

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): September 25, 2023

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada
(State or Other Jurisdiction
of Incorporation)

001-36019
(Commission
File Number)

26-1434750
(IRS Employer
Identification No.)

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

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

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

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

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

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

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

Emerging growth company

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

Item 7.01 Regulation FD Disclosure.

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 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 9.01 Financial Statements and Exhibits.

(d)	Exhibit No.	Description.
	99.01	Corporate Presentation by the Company for September 2023
	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: September 25, 2023

By: /s/ Bradley Saenger

Bradley Saenger
Chief Financial Officer



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.

Investment Highlights



MARKETED PRODUCTS

Tonix Medicines markets two FDA-approved products Zembrace® SymTouch® (sumatriptan injection) and Tosymra® (sumatriptan nasal spray) for the treatment of acute migraine in adults with or without aura



RICH PIPELINE OF THERAPEUTICS CANDIDATES IN DEVELOPMENT

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



IN-HOUSE CAPABILITIES

Internal **capabilities in R&D and biologics process development and GMP manufacturing** to accelerate development timelines.



STRATEGIC PARTNERSHIPS

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

¹Zembrace 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

²Tosymra [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

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

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Pipeline: Key Clinical Development Programs

Candidates*	Indication	Status/Next Milestone
TNX-601 ER	Depression	Phase 2 – Topline expected early November ¹
TNX-1900 ²	Prevention of Chronic Migraine	Phase 2 – Topline expected early December
TNX-102 SL ³	Fibromyalgia (FM) Long COVID (PASC ⁴)	Mid-Phase 3 – Topline expected late December Phase 2 – Topline Reported
TNX-2900 ⁵	Prader-Willi Syndrome - <i>FDA Orphan Drug Designation</i>	Phase 2 ready
TNX-1300 ⁶	Cocaine Intoxication - <i>FDA Breakthrough Designation</i>	Mid-Phase 2, Targeted 4Q 2023 Start
TNX-1500 ⁷	Organ Transplant Rejection/ Autoimmune Conditions	Phase 1 – currently ongoing

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

¹Phase 1 trial for formulation development was completed outside of the U.S.; Other potential indications include PTSD and neurocognitive dysfunction from steroids

²Acquired from Trigemina; license agreement with Stanford University; Investigator-initiated Binge Eating Disorder (BED) and adolescent obesity studies initiated 3Q 2023.

³TNX-102 SL (cyclobenzaprine HCl sublingual tablets) also has active INDs for Agitation in Alzheimer's Disease (AAD), Alcohol Use Disorder (AUD), and Posttraumatic Stress Disorder (PTSD). AAD and AUD are Phase 2 ready, and PTSD is Phase 3 ready..

⁴Post-Acute Sequelae of COVID-19.

⁵Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)

⁶TNX-1300 (double-mutant cocaine esterase) is licensed from Columbia University

⁷anti-CD40L humanized monoclonal antibody –Phase 1 trial in healthy volunteers is currently ongoing

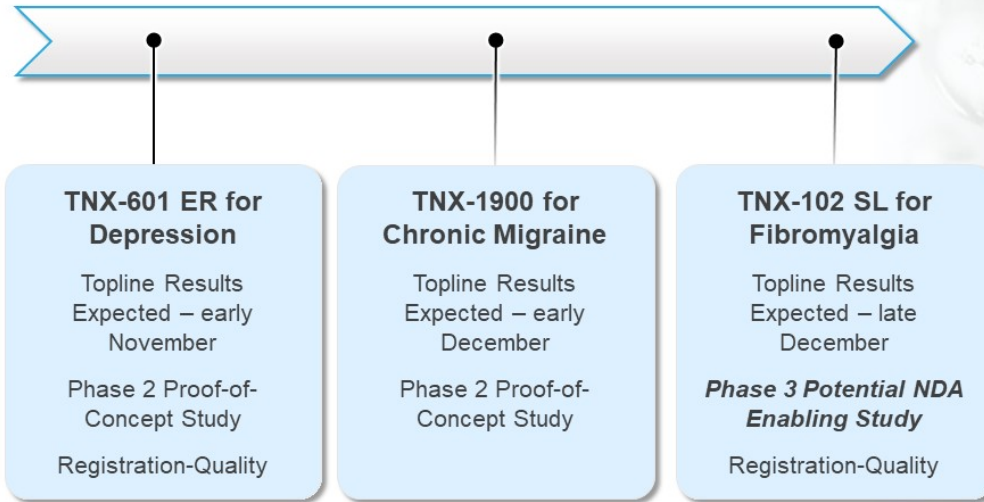
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Upcoming Expected Topline Results

Fourth Quarter 2023



TONIX MEDICINES: MARKETED PRODUCTS



Two Marketed Proprietary Migraine Drugs Autoinjector and Nasal Spray (Non-oral) Formulations of Sumatriptan

Zembrace® SymTouch® (sumatriptan injection) 3 mg¹



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

Tosymra® (sumatriptan nasal spray) 10 mg²



Consolidated Product Sales for the 12 months ended March 31st 2023

- Factory sales: \$30.4M³
- Net sales: \$16.4M³

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

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

¹Zembrace 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
²Tosymra [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
³Upsher-Smith Laboratories, LLC; Data On File, 2023

⁴Mathew NT, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49(12):1271-1276.
⁵Wendt J, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. Clinical Therapeutics. 2006;28(4):517-526.

