

**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 22, 2021

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, Suite 101, 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 Global 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 presentations, which are 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. Copies of the presentations are filed as Exhibits 99.01 and 99.02 hereto and incorporated herein by reference.

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

Item 9.01 Financial Statements and Exhibits.

(d)	Exhibit No.	Description.
	99.01	Corporate Presentation by the Company for June 2021
	99.02	Abbreviated Corporate Presentation by the Company for June 2021



Investor Presentation

NASDAQ:TNXP

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June 2021

Version P0304 6-22-2021 (Doc 0852)

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Cautionary Note on Forward-Looking Statements

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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, risks related to failure to obtain U.S. Food and Drug Administration clearances or approvals and noncompliance with its regulations; our need for additional financing; delays and uncertainties caused by the global COVID-19 pandemic; substantial competition; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties. 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, 2020, as filed with the Securities and Exchange Commission (the "SEC") on March 15, 2021, 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.

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Tonix Pharmaceuticals: Who We Are and What We Do

Mission And Purpose

Clinical-stage biopharmaceutical company that invents, licenses, acquires and develops innovative medicines to help patients manage central nervous system (CNS) and immunology conditions

"Advancing science to improve patient care and public health"

Team of passionate professionals

Advancing innovative programs into the clinic: Phase 2 and Phase 3 clinical data are perceived as value-creating inflection points

Pipeline

Development stage: programs range from preclinical to mid-Phase 3; expect three new programs in Phase 2 by YE 2021

Therapeutic modalities: small molecules, small synthetic peptides, recombinant peptide from *E. coli*, recombinant proteins from CHO cells (monoclonal antibody, fusion protein), live virus vaccines

Route of administration: oral, sublingual, intranasal, *i.v.*, intradermal, percutaneous

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Our Pipeline – CNS Portfolio

CANDIDATES		INDICATION	STATUS
CNS Portfolio	TNX-102 SL ¹	Fibromyalgia (FM) - Lead Program	Mid-Phase 3 – ongoing
		PTSD Agitation in Alzheimer's Alcohol Use Disorder Long COVID (PASC ²)	Phase 3 ready Phase 2 ready Phase 2 ready Clinical – pre-IND ³
	TNX-1300 ⁴	Cocaine Intoxication / Overdose	Phase 2
	TNX-1900 ⁵	Migraine and Craniofacial Pain	Clinical – pre-IND ⁶
	TNX-2900 ⁷	Prader-Willi Syndrome	Clinical – pre-IND
	TNX-601 CR	Depression, PTSD, Neurocognitive Dysfunction from Steroids	Clinical – pre-IND ⁸
TNX-1600 ⁹	Depression, PTSD and ADHD	Preclinical	

¹TNX-102 SL (cyclobenzaprime HCl sublingual tablets) is an investigational new drug and has not been approved for any indication.

²Post-Acute Sequelae of COVID-19.

³Pre-IND (Investigational New Drug) meeting with the FDA scheduled for third quarter 2021 to seek agreement on design of a potential Phase 2 pivotal study.

⁴TNX-1300 (double-mutant cocaine esterase) is an investigational new biologic and has not been approved for any indication; licensed from Columbia University.

⁵Acquired from Trigemina; license agreement with Stanford University

⁶A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900; Phase 2 expected to start Q3'21

⁷Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)

⁸TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 trial for formulation development was completed outside of the U.S.; Phase 2 expected to start Q4'21

⁹Acquired from TRImaran Pharma; license agreement with Wayne State University

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	CANDIDATES	INDICATION	STATUS
Immunology Portfolio	TNX-1800	Covid-19 vaccine – Prioritized Program ¹	Phase 1, 1H 2022*
	TNX-2100	SARS-CoV-2 skin test for T cell immunity ²	First-in-human study Q4'21*
	TNX-3500	COVID-19 (SARS-CoV-2) antiviral ³	Preclinical
	TNX-2300	COVID-19 vaccine ⁴	Preclinical
	TNX-801	Smallpox and monkeypox preventing vaccine ⁵	Preclinical
	TNX-1500	Organ Transplant Rejection/Autoimmune Conditions ⁶	Preclinical
	TNX-1700	Gastric and pancreatic cancers ⁷	Preclinical
	TNX-701	Radioprotection	Preclinical

*Represents expected milestones

¹Live attenuated vaccine based on horsepox virus vector

²In vivo diagnostic: SARS-CoV-2 peptide epitope mixtures for intradermal administration to measure delayed-type hypersensitivity to SARS-CoV-2

³Sangivamycin, for injection

⁴Live attenuated vaccine based on bovine parainfluenza virus vector; option for license with Kansas State University

⁵Live attenuated vaccine based on horsepox virus

⁶anti-CD40L humanized monoclonal antibody

⁷Recombinant trefoil factor 2 (rTFF2) based protein; licensed from Columbia University

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TNX-102 SL¹

- **Drug Product:** cyclobenzaprine HCl – mannitol eutectic sublingual tablets for daily use at bedtime
- **Targeted Indications:** Fibromyalgia, Posttraumatic Stress Disorder (PTSD), Agitation in Alzheimer’s Disease (AAD), Alcohol Use Disorder (AUD)

¹TNX-102 SL is an investigational new drug and has not been approved for any indication.

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TNX-102 SL FM Lead Program Background on Fibromyalgia

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Fibromyalgia (FM):

A chronic condition

Core symptoms:

- widespread pain
- sleep disturbance
- fatigue
- cognitive symptoms.

Significant disabilities (impaired daily function).

Course of disease can last decades

Prevalence
2-4% US Population
(6-12 million individuals)¹

Estimated 4.5MM Diagnosed²

90% Treated With Pharmacotherapy³

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

2 Walitt, B., Nahin, R.L., Katz, R.S., Bergman, M.J., Wolfe, F. (2015) *The Prevalence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey*, PLoS One; 10(9): e0138024.

3. Decision Resources. *Fibromyalgia*, 2012

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Challenges with Current Pharmacotherapy

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Limitations of Current Therapies

Fewer than half of those treated for fibromyalgia receive relief from the three FDA-approved drugs¹

- Lack of overall response leading to discontinuation or augmentation
- Lack of tolerability leading to discontinuation or reduction in dose (underdosing)

Current Treatment Patterns As A Result of Limitations

Switch Rates/Rotation/Discontinuation

- Over 50% of patient starting an FDA approved therapy for FM switch or discontinue therapy after 12 months²

Polypharmacy

- Average patient is using 2.6 drugs for treating their fibromyalgia, 50% of patients take 3 or more medications concomitantly³

Opioid usage is not uncommon

Market Dissatisfaction

Only 43% of patients indicated that they are satisfied with their medication for FM⁵

1. Frost and Sullivan, 2010

2. Liu et al., 2016

3. Robinson et al., 2012; prospective observational study with 1,700 participants with fibromyalgia.

4. Sarmiento et al., J Opioid Manag 2019; 15(5):460-77 – prescription opioid usage among diagnosed FM patients at one site

5. Robinson et al., 2013; prospective observational study with 1,700 participants with fibromyalgia

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Fibromyalgia Unmet Need and Ideal Treatment Profile

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Ideal Treatment Profile:

Unmet Medical Need:

Current treatment patterns indicate that new, more effective, and better-tolerated treatments are necessary for management of FM¹

Treats FM as a syndrome

Relief from major symptoms (pain, sleep disturbances, fatigue)
Reduces disability and improves daily living (global function)

Well tolerated with low discontinuation

- Low systemic side-effects
- No daytime somnolence
- No weight gain or impact on sexual function

Suitable for chronic use

- Not scheduled
- Non opioid
- Non abuse potential

Source: 1. Yang, et al, 2016

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TNX-102 SL: Engineered to Treat FM

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This unique formulation of cyclobenzaprine has been designed to optimize delivery and absorption, while minimizing the potential residual effects of oral formulations of cyclobenzaprine.

