-inflammatory effects
- Natural ligands for PPAR-β/δ include PUFAs (e.g., docosahexaenoic acid, arachidonic acid) and their metabolites
- In brain, high levels PPAR-β/δ in hypothalamus and hippocampus
- Chronic stress reduces PPAR-β/δ levels, whereas overexpression or activation of hippocampal PPAR-β/δ produces antidepressant-like effects



Phase 2 Study



- **Visits (6)**: Screening, Baseline, Week 2, Week 4, Week 6, & Week 8 Safety Follow-Up
- **Eligibility:**
  - Ages 18-65 meeting a DSM-5 diagnosis of MDD, with current MDE > 12 weeks
  - Screening Montgomery-Åsberg Depression Rating Scale (MADRS) ≥ 28
  - Baseline MADRS <25 and >25% change from Screening score are both exclusionary
  - No acute or confounding medical conditions
  - No lifetime bipolar, psychotic, or antisocial or borderline personality disorder
  - No current obsessive-compulsive disorder, PTSD, or anorexia nervosa
  - No past year alcohol or substance use disorder; no lifetime opioid or sedative-hypnotic use disorder
  - No use of antidepressants, antipsychotics, mood stabilizers, stimulants, benzodiazepines, buspirone, or anticonvulsants (exception for migraineurs)
  - Greater than mild traumatic brain injury by history is exclusionary
- **Investigational Product (IP)**: TNX-601 ER (tianeptine hemioxalate extended-release tablets) 39.4 mg; subjects should take 1 tablet daily in morning with breakfast/food.
- **Primary Endpoint:** change from baseline (CFB) in MADRS total score at Week 6
- **Key Secondaries:** CFB in Clinical Global Impression – Improvement score at Week 6; CFB in Sheehan Disability Scale total score at Week 6
- **Safety Measures:** AEs/SAEs; physical/neuro exams; clinical labs; vital signs; ECG; Columbia-Suicide Severity Rating Scale (C-SSRS); Changes in Sexual Functioning Questionnaire short form (CSFQ-14); Misuse, Abuse, Diversion Drug Event Reporting System (MADDERS®) and Subjective Opiate Withdrawal Scale (SOWS) to monitor for abuse, diversion, withdrawal
- Statistical Analyses: mixed model repeated measures (MMRM) approach with covariates that include fixed categorical effects of treatment, site, visit, and treatment by visit interaction; and continuous fixed covariates of baseline score and baseline score by visit interaction. Missing data will be imputed via multiple imputation (MI)
- Phase 1 PK parameters for the developed once-daily TNX-601 ER formulation are in **Table 1**:

CONCLUSIONS

- **First participant enrolled on 14 March 2023; to date, ~15% have been randomized**
- **Interim analysis to occur upon first 50% patient completed, estimated in Q4 2023**
- **As illustrated in the Mechanism of Action panel, isolation of pure enantiomers of tianeptine has led to a new understanding of its mechanism of action as an antidepressant and future potential in other CNS conditions; tianeptine is a PPAR-β/δ and PPAR-γ agonist, binding intracellularly and activating transcription factors; tianeptine's unique properties with respect to restoration of neuroplasticity are explained by the PPAR mechanism, as are the lack of typical monoaminergic side effects such as sexual dysfunction and weight gain; anti-inflammatory, metabolic, and neuroprotective effects suggest potential uses in neurodegenerative conditions such as Alzheimer's disease**
- **"Follow on" development of pure *(S)*-tianeptine isomer (TNX-4300[#]), which is devoid of μ–opioid receptor activity, offers potential for expanded dose range in other CNS conditions without abuse liability at high doses of the racemic**

[#] TNX-4300 is a pre-clinical stage investigational new drug and has not been approved for any indication

ACKNOWLEDGEMENTS

Other Tonix scientists who contributed significantly to the studies on mechanism and formulation development include:

Sina Bavari, Jennifer Cho, Siobhan Fogarty and Herb Harris