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

Administration of Zembrace and Tosymra Bypass the GI Tract



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

- Potential to provide a treatment option for migraines complicated by severe nausea and vomiting

Need for acute non-oral treatments

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

Existing intranasal branded products

- Imitrex® nasal spray (sumatriptan)
 - GSK has announced that this product will be discontinued in January 2024
- Migranal® (dihydroergotamine) nasal spray – developed by Novartis, sold by Bausch Health

New intranasal products bring attention to this non-oral route

- Pfizer’s Zavzpret® (zavegepant), FDA approved in March, 2023¹ is the first intranasal gepant
- Impel NeuroPharma’s Trudhesa® (dihydroergotamine) FDA approved 2021²

¹Pfizer Press Release March 10, 2023. - <https://www.pfizer.com/news/press-release/press-release-detail/pfizers-zavzpretm-zavegepant-migraine-nasal-spray>

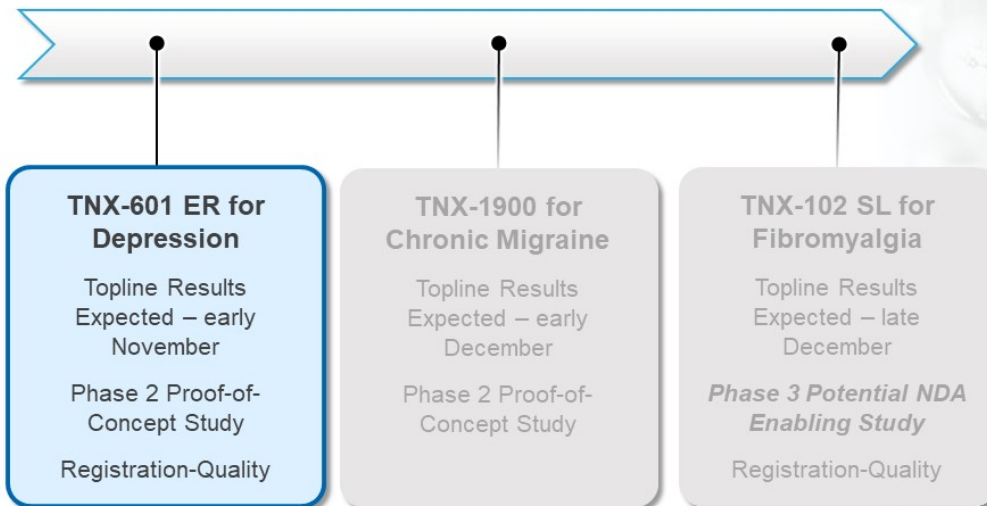
²Impel Press Release September 3, 2021 - <https://impelpharma.com/2021/09/03/impel-neuropharma-announces-u-s-fda-approval-of-trudhesa-dihydroergotamine-mesylate-nasal-spray-for-the-acute-treatment-of-migraine/>

CNS: KEY DEVELOPMENT CANDIDATES

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Upcoming Expected Topline Results

**Fourth Quarter
2023**



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

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 agonist¹

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 marketed²

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Dysfunction From Corticosteroids, Alzheimer’s Disease³

Status: Phase 2 MDD study UPLIFT enrollment complete

Next Steps:

Topline results expected early November 2023

Patents Issued

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

¹Sullivan G et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. <https://bit.ly/42o3inV>

²Summary 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.

³García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720
Abbreviations: IR, immediate release; *t.i.d.*, three times a day

TNX-601 ER - Phase 2 UPLIFT* Study Design

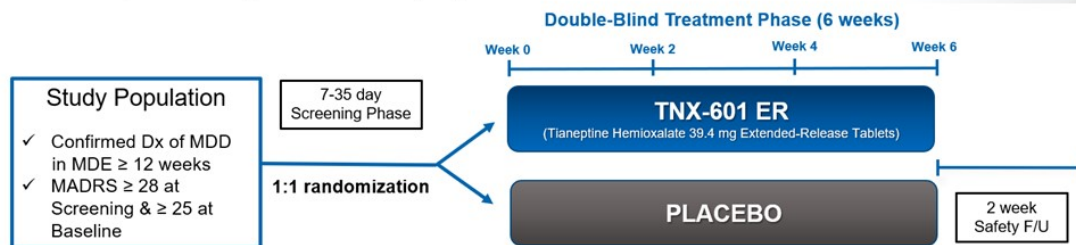


General study characteristics:

- 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

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6 analyzed via MMRM with MI
- Threshold for achieving proof-of-concept is ES > 0.20
- Threshold for potential registrational study is *p*-value < 0.05



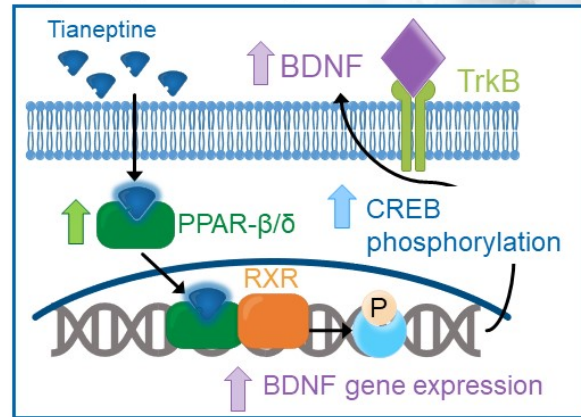
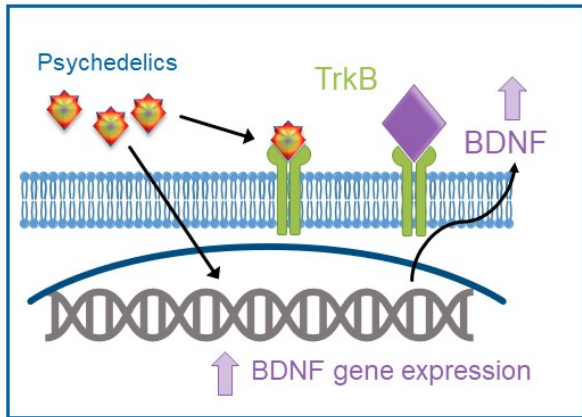
*ClinicalTrials.gov Identifier: NCT05686408

Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number; ES, effect size; MMRM, mixed models for repeated measures; MI, multiple imputation

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 depression¹

- 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

¹de Vos CMH, et al. *Front Psychiatry*. 2021;12:724606

²Moliner R, et al. *Nat Neurosci*. 2023;26(6):1032-1041

³Ji MJ, et al. *Int J Neuropsychopharmacol*. 2015;19(1):pv083

⁴Seo MK, et al. *Psychopharmacology (Berl)*. 2016;233(13):2617-2627

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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 agonism²
 - Risk of abuse or diversion for euphoric effects³

(S)-Tianeptine: PPAR-β/δ agonist, no opioid liability⁴

- New mechanism of action for treating depression

(R)-Tianeptine: opioid liability⁴

- Weak μ-opioid receptor agonism⁴

	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



¹Stablon. Summary of product characteristics. Les Laboratoires Servier Industrie; 2014.