Innovative and proprietary Protectic[®] delivery technology

- Overcomes mucosal absorption barrier
- Allows sublingual (SL) administration to achieve relevant systemic drug exposure
- Stable SL tablet formulation

• Benefits of sublingual delivery

- Rapid drug exposure following nighttime administration
- Lower daytime exposure
- Avoids first-pass metabolism
 - Reduces risk of pharmacological interference from major metabolite

No recognized abuse or dependency concerns

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TNX-102 SL 5.6 mg: Results from Completed Positive Phase 3 RELIEF Study

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Completed Positive Trial in FM:

- Topline results announced in December 2020
- 503 participants randomized across 39 sites in U.S.
- 95% of participants were women

Topline Efficacy Results:

- Achieved statistical significance in the pre-specified primary efficacy endpoint of reducing daily pain (p=0.01)
- Activity shown in key secondary endpoints measuring improvements in sleep, fatigue and global FM symptoms and function

Safety:

- Well tolerated; side effects consistent with known side effects of cyclobenzaprine; no new safety signals observed

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Positive Phase 3 F304/RELIEF Study: Design

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General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia in 39 U.S. sites (full sample size N=503)
- Adaptive Design: one unblinded interim analysis based on 50% of randomized participants

TNX-102 SL once-daily at bedtime

5.6 mg (2 x 2.8 mg tablets)¹

N= 248

Placebo once-daily at bedtime

N= 255

14 weeks

¹Two week run-in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose

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Primary endpoint (Week 14):

- Daily diary pain severity score change (TNX-102 SL 5.6 mg vs. placebo) from baseline in the weekly average as measured by the numerical rating scale (NRS), using mixed model repeated measures analysis with multiple imputation (MMRM with MI)

Key Secondary endpoints (Week 14):

- 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 T-score
- PROMIS Fatigue instrument T-score
- Weekly average of the daily diary assessment of sleep quality

Pivotal efficacy study to support NDA approval



F304/RELIEF Study Topline Data: Statistical Significance Achieved on Pre-specified Primary Efficacy Endpoint (p=0.01)

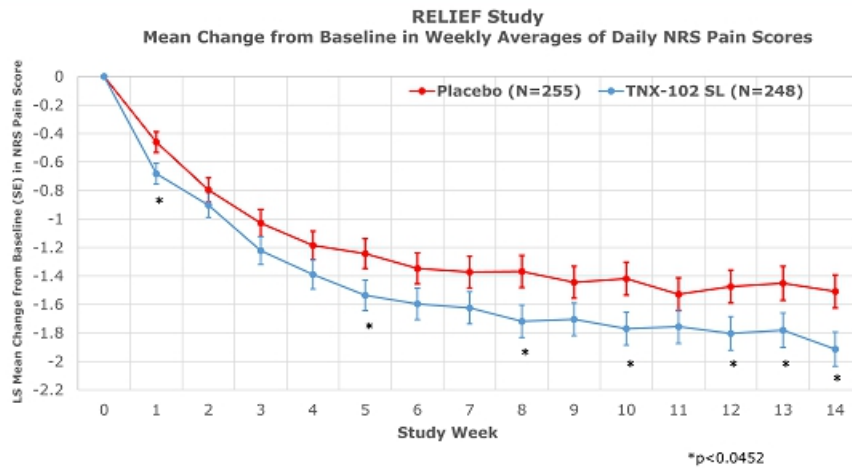
Primary Outcome Measure at Week 14	Placebo (N=255)	TNX-102 SL (N=248)	Treatment Difference	P value
	LS Mean Change from Baseline (SE)	LS Mean Change from Baseline (SE)	Difference in LS Mean Change from Baseline Between TNX-102 SL and Placebo (SE)	
Daily Pain Diary ¹ , NRS	-1.5 (0.12)	-1.9 (0.12)	-0.4 (0.16)	0.010*

Statistical Method: Mixed Model Repeated Measures analysis with Multiple Imputation
 *p<0.0452 (requisite p-value hurdle for full study after Interim Analysis)
¹ Same primary endpoint analysis for FDA approvals of Cymbalta® and Lyrica® in fibromyalgia
 Abbreviations: LS = least squares; NRS = numeric rating scale; SE = standard error

- Primary efficacy analysis also supported by an exploratory 30% responder analysis of daily diary pain, which indicated 46.8% on TNX-102 SL versus 34.9% on placebo achieved a 30 percent or greater reduction in pain (logistic regression; odds ratio [95% CI]: 1.67 [1.16, 2.40]; p=0.006)
 - 30% responder analysis was the primary analysis in F301 AFFIRM study of TNX-102 SL 2.8 mg
 - Also was the same primary endpoint analysis for FDA approval of Savella® for fibromyalgia



F304/RELIEF Study: Primary Efficacy Endpoint Results (continued)





F304/RELIEF Study: Key Secondary Efficacy Endpoints

Outcome Measure at Week 14	Intent-to-Treat Analysis ¹	P-value
Non-Specific		
Patient Global Impression of Change	Responder Analysis: Proportion "Much Improved" or "Very Much Improved"	0.058
Fibromyalgia Syndrome-Related		
FIQ-R Symptom Domain	Mean Change from Baseline	0.007 [#]
FIQ-R Function Domain	Mean Change from Baseline	0.009 [#]
PROMIS Fatigue	Mean Change from Baseline	0.018 [#]
Daily Sleep Quality Diary, NRS	Mean Change from Baseline	<0.001 [#]
PROMIS Sleep Disturbance	Mean Change from Baseline	<0.001 [#]

[#] nominally significant at p<0.0452

¹ Combined periods (pre- and post-interim analysis); responder analysis is by Logistic Regression (missing = non-responder); the five mean change analyses are by Mixed Model Repeated Measures with Multiple Imputation

Abbreviations: FIQ-R = Fibromyalgia Impact Questionnaire - Revised; NRS = numeric rating scale; PROMIS = Patient-Reported Outcomes Measurement Information System

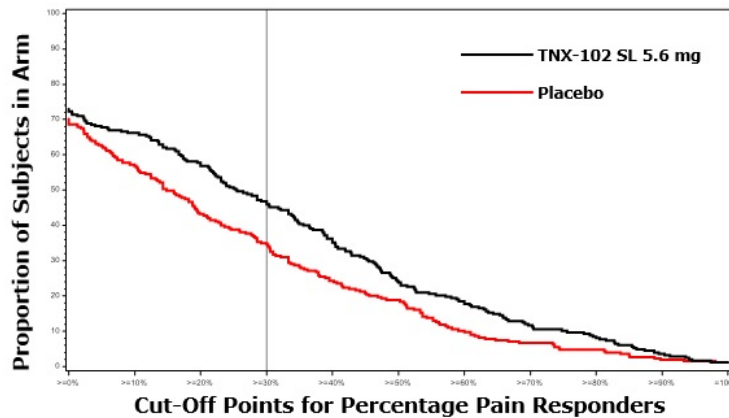
*TNX-102 SL is in clinical stage of development and not approved for any indication

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F304/RELIEF Study: Continuous Responder Analysis (CRA) Graph

- The CRA graph allows one to see the proportion of responders over an entire range of cut-off points
- For example, >=30% improvement in pain is considered clinically meaningful in pain studies
- Looking at that vertical line at >=30% and visualizing a horizontal line to the y-axis tells you the proportion of each arm that achieved that level of pain improvement or better (47% for TNX-102 SL and 35% for placebo)
- It can be seen that TNX-102 SL separates from placebo, always at a higher proportion, up to about >=95% improvement



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Adverse Events*(AEs) in F304/RELIEF Study

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Those AEs reported at rate of greater than 5% in either treatment arm

Systemic Adverse Events	Placebo N=255	TNX-102 SL 5.6 mg N=248
Somnolence/Sedation	1.2%	5.6%
Local Administration Site Reactions		
Tongue/mouth numbness	0.8%	17.3%
Tongue/mouth pain/discomfort	2.0%	11.7%
Taste impairment	0.4%	6.5%
Tongue/mouth tingling	0.4%	5.6%

* Table reports only AEs at rate of greater than 5% in either treatment arm

Discontinuation rate due to adverse events: 8.9% TNX-102 SL compared to 3.9% for placebo

No serious and unexpected AEs in RELIEF related to TNX-102 SL

- Systemic AEs comparable with prior studies
- Oral AEs similar to prior studies with TNX-102 SL, although tongue/mouth numbness at about half the rate in RELIEF

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Safety and Tolerability in F304/RELIEF Study

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- No new safety signals in RELIEF at TNX-102 SL 5.6 mg dose
- 82.3% in active arm and 83.5% in placebo arm completed the study
- 8.9% in active arm and 3.9% in placebo arm discontinued due to adverse events
- 7 SAEs in study: 2 in active arm and 5 in placebo arm
 - Of 2 in active arm, one was motor vehicle accident with multiple bone fractures, and other was pneumonia due to infection; both deemed unrelated to TNX-102 SL
- Similar oral administration site reactions as in prior studies with TNX-102 SL
- Overall low rates of systemic side effects, highest being somnolence/sedation at 5.6% in active group, 1.2% in placebo

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TNX-102 SL 5.6 mg for Fibromyalgia: 2nd Phase 3 F306/RALLY Study – Enrollment Ongoing