²PubChem. Accessed November 10, 2022. <https://pubchem.ncbi.nlm.nih.gov/compound/Tianeptine>

³Drug Enforcement Administration. May 2019. Accessed November 11, 2022. https://www.deadiversion.usdoj.gov/drug_chem_info/tianeptine.pdf

⁴Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. <https://bit.ly/42o3inv>

⁵Rat Novel Object Recognition Test

⁶Mouse Porsolt Forced Swim Test

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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 ER¹
 - 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

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Disorder From Corticosteroids, Alzheimer's Disease²

Status: Pre-clinical

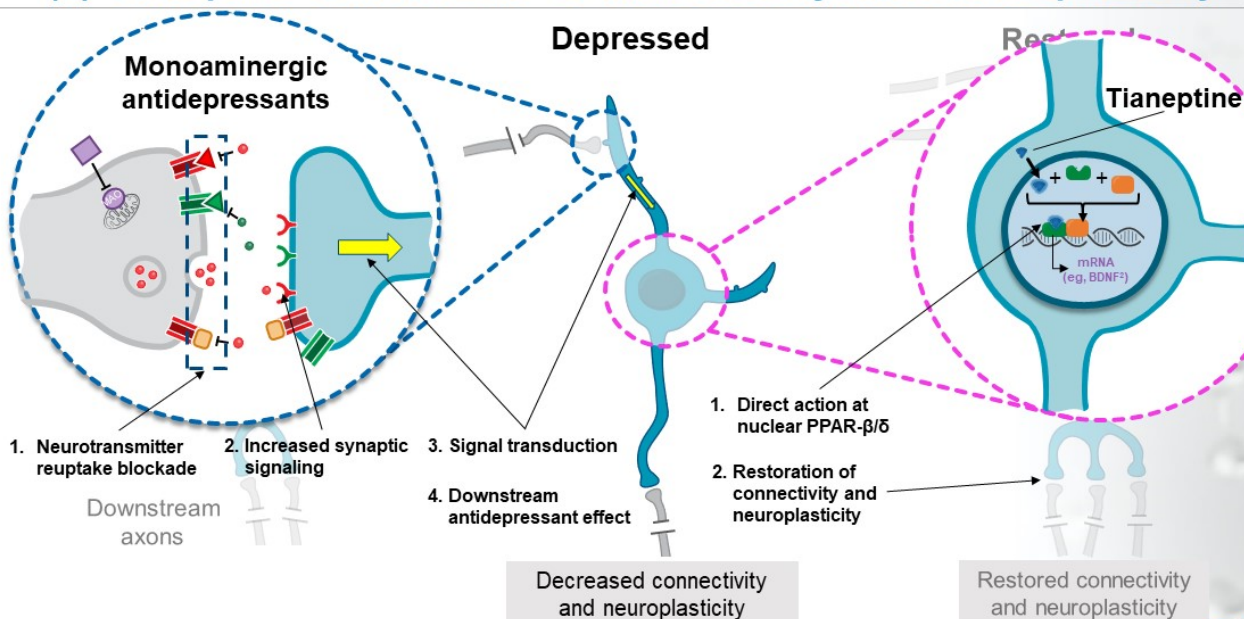
Next Steps: Potential for IND to be supported by pre-clinical and clinical data from TNX-601 (racemic tianeptine) development

Patents Issued

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

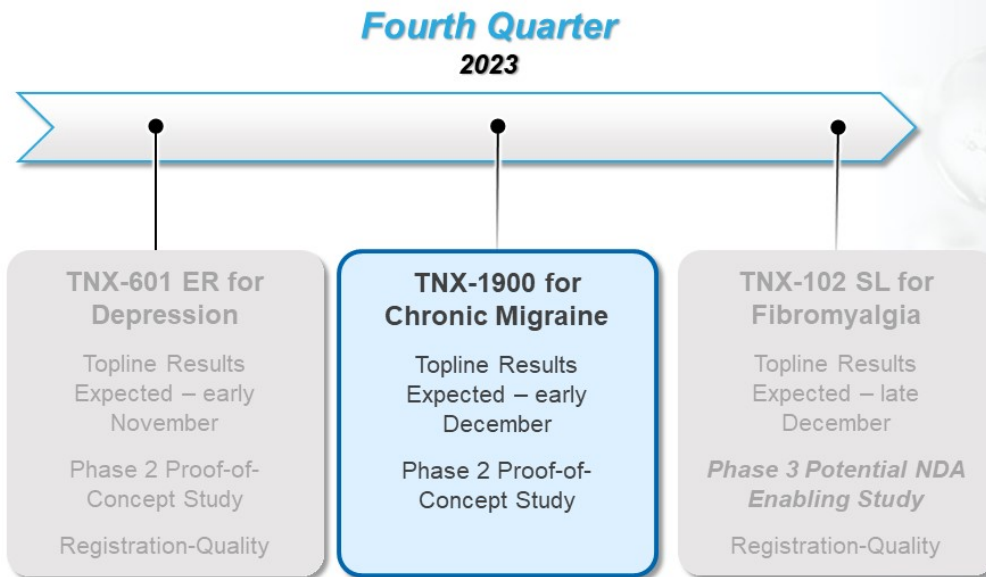
¹Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. <https://bit.ly/42o3inV>
²García-Alberca et al., 2022. J Alzheimers Dis. 88(2):707-720

While Monoaminergic Antidepressants Work at the Synapse, (S)-Tianeptine “Cuts in Line” to More Directly Affect Neuroplasticity¹



¹Sullivan GM et al. Poster presentation at the American Society of Clinical Psychopharmacology, June 2023. <https://bit.ly/42o3inV>
²BDNF=brain-derived neurotrophic factor.