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General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia in approximately 40 U.S. sites (N=670)
- Adaptive Design: one unblinded interim analysis based on 50% of randomized participants¹

TNX-102 SL once-daily at bedtime

5.6 mg (2 x 2.8 mg tablets)²

N= ~335

Placebo once-daily at bedtime

N= ~335

14 weeks

Primary endpoint (Week 14):

- Daily diary pain severity score change (TNX-102 SL 5.6 mg vs. placebo) from baseline in the weekly average as measured by the numerical rating scale (NRS), using mixed model repeated measures analysis with multiple imputation (MMRM with MI)

Key Secondary endpoints (Week 14) include¹:

- Daily diary sleep quality NRS score change
- Fibromyalgia Impact Questionnaire – Revised (FIQR): Symptoms Domain change
- PROMIS Fatigue instrument change

Interim results expected in 3rd quarter 2021

- Interim cohort recruited in March 2021

Topline results expected in 1st quarter 2022

Potential pivotal efficacy study to support NDA approval

¹Pending agreement from FDA on statistical analysis plan

²Two week run in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose

PROMIS = Patient-Reported Outcomes Measurement Information System

Approved Fibromyalgia Pharmacotherapies

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Pfizer

- Drug: Lyrica® or pregabalin (U.S. patent expired in 2018)
- Approved: 2004
- Mechanism: modulates nerve impulses involved in the transmission of pain through selective binding to the alpha2-delta protein of the voltage-gated calcium channels in CNS tissues
- Peak Sales: Approximately \$5 billion (including all approved indications)

Lilly

- Drug: Cymbalta® or duloxetine (U.S. patent expired 2014)
- Approved: 2004
- Mechanism: serotonin and norepinephrine reuptake inhibitor (SNRI)
- Peak Sales: Approximately \$5 billion (including all approved indications)

Abbvie (developed by Forest Laboratories)

- Drug: Savella® or milnacipran (on patent)
- Approved: 2009
- Mechanism: serotonin and norepinephrine reuptake inhibitor (SNRI)
- Peak Sales: Approximately \$130 million (approved for fibromyalgia indication only)



Other Fibromyalgia Pharmacotherapies in Development in the U.S.

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Axsome Therapeutics - AXS-14

- Drug: esreboxetine
- Mechanism: Selective norepinephrine reuptake inhibitor
- Developmental Stage: At least mid-Phase 3 (Phase 2 and Phase 3 trial positive*)

Aptinyx - NYX-2925

- Drug: ((2S, 3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspiro(3.4)octan-2-yl)butanamide)
- Mechanism: NMDA receptor modulator
- Developmental Stage: Phase 2 study is "active, not recruiting"

Teva - Ajoovy®

- Drug: fremanezumab
- Anti-CGRP antibody
- Developmental Stage: Phase 2 proof-of-concept study "recruiting"

Virios Therapeutics - IMC-1

- Drug: Combination of famciclovir and celecoxib
- Anti-viral (herpes simplex) and COX-2 inhibitor non-steroidal anti-inflammatory drug (NSAID)
- Developmental Stage: Phase 2a completed

*licensed from Pfizer, Jan 2020

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TNX-102 SL Intellectual Property – U.S. Protection expected until 2035

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Composition of matter (eutectic): Protection expected to 2034/2035

- United States Patent and Trademark Office (USPTO) issued United States Patent No. 9636408 in May 2017, Patent No. 9956188 in May 2018, Patent No. 10117936 in November 2018, and Patent No. 10864175 on December 2020
- European Patent Office (EPO) issued European Patent No. 2968992 in December 2019 (validated in 37 countries). Opposition filed in October 2020 by Hexal AG
- China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019
- Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018
- 8 granted patents (Indonesia, Saudi Arabia, New Zealand, Australia, Mexico, Taiwan, Israel, South Africa)
- 11 patent applications pending (1 being allowed in Canada)

Composition of matter (sublingual): Protection expected to 2033

- NZIPO issued New Zealand Patent No. 631144 in March 2017 and Patent No. 726488 in January 2019
- Taiwanese Intellectual Property Office issued Taiwanese Patent No. 1590820 in July 2017, Patent No. 1642429 in December 2018 and Patent No. 1683660 in February 2020
- Australian Patent Office issued Australian Patent No. 2013274003 in October 2018 and Patent No. 2018241128 in September 2020
- JPO issued Japanese Patent No. 6259452 in December 2017
- 20 patent applications pending (1 being allowed in Mexico)

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Long COVID or Post-acute Sequelae of COVID-19 (PASC)

- Symptoms can include fatigue, sleep disorders, pain, fevers, shortness of breath, cognitive impairment described as "brain fog", gastrointestinal symptoms, anxiety, and depression
- Can persist for months and can range in severity from mild to incapacitating
- Occurs in more than 30% of patients.²
- While typically associated with moderate or severe COVID-19, Long COVID can occur after mild COVID-19 or even after asymptomatic SARS-CoV-2 infection

Long COVID Overlap with Fibromyalgia

- Long COVID has been compared to fibromyalgia because of the common symptoms of sleep disturbance, persistent pain, fatigue, and brain fog³
- Like fibromyalgia, is experienced by women at a higher rate, approximately four times more, than that of men⁴
- Long COVID is a chronic disabling condition that is expected to result in a significant global economic burden⁵
- In response to the urgent need for therapies that address PASC, Congress awarded \$1.15 billion to the National Institutes of Health to study Long COVID last December⁶

¹Feb. 24, 2021 - White House COVID-19 Response Team press briefing; Feb 25, 2021 - policy brief from the World Health Organization on long COVID

²Halbandian, Ani, et al. "Post-acute COVID-19 syndrome." *Nature Medicine* (2021): 1-15.

³Clewley DJ, et al. *Pain*, 2020 Aug; 161(8): 1694-1697.

⁴Cox, D. "Why are women more prone to long Covid?" *The Guardian*. 13 Jun 2021 <https://www.theguardian.com/society/2021/jun/13/why-are-women-more-prone-to-long-covid>

⁵Briggs, Andrew, and Anna Vassalli. "Count the cost of disability caused by COVID-19." (2021): 502-505.

⁶The NIH provision of Title III Health and Human Services, Division M--Coronavirus Response and Relief Supplemental Appropriations Act, 2021, of H.R. 133, The Consolidated Appropriations Act of 2021. The bill was enacted into law on 27 December 2020, becoming Public Law 116-260.

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Role of sleep disturbance more established in common psychiatric and neurological/pain disorders

- Recognized as a core symptom of many of these disorders
- Traditional sleep medications, which increase sleep quantity, may not provide benefit (benzodiazepines in major depression) or are contraindicated

Psychiatric Disorders

- Stress Disorders (PTSD)
- Mood Disorders (Depression)
- Anxiety Disorders
- Addiction (Alcohol Use Disorder)

Psychiatric Symptoms of Neurological Disorders

- Agitation in Alzheimer's
- Psychosis in Parkinson's, Alzheimer's and other dementias

Chronic Pain States

- Chronic wide-spread pain (fibromyalgia)
- Osteoarthritis

Growing recognition that there are many disorders where sleep disturbances may have a role in the pathophysiology (cardiovascular, metabolic, neurologic)

- Sleep quality plays a homeostatic role *in several disorders*



TNX-1800¹

- **Drug Product:** modified recombinant horsepox live virus vaccine produced in cell culture for percutaneous administration
- **Targeted Indication:** COVID-19 vaccine

¹TNX-1800 is an investigational new biologic and has not been approved for any indication.

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TNX-1800¹: a COVID-19 Vaccine Candidate

- **Utilizes Tonix's proprietary horsepox virus as a vector**
 - Encodes a protein from SARS-CoV-2, the cause of COVID-19
 - Developed in collaboration with University of Alberta, Canada
- **Animal testing with Southern Research Institute**
 - Non-human primate immune response positive results reported in 4th quarter 2020
 - Non-human primate CoV-2 challenge testing positive data reported in 1st quarter 2021
 - TNX-1800 vaccinated animals had undetectable² CoV-2 by PCR in upper and lower airways³
- **Manufacturing agreement with FUJIFILM Diosynth**
 - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
 - Expect GMP⁴ clinical supply to be ready for human trials targeted to begin in 1st half of 2022⁵

¹TNX-1800 (horsepox/CoV-2 spike live vaccine) is at the pre-IND stage of development

²Less than 1,000 genomes by PCR

³Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage

⁴Good Manufacturing Practice = GMP

⁵We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones

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COVID-19 Vaccines with Emergency Use Authorization (EUA): Still Uncertainty

Durability of protection

- Are vaccinated people protected one year later?
- Need for annual vaccinations with mRNA vaccines? Will annual boosters work?
- Durable protection is associated with T cell response

Detecting and mitigating vaccine failure

- Need a strategy for identifying individuals at risk after vaccination and second line vaccines

No biomarker of protection

- No test to establish vaccine protection

Current and future variants

- Unknown effectiveness of existing vaccines



Potential Profile of TNX-1800 Compared to EUA Covid-19 Vaccines

Criteria	EUA Vaccines	TNX-1800
Number of shots	One – two	One
Duration	Unknown	Years / decades
Boosters	Unknown	Not required
Protection from variants	Unknown	Likely provides protection
Forward Transmission	Probably prevents (for PFE)	Likely prevents
Biomarker	None	Yes - "Take"
Manufacturing	Complex	Conventional
Glass sparing packaging	No	Yes
Shipping and storage	Cold Chain	Standard refrigeration
Protection from smallpox	No	Yes



Warp-Speed COVID-19 Vaccines: Live Virus Vaccines Take Longer to Develop

• **mRNA**

- Moderna (mRNA-1273, LNP¹-encapsulated CoV-2 Spike ["Spike"] mRNA) EUA²
- Pfizer & BioNTech (LNP-encapsulated Spike mRNA) EUA

• **Subunit**

- Sanofi/GSK (recombinant Spike protein with adjuvant³) In Phase 3
- Novavax (NVX-CoV2373, recombinant Spike protein with adjuvant⁴) In Phase 3

• **Non-replicating virus**

- J&J (Ad26.COV2-S, Ad26 encoding Spike) EUA in U.S. and Canada
- Astra-Zeneca/Oxford (AZD1222, ChAdOx-1 encoding Spike) In Phase 3 (EUA in UK, Europe, Canada and India)

• **Live attenuated virus**

- Merck (TMV-083, modified measles⁵-encoding Spike) Terminated Jan '21 - Phase 1⁶
- Merck (V591, pseudo-typed VSV⁷-encoding Spike) Terminated Jan '21 - Phase 1⁶

¹Lipid Nanoparticle = "LNP"

²Emergency Use Authorization = "EUA"

³GSK adjuvant A503 contains squalene, DL- α -tocopherol and polysorbate

⁴Novavax adjuvant Matrix-M1 contains saponin extracted from the Quillaja saponaria Molina tree

⁵Measles-based vaccine, acquisition of Themis, collaboration with Institute Pasteur

⁶[Merck Discontinues Development of SARS-CoV-2/COVID-19 Vaccine Candidates; Continues Development of Two Investigational Therapeutic Candidates - Merck.com](#)

⁷VSV = vesicular stomatitis virus; collaboration with IAVI = International AIDS Vaccine Initiative



COVID-19 Vaccine Landscape

• **We expect more than one vaccine will be approved by FDA**

- Different vaccines for different individuals

• **More than 150 vaccines in development**

- Diversity of approaches is important since protective immunity is not yet understood
- Technologies range from never tested before (mRNA) to 220 years old
- Uncertainty exists around efficacy, durability and importantly, safety

• **Live attenuated vector systems in development include:**

- Tonix (horsepox), Tonix (bovine parainfluenza), Zydus Cadila (measles-based)



Live, Attenuated Virus Vaccines for Other Infectious Diseases¹

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- **Long term, durable immunity**
 - Expected to stimulate T cells and provide years to decades of protection
- **Single administration, scalable manufacturing**
 - Low dose is amplified by replication, mRNA and protein synthesis at vaccination site
- **Block forward transmission (infectivity)**
 - Key to conferring herd immunity and protecting immunocompromised

¹For example, the eradication of smallpox, containment of measles, mumps, and rubella
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TNX-1800¹: Engineered for Long-term Immunity

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Based on “vaccinia” vaccine developed more than 200 years ago by Dr. Edward Jenner to prevent smallpox

- TNX-1800 has 99.7% colinear identity with circa 1860 smallpox vaccine²
- Eradicated smallpox (only viral disease ever eradicated)
- Elicits durable (many decades) T cell immunity
- Single dose protection without adjuvants
- Manufacturable at scale
- Minimal “cold chain” supply issues
- Glass-sparing packaging owing to small unit dose

Genetic analysis of early vaccines indicates that Tonix’s “horsepox” is closely related to Edward Jenner’s “vaccinia”

- Modern “vaccinia” evolved during the 220 years it was propagated by primitive methods – for over 120 years before “viruses” were identified

¹TNX-1800 (horsepox/Cov-2 spike live vaccine) is at the pre-IND stage of development

²Brinkmann A et al, Genome Biology (2020) 21:286 <https://doi.org/10.1186/s13059-020-02202-0>

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TNX-1800 Vaccination of Non-Human Primates Elicited Anti-SARS-CoV-2 Neutralizing Antibodies and Skin Reaction or “Take” in All Eight Animals

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STUDY DESIGN:

- Compares TNX-1800 to TNX-801 (horsepox virus, no CoV-2 protein) at two doses in non-human primates. A control group received a placebo vehicle control.
- Each of these five groups (TNX-1800 high and low dose; TNX-801 high and low dose and placebo) includes four animals.

TOLERABILITY:

- TNX-1800 and TNX-801 were well tolerated at both doses.

NEUTRALIZING ANTI-CoV-2 ANTIBODIES:

- At Day 14 after a single vaccination, all eight of the TNX-1800 vaccinated animals made anti-CoV-2 neutralizing antibodies ($\geq 1:40$ titer).
- None of the eight TNX-801 vaccinated control animals, or any of the four animals in the placebo group, made anti-CoV-2 neutralizing antibodies ($\leq 1:10$ titer).
- Level of neutralizing anti-CoV-2 antibody production was similar between the low and high dose TNX-1800 groups (1×10^6 Plaque Forming Units [PFU]) and 3×10^6 PFU, respectively.

SKIN TAKE BIOMARKER:

- All 16 animals vaccinated with either dose of TNX-1800 or the control TNX-801 manifested a “take”, or cutaneous response, signaling that the horsepox vector elicited a strong T cell immune response.

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TNX-1800 Vaccination and SARS-CoV-2 Challenge of Non-Human Primates Findings and Conclusions

34

CHALLENGE WITH SARS-COV-2:

- Six days after challenge with SARS-CoV-2, TNX-1800 vaccinated animals had undetectable¹ SARS-CoV-2 in upper or lower airways².

DOSE:

- Supports the expectation that TNX-1800 at the low dose of 1×10^6 PFU is an appropriate dose for a one-shot vaccine in humans.
- Indicates that 100 doses per vial is the target format for commercialization, which is suited to manufacturing and distribution at large scale.

CONCLUSIONS:

- TNX-1800 induces a strong immune response to SARS-CoV-2 in non-human primates and is capable of decreasing viral load in upper and lower airways consistent with decreased transmission.
- Data confirm that “take” is a biomarker of a strong immunological response to TNX-1800’s vector, horsepox virus vaccine, and also indicate that “take” is predictive of a neutralizing antibody response to CoV-2 spike protein and protection of upper and lower airways.

¹Less than 1,000 genomes by PCR

²Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage

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Why Use a Horsepox Platform for a Vaccine?

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Horsepox can be engineered to express foreign genes

- Lack of persistence or genomic integration in the host
- Strong immunogenicity as a vaccine
- Readily manufacture at scale
- Live, attenuated vaccine – direct antigen presentation



Potential advantages of horsepox over vaccinia

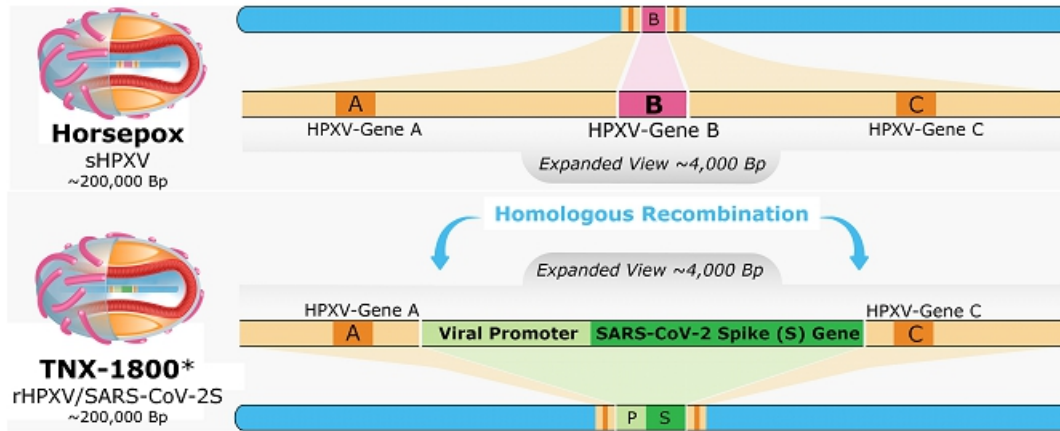
- Maintains strong immunogenicity with potentially improved tolerability
- Relative to non-replicating vaccinia, horsepox's replication in human cells provides direct antigen presentation, which is expected to trigger a T cell immune response, by Class I Major Histocompatibility Complex (MHC) Antigens
- Horsepox may behave differently than vaccinia as a vector, in part because of its different repertoire of genes that modulate immune responses and host range