Upcoming Expected Topline Results



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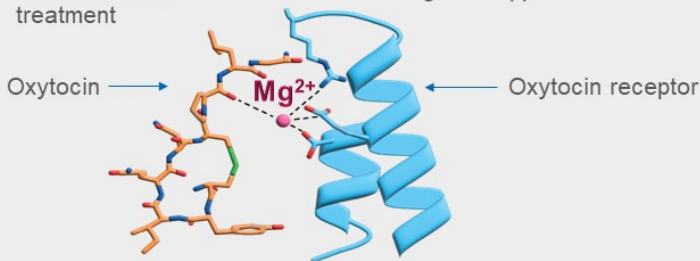
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TNX-1900*: Prevention of Headache in Chronic Migraine Intranasal Potentiated Oxytocin (OT) with Magnesium

PROFILE

- Intranasal OT has potential utility in treating migraine¹
- Magnesium is known to potentiate the binding of OT to its receptor^{2,3}
- One billion individuals worldwide suffer from migraines

Differentiator: Novel non-CGRP antagonist approach to treatment



Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Chronic Migraine

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

Status: Phase 2 study PREVENTION enrollment complete⁴

Next Steps: Topline results from PREVENTION expected early December 2023

Investigator initiated Phase 2 trials in adolescent obesity, social anxiety disorder, and binge eating disorder are enrolling 3Q 2023

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



CNS PORTFOLIO

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¹Tzabazis et al., 2017, *Headache*, 57 Suppl 2:64-75

²Antoni et al., 1989, *Biochem J*, 257(2):811-4

³Meyerowitz et al., 2022, *Nat Struct Mol Biol*, (3):274-281

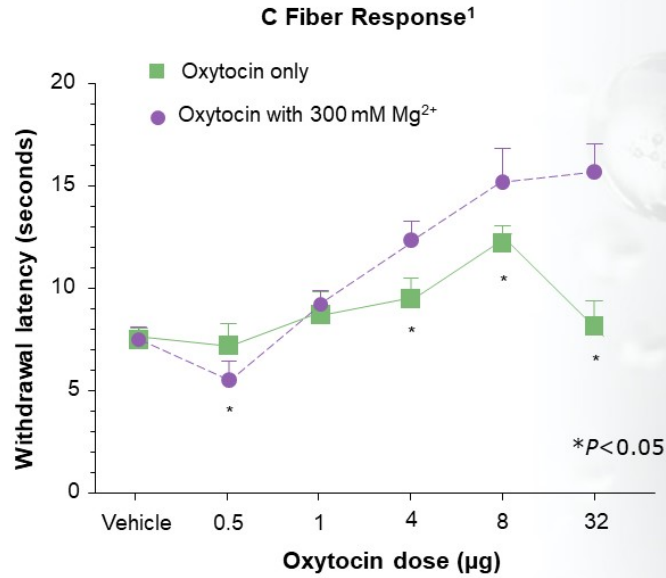
⁴A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900



Oxytocin Effects – Addressing the “Inverted U” Dose Response Addition of Mg²⁺ Augments Oxytocin-Induced Analgesia in Animal Model

- A **nonlinear dose response** decreases efficacy at higher doses
- Addition of **Mg²⁺ rescues the efficacy** of oxytocin at high doses

In vivo effect of Mg²⁺ ion addition with intranasal oxytocin-induced craniofacial analgesia on the withdrawal response time to noxious heat stimulation of the cheek of pre-inflamed rat²



¹Adapted from: Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.
²Oxytocin receptors are upregulated in response to stress, including inflammation

TNX-1900: Phase 2 PREVENTION Study Design



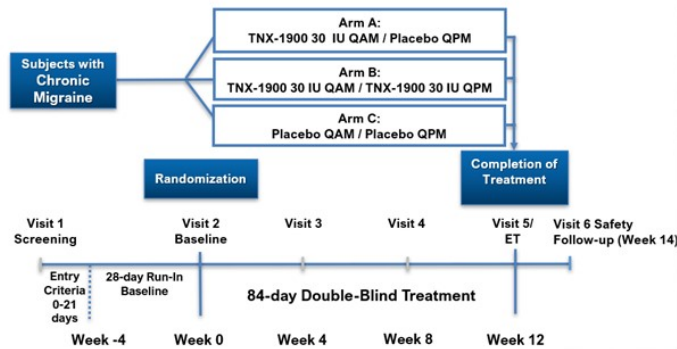
General study characteristics:

- Randomized, double-blind, placebo-controlled study (three arms— two oxytocin treatment regimens and one placebo) in chronic migraine
- U.S. sites only
- Fully enrolled with 88 patients
- Topline results expected 4Q'23

Primary Endpoint:

- Mean change in the number of migraine headache days between the 28-day Run-In phase and the last 28-days of the Treatment phase (TNX-1900 vs. placebo), analyzed via MMRM
- Threshold for achieving proof-of-concept is ES > 0.2

Study TNX-OX-CM201

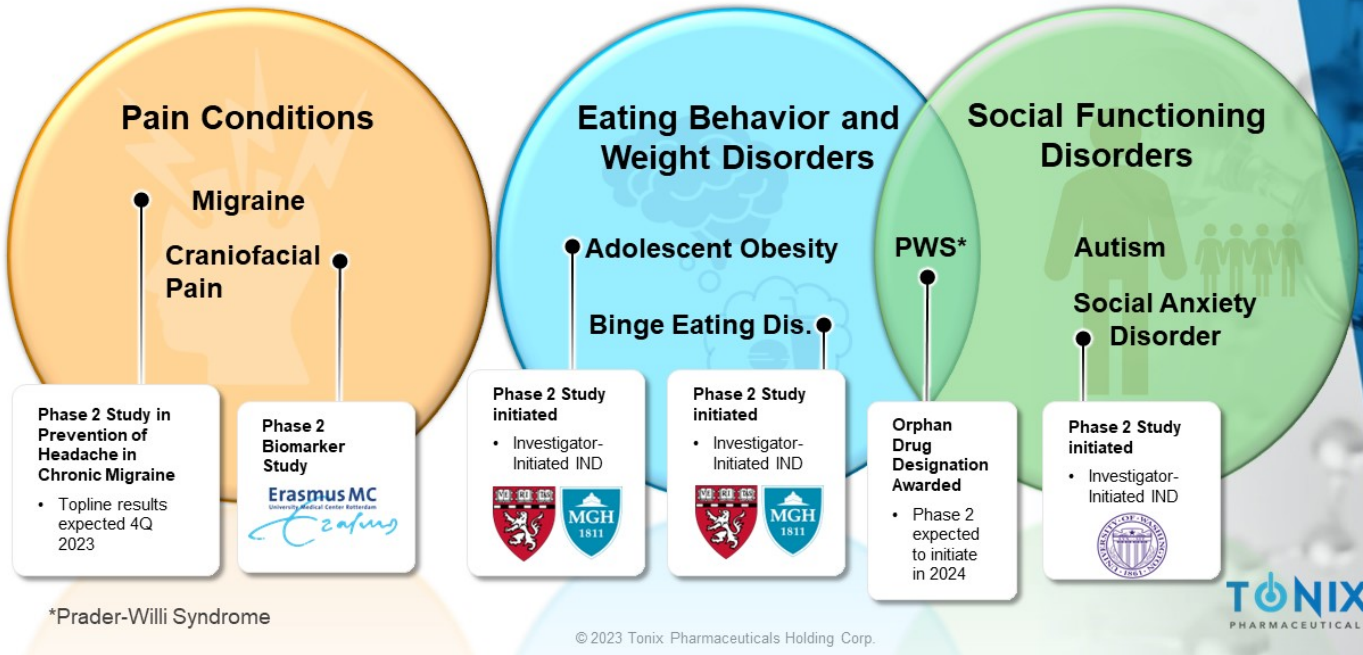


ClinicalTrials.gov Identifier: NCT05679908
A Study to Evaluate the Efficacy and Safety of TNX-1900 in Patients With Chronic Migraine (PREVENTION)

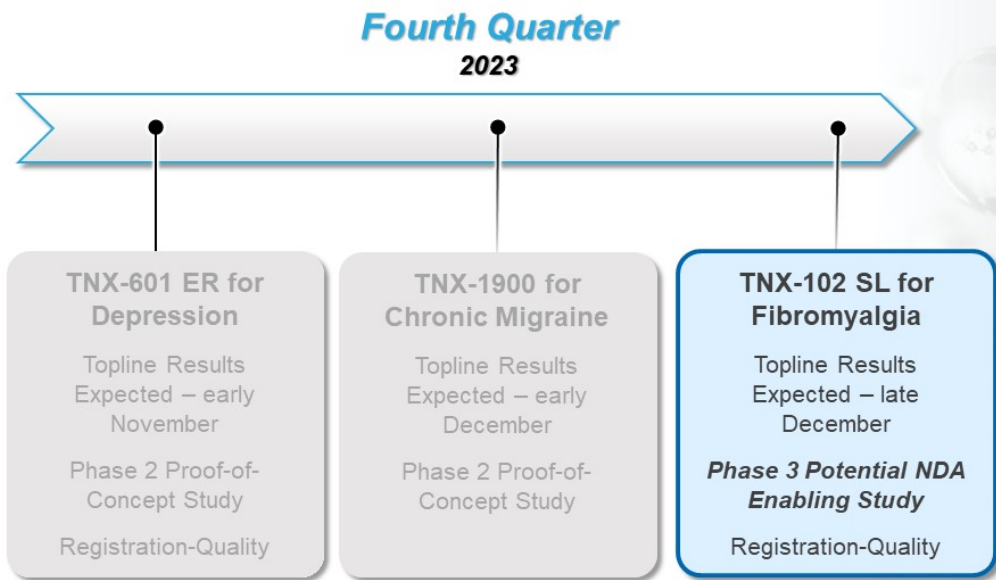




Potential Applications of TNX-1900 and TNX-2900



Upcoming Expected Topline Results



TNX-102 SL*

Cyclobenzaprine (Protectic®) Pipeline in a Product

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

Potent binding and antagonist activities at the serotonergic-5-HT_{2A}, adrenergic- α 1, histaminergic-H1, and muscarinic-M1 cholinergic receptors to facilitate restorative sleep

Innovative and proprietary PROTECTIC® Rapid drug exposure following nighttime administration

Differentiators:

Relative to Oral Cyclobenzaprine

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

Relative to Standard of Care

- Potential for better tolerability while maintaining efficacy
- Not scheduled with no recognized abuse potential

Patents Issued

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

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Fibromyalgia

Status: Mid-Phase 3

- One positive Phase 3 study (RELIEF) completed
- Second Phase 3 study (RALLY) missed primary endpoint
- Confirmatory Phase 3 study (RESILIENT) enrollment complete

Next Steps: Topline results expected late December 2023

Fibromyalgia-Type Long COVID

Status: Phase 2

- Phase 2 study (PREVAIL) enrollment complete

Next Steps: Topline results reported 3Q 2023

Planning End of Phase 2 Meeting with FDA 1Q 2024

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

PROFILE

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

- Afflicts an estimated 6-12 million adults in the U.S., predominantly women¹
- Symptoms include chronic widespread pain, nonrestorative sleep, fatigue, and cognitive dysfunction
- Patients struggle with daily activities, have impaired quality of life, and frequently are disabled
- Physicians and patients report common dissatisfaction with currently marketed products



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

Patents Issued

¹American Chronic Pain Association (www.theacpa.org, 2019)

²Lederman 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.