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TNX-1800 is Based on a Horsepox Virus (HPXV) Vector Designed to Express SARS-CoV-2 S Protein

36



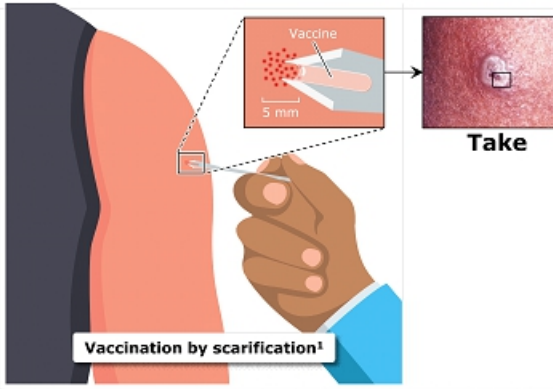
*TNX-1800 is at the pre-IND stage of development

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Vaccinia Induces a Skin Reaction Called "Take" – Described by Dr. Edward Jenner

37



Vaccination by scarification¹

Take

- **Biomarker of protection**
 - Smallpox was eradicated using this marker
 - Revaccination indicated for recipients without "take"
- **Measure of T cell immunity**
 - No need for blood draws or complex laboratory studies
 - No other functional T cell assay is approved or in clinical use for vaccination

¹Example of major cutaneous reaction, or "take," resulting from a replication-competent live-virus vaccine delivered via scarification, indicating successful vaccination¹⁻³

1. Fulginiti VA, et al. *Clin Infect Dis*. 2003;37(2):241-250.

2. Liu L, et al. *Nature Med*. 2010;16(2):224-228.

3. Centers for Disease Control and Prevention. Accessed April 15, 2020.

<https://phil.cdc.gov/Details.aspx?pid=3276>

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Unique Challenges of SARS-CoV-2

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<p>SARS</p> <p>Rate of death^{1,2} ~10%</p> <p>Deaths² 744</p> <p>Rate of infectivity¹ 0.4</p> <p>Incubation time² 2-7 days</p> <p>Asymptomatic³ ~13%</p>	<p>The death rate for COVID-19 is significantly lower compared to SARS.^{1,2,4} However, due to its virulence, SARS-CoV-2 has resulted in far more deaths⁵</p> <p>SARS-CoV-2 is more infectious, has a longer incubation time, and presents asymptotically in more individuals, making it highly spreadable¹</p>	<p>SARS-CoV-2</p> <p>Rate of death^{1,4} 0.003% - 5.4%</p> <p>Deaths (as of May 2021)⁵ >3.2M</p> <p>Rate of infectivity^{1,4} ~2.5</p> <p>Incubation time^{2,4} 6-14 days</p> <p>Asymptomatic⁴ ~40%</p>
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1. Ceccarelli M, et al. *Eur Rev Med Pharmacol Sci*. 2020;24(2781-2783).

2. Rabaan AA, et al. *Le Infezioni in Medicina*. 2020;28(2):174-184.

3. Wilder-Smith A, et al. *Emerg Infect Dis*. 2020;11(7):1142-1145.

4. Centers for Disease Control and Prevention. Accessed November 2020. <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/planning-scenarios.html>

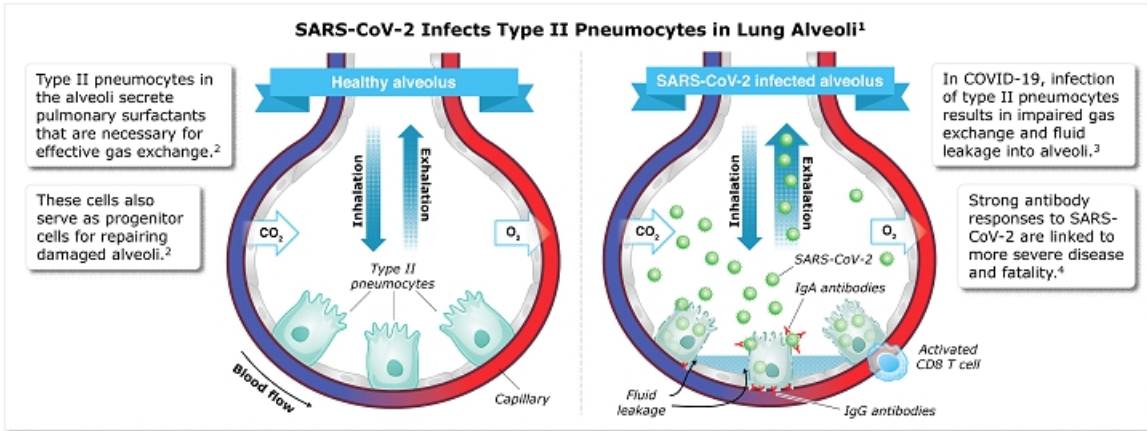
5. Johns Hopkins University. Accessed May 2021. <https://coronavirus.jhu.edu/map.html>

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Infection of Type II Pneumocytes Can Lead to Lethal Respiratory Illness

39



1. Knudsen L, et al. *Astrochem Cell Biol*. 2018;150(6):661-676.
2. Mason RJ. *Am J Physiol Lung Cell Mol Physiol*. 2020;319(3):L119-L120.

3. Xu Z, et al. *Lancet Respir Med*. 2020;8(4):420-422.
4. Lee WS, et al. *Nat Microbiol*. 2020;5:1185-1191.

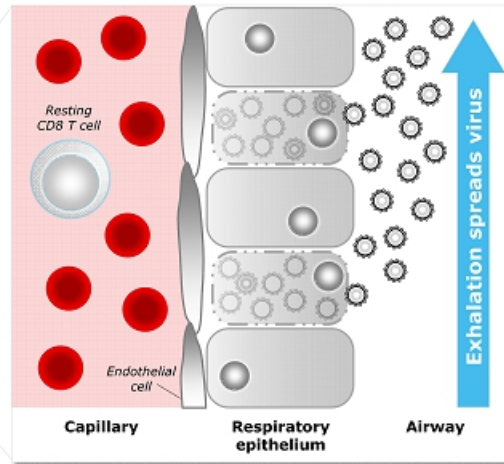
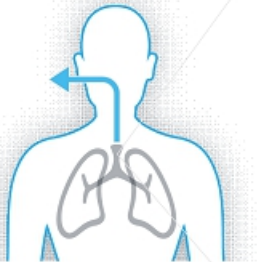
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SARS-CoV-2 Hijacks the Respiratory System to Spread Contagious Virus

40

- Virus factories release virions by continuous budding
- Breathing, speaking or coughing has the potential to release virions into the air and transmit infection to others



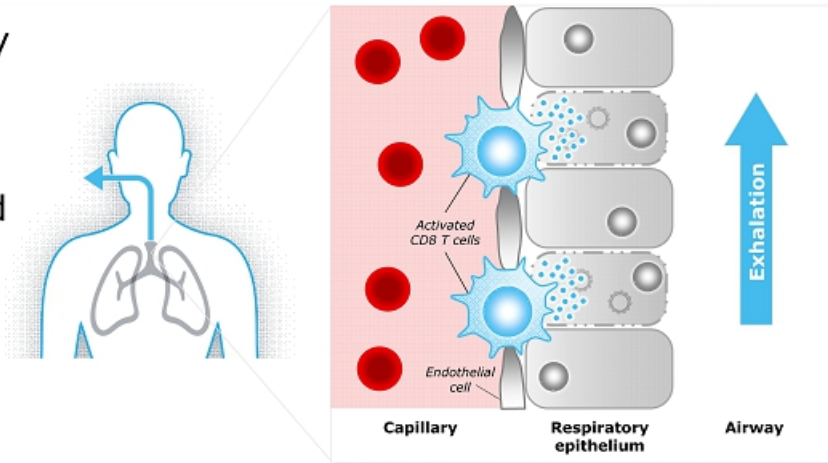
Bar-On YM, et al. *Sci*. 2020;9:e57309.