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DEVELOPMENT PROGRAM

Market Entry: Fibromyalgia

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

Status: One Positive Phase 3 study RELIEF completed²

Second Phase 3 study RALLY missed primary endpoint

Confirmatory Phase 3 study RESILIENT enrollment complete

Next Steps: Topline results expected late December 2023

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

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CNS PORTFOLIO

TNX-102 SL: Phase 3 RESILIENT Study Design

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 analyzed via MMRM with MI
- 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

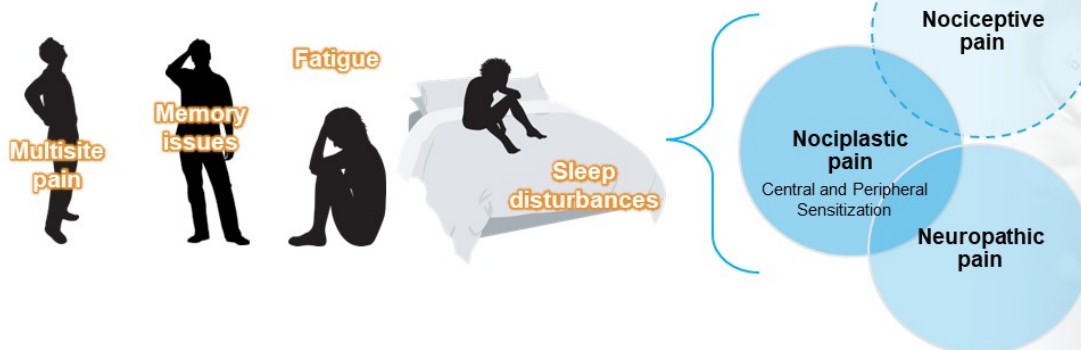


*Two week run in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose

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)
 MMRM, mixed models for repeated measures; MI, multiple imputation
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Fibromyalgia-Type Long COVID

- Long COVID is a heterogeneous condition that displays elements of nociplastic pain in many individuals, who experience otherwise unexplained symptoms¹⁻³



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

Nociplastic pain⁴: (*new term for "Central and Peripheral Sensitization"*) Pain that arises from altered nociception despite no clear evidence of tissue damage, or for disease or lesion of the somatosensory system causing the pain

¹Bierle et al., 2021. *J Prim Care Community Health*. 12:21501327211030826
²Moghimi et al., 2021. *Curr Neurol Neurosci Rep*. 21(9):44
³Thaweethai T, et al. 2023. *JAMA*. 2023 329(22):1934-1946
⁴Trouvin et al., 2019. *Best Pract Res Clin Rheumatol*. 33(3):101415



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

PROFILE

- Occurs in approximately 19% of recovered COVID-19 patients¹
- As many as 40% of Long COVID patients experience multi-site pain, a hallmark of fibromyalgia^{2,3}
- Symptoms of Long COVID, like multi-site pain, fatigue and insomnia, are the hallmarks of chronic pain syndromes like fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- In August 2022, the HHS released the National Research Action Plan on Long COVID⁴ which endorses the connection between Long COVID and ME/CFS

DEVELOPMENT PROGRAM

Market Entry: Fibromyalgia-Type Long COVID (PASC)

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

Status: Phase 2 study PREVAIL topline reported

Next Steps: End of Phase 2 Meeting with FDA expected 1st Quarter 2024

Patents Issued

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

¹June 22, 2022-CDC - https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm

⁴Department of Health and Human Services, Office of the Assistant Secretary for Health. 2022. National Research Action Plan on Long COVID.

²Harris, H, et al. Tonix data on file. 2022

³TriNetX Analytics

TNX-102 SL: Phase 2 PREVAIL Study Design Proof-of-Concept Study



PREVAIL Study

Study characteristics:

- Randomized, double-blind, placebo-controlled study of TNX-102 SL in fibromyalgia-type Long COVID
- U.S. sites only, 63 patients enrolled

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



PREVAIL Topline Results¹

TNX-102 SL showed a robust effect size of 0.5 in improving fatigue and showed consistent activity across secondary measures of sleep quality, cognitive function, disability and Patient Global Impression of Change, but did not meet the primary endpoint of multi-site pain reduction at week 14

- There is currently no drug approved to treat Long COVID

TNX-102 SL 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

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

- Fatigue is the signature symptom of Long COVID and it has been identified as the dominant symptom contributing to disability²
- In both of our prior Phase 3 studies of TNX-102 SL 5.6 mg in fibromyalgia, we observed numerical improvement in the PROMIS fatigue score (in RELIEF $p=0.007$ MMRM and in RALLY $p=0.007$ MMRM)
- Although the validity of PROMIS Fatigue is not yet established in Long COVID, we believe the results of PREVAIL, together with extensive data from studies in other chronic conditions³⁻⁵ – including Tonix's studies in fibromyalgia – make PROMIS Fatigue a solid candidate for the primary endpoint of future Long COVID registrational studies.

¹Tonix Press Release, September 5, 2023 - <https://bit.ly/3Z6FOHQ>

²Walker S, et al. *BMJ Open* 2023;13:e069217. doi:10.1136/bmjopen-2022-069217

³Cook, K.F., et al. 2016. *Journal of Clinical Epidemiology*, 73, 89-102

⁴Cella, D., et al. 2016. *Journal of Clinical Epidemiology*, 73, 128-134

⁵Lai, J.S., et al. 2011. *Archives of Physical Medicine and Rehabilitation*, 92(10 Supplement), S20-S27.