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CoV-2 Specific T Cells Kill the Virus Factories

41

- Natural immunity or vaccine protection has the potential to decrease forward transmission
- T cells specifically kill virally infected cells



Bar-On Y, et al. *et al.* 2020;9:e57309.

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Contrasting T cell and Antibody Immunity

42

• T cell immunity

- **Durable or long-lived (many years)**
- Recognize fragments of pathogens on the surfaces of infected cells
- Cannot recognize pathogens directly
- Potential to clear viral infections (by killing infected cells)
- Potential to block forward transmission (contagion) by infected people

• Antibody immunity

- **Temporary or short-lived (typically 3-6 months)**
- Recognize pathogens directly
- Potential to block viral entry (by recognizing pathogens)
- Can only recognize virally infected cells that express viral surface proteins

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TNX-1800: Potential Development and Uses

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- **Potential to protect against CoV-2 Variants**

- T cell epitopes are short stretches of peptides (~8-14 aa fragments) that so far seem to be conserved between variants
- Clinical trials will test potential protection against CoV-2 variants
 - For example, the "British" (B.1.1.7), "Brazilian" (P.1) and "South African" (B.1.351) strains have emerged
 - B.1.351 may elude the protection conferred by certain vaccines against other strains

- **Pre- and Post-pandemic vaccine**

- Development will begin with clinical trials in adults
- Subsequent development will focus on children
 - Analogous to the historical use of horsepox and vaccinia as childhood immunizations to prevent (and ultimately eradicate) smallpox
- Potential to block forward transmission (contagion) by infected people
- Trial participants will be stratified by pre-existing antibody and T cell immunity
 - TNX-2100¹ skin test may be used to stratify for T cell immunity

¹TNX-2100 (SARS-CoV-2 epitope peptide mixtures for intradermal administration) is at the pre-IND stage of development
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TNX-3500¹

- **Drug Product**: sangivamycin
- **Targeted Indication**: COVID-19 antiviral

¹TNX-3500 is an investigational new drug and has not been approved for any indication.

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TNX-3500¹: SARS-CoV-2 Antiviral for the Treatment of COVID-19

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TNX-3500 (sangivamycin) – potential monotherapy antiviral²

- Licensed from OyaGen, April 2021
- Demonstrated broad spectrum antiviral (nanomolar activity against SARS-CoV-2, MERS, Ebola, and Lassa)
- Demonstrated human tolerability for chronic dosing from US National Cancer Institute studies³
- 65 times more potent than remdesivir in inhibiting SARS-CoV-2 in cell culture infectivity studies (dose to achieve IC₉₀)⁴

Potential COVID-19 combination therapy with remdesivir

- TNX-3500 antiviral effect is additive when combined with remdesivir and reduces the amount of each drug necessary for an IC₉₀
- Combination therapies for other viruses have reduced the emergence of drug resistant viral strains

Development plans

- 2nd quarter 2021: Plan to initiate animal pharmacokinetic and efficacy studies

¹TNX-3500 is in the pre-IND stage of development and has not been approved for any indication.

²Bennett, RP et al., *Viruses*. 2020 13(1):52. doi: 10.3390/v13010052.

³Cavins JA et al., *Cancer Chemotherapy Reports*. 1967. 51(4)

⁴Data on file, live virus BSL-4 testing conducted by NIAID in collaboration with OyaGen



46

TNX-2300¹

- **Drug Product:** modified parainfluenza virus live virus vaccine for percutaneous administration produced in cell culture
- **Targeted Indication:** COVID-19 vaccine

¹TNX-2300 is an investigational new biologic and has not been approved for any indication.



TNX-2300, 2nd SARS-CoV-2 Vaccine Platform: Bovine Parainfluenza (BPI) Virus

47

Collaboration with Kansas State University to develop a vaccine candidate for the prevention of COVID-19

- Utilizes a novel live attenuated vaccine vector platform and the CD40-ligand to stimulate T cell immunity
- TNX-2300¹ drives expression of CoV-2 spike and CD40-L

Live attenuated vaccines based on bovine parainfluenza virus²⁻⁶

- Previously has been shown to be an effective antigen delivery vector in humans, notably well tolerated in infants and children
- Vector is well suited for mucosal immunization using a nasal atomizer, but it can also be delivered parenterally

¹Pre-IND stage of development; ²Halle, AA et al. *J Gen. Virology* (2003) 84:2153–2162; ³Halle, AA et al. *J Virology* (2000) 74 (24): 11626–11635; ⁴Karron RA et al. *J Inf Dis* (1995) 171: 1107–14; ⁵Karron RA et al. *Vaccine* (2012) 30: 3975– 3981; ⁶Schmidt AC et al. *J Virology* (2001) 75(10): 4594–4603
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48

TNX-2100¹

- **Drug Product:** synthetic peptides derived from the sequence of SARS-CoV-2 and related variants for intradermal administration
- **Targeted Indications:** *in vivo* diagnostic skin test for SARS-CoV-2 Exposure, measurement of delayed-type hypersensitivity (DTH) to SARS-CoV-2; aid to the diagnosis and management of COVID-19

¹TNX-2100 is an investigational new *in vivo* diagnostic and has not been approved for any indication.

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TNX-2100¹: Potential Skin Test to Measure SARS-CoV-2 Exposure and T Cell Immunity

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TNX-2100 (SARS-CoV-2 epitope peptide mixtures for intradermal administration)

- Based on mixtures of synthetic peptides for intradermal administration
- Designed to elicit delayed-type hypersensitivity (DTH) in individuals who have been exposed to SARS-CoV-2 or who have been successfully vaccinated
- Potential to measure the presence and strength of functional *in vivo* T cell immunity

Potentially scalable test for widespread use

- Adaptive Biotech's T Detect™ COVID received FDA EUA – based on genetic analysis of T cell receptors
- Other tests² for T cell immunity to SARS-CoV-2 require specialized laboratories and are not amenable to standardization

¹TNX-2100 is in the pre-IND stage of development and has not been approved for any indication.

²Intracellular cytokine staining (ICS) measured by flow cytometry after *in vitro* stimulation of purified peripheral blood mononuclear cells
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TNX-2100: Potential Uses and Development Plans

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TNX-2100 has the potential to serve as:

- a biomarker for cellular immunity and protective immunity
- a method to stratify participants in COVID-19 vaccine trials by immune status
- an endpoint in COVID-19 vaccine trials
- a biomarker of durability of vaccine protection

FDA feedback on pre-IND meeting questions received in February 2021

Development plans

- 4th quarter 2021: Plan to initiate first-in-human clinical testing pending clearance of IND



TNX-1300¹

- **Drug Product:** recombinant T172R/G173Q double-mutant cocaine esterase, produced in *E. coli*, delivered as a 200 mg lyophilized drug product for *i.v.* administration
- **Targeted Indication:** for the treatment of cocaine intoxication
- **FDA Breakthrough Therapy Designation**

¹TNX-1300 is an investigational new biologic and has not been approved for any indication.

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TNX-1300* for the Treatment of Cocaine Intoxication

Recombinant protein that degrades cocaine in the bloodstream¹

- Double-mutant cocaine esterase (CocE)
- CocE was identified in a bacterium (*Rhodococcus*) that use cocaine as its sole source of carbon and nitrogen and that grow in soil surrounding coca plants²
- CocE catalyzes the breakdown of cocaine into metabolites ecgonine methyl ester and benzoic acid

Phase 2 study completed by Reckitt Benckiser (TNX-1300 was formerly RBP-8000)³

- Volunteer cocaine abusers received cocaine 50 mg *i.v.* infusion over 10 minutes
- TNX-1300 given one minute after completion of cocaine infusion
 - Rapidly reversed the physiologic effects of cocaine; cocaine plasma exposures dropped by 90% within two minutes
 - Well tolerated with the most frequently reported adverse events being gastrointestinal disorders (including dry mouth, nausea); nervous systems disorders (including headache, dizziness) and skin and subcutaneous tissue disorders (including hyperhidrosis, dermatitis)

*TNX-1300 (T172R/G173Q double-mutant cocaine esterase 200 mg, *i.v.* solution) is an investigational new biologic and has not been approved for any indication.

¹ Gao D et al, Mol Pharmacol. 2009. 75(2):318-23.

² Bresler MM et al, Appl Environ Microbiol. 2000. 66(3):904-8.