PREVAIL Next Steps

Tonix plans to meet with FDA to discuss a path to registration

- Expected date of End of Phase 2 meeting is 1st Quarter 2024

Fatigue is the principal symptom overlapping with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and fibromyalgia syndromes

- Expected date of fibromyalgia topline is late December 2023



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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 (Fc γ R)

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

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

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

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Prevention of Allograft Rejection

Status: Phase 1 currently enrolling

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

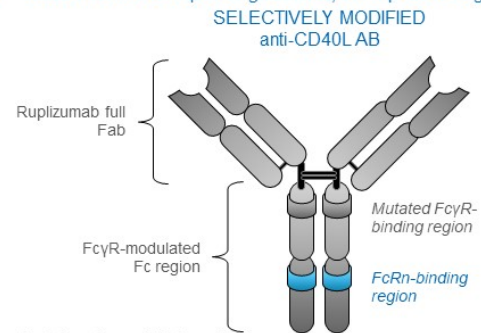
Next Steps: Initiate Phase 2 study in Kidney Transplant Recipients

Autoimmune Diseases

Status: Planning for future indications including:

Sjögren's Syndrome, Systemic Lupus Erythematosus and Multiple Sclerosis

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

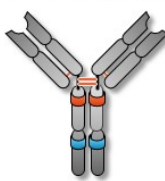
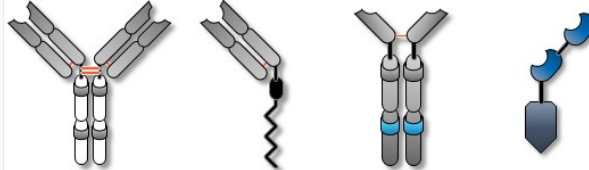
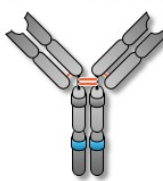


Contains the full ruplizumab Fab and the engineered Fc region that modulates Fc γ R-binding, while preserving FcRn function.

TONIX
PHARMACEUTICALS

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



First-generation anti-CD40L mAbs	Second-generation anti-CD40L proteins	Third-generation anti-CD40L mAbs*
 Ruplizumab	 Aglycosyl Ruplizumab Dapirolizumab Letolizumab Dazodalibep	 TNX-1500
Constant fragment (Fc) domain interacted with Fc γ RIIA (CD32A), which suggested a mechanism for the increased risk of thrombosis. ^{1,2}	Second-generation anti-CD40L proteins exhibited dramatically reduced binding to Fc γ RIIA ³⁻⁶ but had other issues, including decreased efficacy, shortened half-life, or engendering of anti-drug antibodies (ADAs). ⁷⁻⁹	TNX-1500 is engineered to target CD40L therapeutically while reducing Fc γ RIIA 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

¹Inwald et al., 2003. *Circ Res*. 92(9):1041-1048

²Robles-Carrillo et al., 2010. *J Immunol*. 185(3):1577-1583

³Shock et al., 2015. *Arthritis Res Ther*. 17(1):234

⁴Xie et al., 2014. *J Immunol*. 192(9):4083-4092

⁵Ferrant et al., 2004. *Int Immunol*. 16(11):1583-1594

⁶Karnell et al., 2019. *Sci Transl Med*. 11(489):eaar6584

⁷ClinicalTrials.gov identifier: NCT02273960. Updated July 16, 2019. Accessed June 1, 2021. <https://clinicaltrials.gov/ct2/show/results/NCT02273960?view=results>

⁸Waters, 2018. *Biocentury*.

⁹Company data

TNX-1500 anti-CD40L Monoclonal Antibody

Proposed indication - prevention of rejection in kidney transplant:

- Supported by pre-clinical studies

Phase 1 study initiated:

- A Phase 1 study of TNX-1500 was initiated in the third quarter of 2023.

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}

¹Lassiter, 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>

²Miura, 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>



Other anti-CD40L Monoclonal Antibodies in Development

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) – positive results reported^{1,2}
- Frexalimab, f.k.a. SAR441344 (Fc-modified)

Horizon (being acquired by Amgen) – Sjögren's Syndrome (SjS)

- Two Positive Phase 2 studies reported^{3,4}
- Dazodalibep (tn03 fusion protein)

Eledon – 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)

UCB (Co-developed with Biogen) – Systemic Lupus Erythematosus (SLE)

- Phase 3 Trial Currently Enrolling (NCT04294667)
 - Topline results expected 1H 2024⁵
- Dapirolizumab pegol (pegylated Fab)

¹Sanofi press release May 31, 2023 "Press Release: Positive Phase 2 data of novel investigational anti-CD40L antibody frexalimab show significantly reduced disease activity in relapsing multiple sclerosis": www.sanofi.com/en/media-room/press-releases/2023/2023-05-31-05-00-00-2678991 (accessed August 11 2023)

²Cavalho, T. *Nature Medicine* (News) (2023), 29:1882

³Horizon press release September 12, 2022 "Horizon Therapeutics plc Announces Phase 2 Trial Evaluating Dazodalibep for the Treatment of Sjögren's Syndrome Meets Primary Endpoint" <https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating> (accessed August 11 2023)

⁴Horizon Press Release 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

⁵<https://www.ucb.com/our-science/pipeline>

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



Potential New Cancer Treatment

- TNX-1700 (rTFF2) has effects on cancer by altering the tumor micro-environment
- Mechanism of action: suppresses myeloid-derived suppressor cells and activates anti-cancer CD8+ T cells
- Potential synergy with anti-PD-1 or anti-PD-L1 monoclonal antibodies (mAbs)

Preclinical Evidence for Inhibiting Growth of Cancer Cells

- Data showed that mTFF2-CTP augmented the efficacy of mAb anti-PD-1 therapy. Anti-PD-1 in combination with TFF2-CTP showed greater anti-tumor activity in PD-L1-overexpressing mice
- mTNX-1700 (mTFF2-MSA fusion protein) and anti-PD-1 monotherapy each was able to evoke anti-tumor immunity in the MC38 model of colorectal cancer¹
- mTNX-1700 augmented the anti-tumor efficacy of anti-PD-1 therapy in both the MC38 and the CT26.wt models¹

Patents Filed

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

Status: Preclinical

Next Steps: Animal studies ongoing

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

Licensed from Columbia University

- Developing in partnership under sponsored research agreement

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

¹Daugherty, B. et al. March 6, 2023 Keystone Poster, www.tonixpharma.com/wp-content/uploads/2023/03/mTFF2-MSA_mTNX-1700_Suppresses-Tumor-Growth-and-Increases-Survival-in-an-Anti-PD-1-Treated-MC38-Colorectal-Cancer-Model-by-Targeting-MDSCs.pdf



INFECTIOUS DISEASE: KEY CANDIDATES

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Internal Development & Manufacturing Capabilities

R&D Center (RDC) – Frederick, MD

- **Functions:**
 - Research advancing CNS and immunology drugs
 - Accelerated development of vaccines and antiviral drugs against COVID-19, its variants and other infectious diseases
- **Description:** ~48,000 square feet, BSL-2 with some areas designated BSL-3
- **Status:** Operational



Advanced Development Center (ADC) – North Dartmouth, MA

- **Function:** Development and clinical scale manufacturing of biologics
- **Description:** ~45,000 square feet, BSL-2
- **Status:** Operational



INFECTIOUS DISEASE PORTFOLIO



Broad Spectrum Antivirals

New DoD approach^{1,2} raises importance of broad-spectrum medical counter measures

- Need to improve medical readiness of the warfighter in biological threat environments
- Beyond “one bug, one drug” approach
- Issued Dec 2022

**Approach for Research, Development,
and Acquisition of Medical
Countermeasure and Test Products**

 2022

 Chemical and Biological Defense Program

¹Vergun, D. DOD News. January 10, 2023. DoD aims to shield warfighters from novel biological agents. <https://www.defense.gov/News/News-Stories/Article/Article/3261095/dod-aims-to-shield-warfighters-from-novel-biological-agents/>

²US Department of Defense, Chemical and Biological Defense Program, “Approach for Research, Development and Acquisition of Medical Countermeasure and Test Products, Dec. 2022. <https://media.defense.gov/2023/Jan/10/2003142624/-1/-1/0/APPROACH-RDA-MCM-TEST-PRODUCTS.PDF>



DTRA RFP for Broad Spectrum Antivirals Through Medical CBRN

DTRA Through Medical CBRN Defense Consortium: New DoD approach raises importance of broad-spectrum medical counter measures

- MCDC issued a request for project proposals in the Fall of November 2021 on behalf of DTRA for, “Novel Biologics as Medical Countermeasures(MCM) against Biological Threats of Concern.”



Who We Are

The Medical CBRN Defense Consortium (MCDC) was formed in response to the Government’s expressed interest to establish an Other Transaction Agreement (OTA) with an eligible entity or group of entities, to include industry, academic, and not-for-profit partners, for advanced development efforts to support the Department of Defense’s (DoD) medical, pharmaceutical and diagnostic requirements as related to enhancing the mission effectiveness of military personnel.

Through the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), the Medical Countermeasures Systems (MCS) Joint Project Management Office is always looking for innovative, safe and effective medical solutions to counter CBRN threats. The usage of an OTA allows government to partner with the MCDC to leverage cutting edge R&D and develop prototypes from commercial sources. This gives MCS an agile and flexible way to develop medical countermeasures using new and innovative technology.

RFP = request for proposals
 DTRA = Defense Threat Reduction Agency
 CBRN = Chemical, Biological, Radiological and Nuclear



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



TNX-801*



Recombinant Pox Vaccine (RPV) Platform Using Live Virus Technology

Differentiators:

- **Live virus vaccines are the most established vaccine technology**
 - Starting with Edward Jenner's smallpox vaccine, the first vaccine, which eradicated smallpox
 - Prevents forward transmission
 - Effective in eliciting durable or long-term immunity
- **Economical to manufacture at scale**
 - Low dose because replication amplifies dose in vivo
 - Single shot administration
- **Standard refrigeration required for shipping and storage**

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

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



Mpox and Smallpox Vaccine

Status: Preclinical

- TNX-801 is a cloned version of horsepox¹ (without any DNA insert) purified from cell culture

Milestone: Successful completion of pre-IND meeting

Next Steps: Preparation of IND submission

Vaccine for Future Emerging Infectious Diseases

Example: TNX-1850 for COVID-19

Status: Model System

**TEAM,
NETWORK, &
UPCOMING
MILESTONES**

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Key Development Partners



TNX-1500: ALLOGRAFT REJECTION

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



TNX-1900: MIGRAINE & OTHER INDICATIONS

**TNX-801: SMALLPOX AND MONKEYPOX VACCINE
TNX-1850: COVID-19 VACCINE**



TNX-2900: PRADER-WILLI SYNDROME

TNX-1900: Binge Eating Disorder, Adolescent Obesity

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Upcoming: Expected Topline Clinical Data and Trial Initiations 2023

4th Quarter

- Phase 2 UPLIFT study of TNX-601 ER for major depressive disorder – expected early November
 - Affects approximately 47 M adults in the U.S (18.4% of population)¹
- Phase 2 PREVENTION study of TNX-1900 for chronic migraine – expected early December
 - Affects approximately 3-7 M adults in the U.S²
- Phase 3 RESILIENT study of TNX-102 SL for fibromyalgia – expected late December
 - Affects approximately 6-12 M adults in the U.S³

3rd Quarter Clinical Trial Initiations

- Phase 1 study of TNX-1500 for prevention of allograft rejection - started

4th Quarter Clinical Trial Initiations

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

¹CDC - https://www.cdc.gov/mmwr/volumes/72/wr/mm7224a1.htm?s_cid=mm7224a1_w

²Natoli et al., Global prevalence of chronic migraine: a systematic review, Cephalgia, 2010, 30:599-609

³American Chronic Pain Association (www.theacpa.org, 2019)

THANK YOU



Zembrace® IMPORTANT SAFETY INFORMATION (1 of 2)

Zembrace Sym Touch (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.



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.



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.