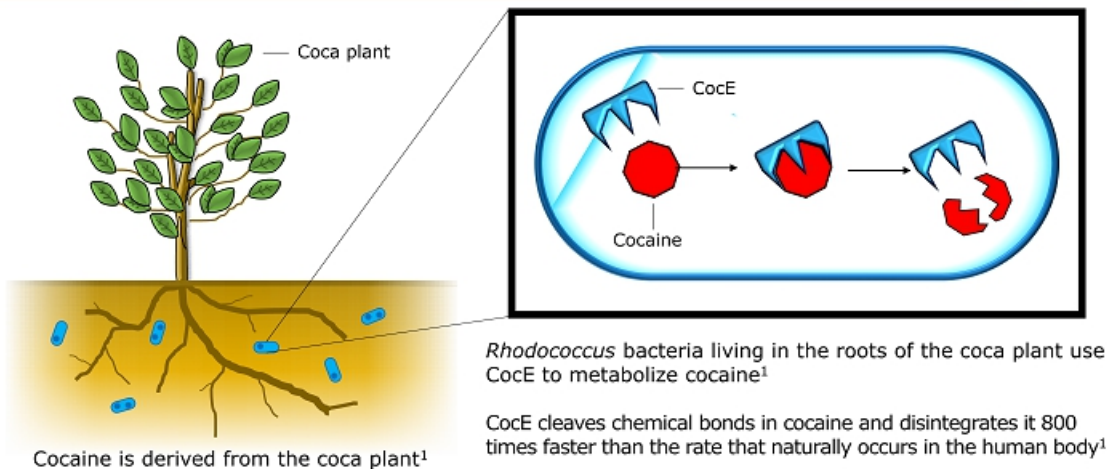
³ Nasser AF et al, J Addict Dis. 2014;33(4):289-302.

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TNX-1300 (Cocaine Esterase or CocE) Is a Fast-acting Cocaine Antidote

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¹Narasimhan D et al. *Future Med Chem.* 2012.

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TNX-1300 Development Plan

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- **Targeting to initiate a Phase 2 open-label, randomized pilot study of TNX-1300 in the third quarter of 2021**
- **Emergency department (ED) setting with patients coming in for treatment of cocaine and/or polysubstance intoxication**
- **Objectives**
 - Primary: To evaluate the safety of TNX-1300 in the ED setting
 - Secondary:
 - To evaluate TNX-1300 in the management of cardiovascular (CV) and other signs and symptoms associated with cocaine intoxication compared to usual care (UC) alone
 - To demonstrate reduction of plasma cocaine, cocaethylene, and ecgonine methyl ester levels after TNX-1300 administration and compare cocaine and cocaethylene levels of TNX-1300 group to those in UC alone

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TNX-1900¹

- **Drug Product**: potentiated oxytocin nasal spray solution
- **Targeted Indications**: for the treatment of migraine, craniofacial pain, and insulin resistance

¹TNX-1900 is an investigational new drug and has not been approved for any indication.

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TNX-1900 (Intranasal Potentiated Oxytocin) for the Treatment of Migraine and Craniofacial Pain – Overview

Novel intranasal (*i.n.*) oxytocin (OT) formulation being developed as a prophylactic treatment for chronic migraine

- Based on a propriety formulation of oxytocin*, a naturally occurring human hormone that acts as a neurotransmitter in the brain, and magnesium
- Magnesium is known to potentiate the binding of oxytocin to its receptor¹

Clinical and preliminary research has shown that low oxytocin levels in the body can lead to increase in headache frequency, and that increased oxytocin levels can relieve headaches

- Certain other chronic pain conditions are also associated with decreased oxytocin levels

Oxytocin when delivered via the nasal route, results in enhanced binding of oxytocin to receptors on neurons in the trigeminal system, inhibiting transmission of pain signals

Intranasal oxytocin has been shown in animals that it can also block CGRP release, a pathway known to be critical to the pathogenesis of migraine attacks.

*Oxytocin is approved by the U.S. Food and Drug Administration (FDA) as Pitocin®, an intravenous infusion or intramuscular injection drug, for use in pregnant women to induce labor. An intranasal form of oxytocin was marketed by Novartis to assist in nursing as Syntocinon®, but the product was withdrawn and the New Drug Application (NDA) has been discontinued.
1. Antoni and Chadio, 1989

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TNX-1900 for the Treatment of Migraine – Prevalence

57

One billion individuals worldwide suffer from migraines (~14% of population)¹

Migraine is the second leading cause of years lived with disability¹

In U.S., the estimated cost of all migraine headaches was \$78 billion in 2014²

- Approximately 30% of those costs (\$23 billion) were direct medical costs

Chronic migraine (≥ 15 headaches / month) effects about 1-2% of individuals³

- 75-150 million individuals worldwide
- 3-7 million in the U.S.

CGRP antibodies are the only migraine specific prophylaxis drugs approved in decades

- Requires parenteral administration (systemic effects on peripheral CGRP pathways)
- Long term safety concerns with prolonged systemic blockade of CGRP receptor⁴

¹ GBD 2016 Headache Collaborators, Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol 2018; 17: 954–76

² Gooch, C. L., et al., The Burden of Neurological Disease in the United States: A Summary Report and Call to Action. Ann Neurol. 2017; 81:479-484

³ Natoli et al., Global prevalence of chronic migraine: a systematic review, Cephalgia, 2010, 30:599-609

⁴ Robbins, At Stake: The Possible Long-Term Side Effects of CGRP Antagonists, <https://www.practicalpainmanagement.com/pain/headache/stake-possible-long-term-side-effects-cgrp-antagonists>, accessed November 8, 2020.



TNX-1900 for the Treatment of Migraine – Mechanism of Action

58

Preclinical research showed that nasally applied TNX-1900 selectively inhibits the activity of trigeminal pain-sensing nerve cells and blocks the release of CGRP

- TNX-1900 is believed to interrupt pain signals at the trigeminal ganglia by suppressing electrical impulses, a potentially different activity than drugs that just block CGRP

Migraine attacks are caused, in part, by the release of CGRP from pain-sensing nerve cells that are part of the trigeminal system

- The CGRP binds to receptors on other nerve cells and starts a cascade of events that eventually results in a severe headache. This, in turn, reduces various kinds of trigeminal nerve associated pain and prevents CGRP from acting at receptors in the central nervous system that are involved in migraine.

We believe targeted delivery of oxytocin could translate into selective blockade of CGRP release in the trigeminal ganglion and not throughout the body, which could be a potential safety advantage over systemic CGRP inhibition

- In addition, daily dosing is more quickly reversible, in contrast to monthly or quarterly dosing, giving physicians and their patients greater control



TNX-1900 for the Treatment of Migraine – Mechanism of Action (continued)

CGRP: NEUROTRANSMITTER THAT HAS BEEN VALIDATED AS KEY MIGRAINE TARGET

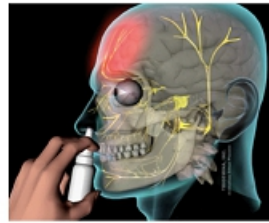
TNX-1900 believed to partially block release of CGRP in the trigeminal nerve

Proprietary Nasal to Brain Delivery

Permeates nasal mucosa
Transported to trigeminal system and brain
Oxytocin Receptors Co-Localize with CGRP in most Trigeminal Ganglia Neurons



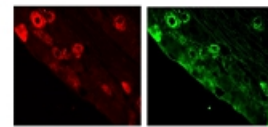
HEAD PAIN



PATIENT USES
TNX-1900



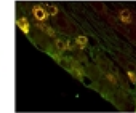
TARGETED
DELIVERY



Oxytocin Receptors

CGRP

Overlay of Oxytocin Receptors and CGRP Staining



Abbrev. CGRP, calcitonin gene-related peptide

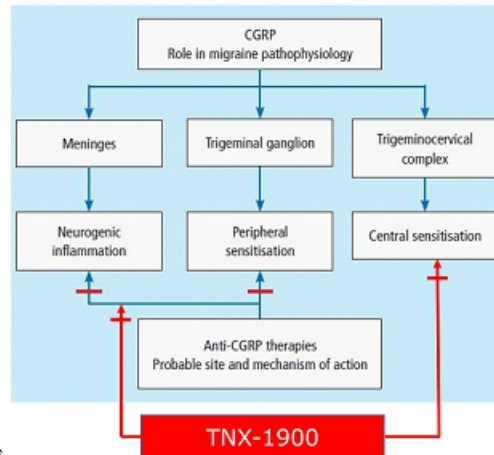


TNX-1900: Mechanism of Action (continued)

In animal models, intranasal oxytocin concentrates in the trigeminal system

Inhibits trigeminal neuronal firing, and decreases CGRP (and PACP) release onto meningeal vasculature and within the brainstem

- **Believed to have effects on:**
 - Neurogenic inflammation
 - Peripheral sensitization, where CGRP otherwise promotes neuronal-glia signaling of pain to trigeminal ganglion
 - Central sensitization, in which CGRP otherwise causes sensitization of NMDA receptor, reducing threshold for glutamate – creating allodynia
- **Anti-CGRP antibodies may only work on inflammation and peripheral sensitization**
 - Due to poor blood brain barrier penetration



Abbrev. CGRP, calcitonin gene-related peptide; PACP, pituitary adenylate cyclase-activating peptide
Figure adapted from Krishnaswamy R et al. Anti-CGRP monoclonal antibodies: breakthrough in migraine therapeutics. Progress in Neurology and Psychiatry. Vol 23.03, July-Sept, 2019.



TNX-1900 for the Treatment of Migraine – Development Status

61

In June 2020, Tonix acquired a proprietary formulation of nasal oxytocin solution for intranasal delivery from Trigemina

Also acquired migraine and pain treatment technologies of Trigemina, Inc. and assumed license for some of technologies from Stanford University

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

Completed by Trigemina prior to acquisition

Targeting start of a Phase 2 study of TNX-1900 for the prophylactic treatment of chronic migraine in the U.S. in the third quarter of 2021

- Primary endpoint expected to be mean change in number of migraine headache days from the last 28 days of baseline to the last 28 days of treatment in each treatment group

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TNX-2900¹

- **Drug Product**: oxytocin nasal spray solution
- **Targeted Indication**: for the treatment of Prader Willi Syndrome

¹TNX-2900 is an investigational new drug and has not been approved for any indication.

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TNX-2900 for the Treatment of Prader-Willi Syndrome – Overview

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TNX-2900 is also based on Tonix’s patented intranasal potentiated oxytocin formulation and expands on this work

Prader-Willi syndrome is the most common genetic cause of life-threatening childhood obesity¹

- Results in lack of suckling in infants and, in children and adults, severe hyperphagia, an overriding physiological drive to eat, leading to severe obesity and other complications associated with significant mortality
- No approved treatment for either the suckling deficit in babies or the obesity and hyperphagia in older children associated with Prader-Willi syndrome.
- Orphan disease occurring in approximately one in 15,000 births

Intranasal oxytocin has been shown to improve suckling in newborn animals but also suppresses feeding behaviors in adult animal models.

- Tonix’s patented potentiated oxytocin formulation is believed to increase specificity for oxytocin receptors relative to vasopressin receptors as well as to enhance the potency of oxytocin.

Tonix intends to submit applications to the FDA for Orphan Drug and Fast Track designations for TNX-2900

¹Foundation for Prader-Willi Research (fpwr.org).

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TNX-601 CR¹

- **Drug Product**: tianeptine oxalate and naloxone HCl controlled-release tablet for once-daily use
- **Targeted Indications**: for the treatment of major depressive disorder (MDD), posttraumatic stress disorder (PTSD) and cognitive dysfunction associated with corticosteroid use

¹TNX-601 CR is an investigational new drug and has not been approved for any indication.

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TNX-601 CR* (Tianeptine Oxalate and Naloxone HCl Controlled Release) Tablets for the Treatment of Major Depressive Disorder (MDD)

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Proprietary new controlled release formulation for once-daily dosing

- Expect to open IND with a Human Abuse Potential study pending IND clearance
- Pending toxicology results, expect to start Phase 2 study in 4Q 2021
- Suitability for once-daily dosing established in Phase 1 pharmacokinetic study, completed outside of the U.S.
 - Well tolerated in study and side effects were consistent with the known safety profile of tianeptine sodium
- Tianeptine sodium immediate release is approved and marketed outside of the U.S. for three times a day dosing for the treatment of depression
 - Once-daily dosing for TNX-601 CR believed to have an adherence advantage over three times a day dosing with tianeptine sodium

Proprietary new oxalate salt with improved pharmaceutical properties

- Tianeptine oxalate is crystalline, while tianeptine sodium is amorphous

Issued patents directed to tianeptine and tianeptine oxalate

- **Composition of Matter:** Issued US patent directed to oxalate salt, U.S. Patent No. 10,449,203 and 10,946,027
- **Method of Use:** Issued European patent directed to methods of treating cognitive impairment associated with corticosteroid treatment, European Patent No. 3246031

**TNX-601 (tianeptine oxalate and naloxone HCl controlled-release tablets) is in the pre-IND stage in the U.S. and has not been approved for any indication.*

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TNX-601 CR: A Potential Treatment for Depression

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TNX-601 CR's proposed mechanism of action is completely distinct from any approved antidepressant in the U.S.

- Antidepressant activity is believed to relate to indirect modulation of the glutamatergic system
 - Known to modulate AMPA receptor trafficking and to promote synaptic plasticity in the hippocampus under conditions of stress or corticosteroid use.
- Tianeptine sodium is reported to have prominent anti-anxiety effects in depression with a low incidence of sexual side effects
- TNX-601 CR leverages the established efficacy and safety of tianeptine sodium IR as a treatment for depression outside of the U.S.
- Johnson and Johnson acquired TransForm in 2005 to develop a CR version of tianeptine for the US

Significant interest and need for new treatments, particularly for medicines that modulate the glutamatergic system

- Majority suffering from depression do not have an adequate response to initial antidepressant therapy
- Recently Spravato® (esketamine) a glutamine system modulator was approved for the treatment of depression with Breakthrough Therapy designation

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Tonix Approach to Abuse Liability of Tianeptine for the Development of TNX-601 CR

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Addition of naloxone to formulation is designed as a deterrent to illicit parenteral abuse of crushed tablets

- Naloxone is a mu-opioid antagonist that is used as a parenteral abuse deterrent in other drugs (e.g., Suboxone®, Talwin Nx® and Targeniq®)
- Naloxone is 100% bioavailable by intravenous injection, about ~30% bioavailable by nasal insufflation and ~2% bioavailable by oral administration (due to first pass hepatitis metabolism)

Based on FDA pre-IND meeting minutes, expect to open IND with human abuse potential study

- To determine whether a dose of tianeptine at 2-3 times the proposed dose of TNX-601 CR will have a signal in comparative "liking" study¹
- Illicit use of tianeptine to achieve a euphoric effect through parenteral (typically *i.v.*) administration requires high doses that are many multiples of therapeutic dose in MDD

¹Pending a meeting and agreement on study design with FDA controlled substances staff (CSS)
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TNX-601 CR Intellectual Property – U.S. Protection expected until 2037

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Composition of matter (crystalline oxalate salt) and method of use: Protection expected to 2037

- United States Patent and Trademark Office (USPTO) issued United States Patent No. 10,449,203 in October 2019, Patent No. 10,946,027 in March 2021.
- USPTO Provisional patent filed March 2021
- 16 patent applications pending (Australia, Brazil, Canada, China, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Saudi Arabia, Singapore, South Africa, EPO, Hong Kong)

Methods of Use: Protection expected to 2029/2030

- United States Patent and Trademark Office (USPTO) issued United States Patent No. US 9,314,469 in April 2016 for treating cognitive impairment associated with corticosteroid treatment
- European Patent Office (EPO) issued European Patent Nos. EP 2,299,822 in July 2017 and EP 3,246,031 in February 2019 for treating neurocognitive side effects associated with corticosteroid treatment (validated in 11 countries)
- Canadian Patent Office issued Canadian Patent No. CA 2,723,688 in June 2018 for treating cognitive impairment associated with corticosteroid treatment
- 1 patent application pending (United States)



TNX-1500¹

- **Drug Product:** recombinant Fc-modified anti-CD40-ligand monoclonal antibody, from cell culture, for injection
- **Targeted Indications:** for the prevention of organ transplant rejection, treatment of autoimmune diseases

¹TNX-1500 is an investigational new drug and has not been approved for any indication.

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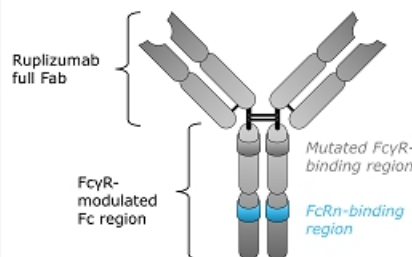
TNX 1500, a New CD40 Ligand (CD40L) Antibody, for the Prevention of Allograft Rejection

The CD40-CD40L pathway is a pivotal immune system modulator and is a well-established and very promising treatment target to more safely prevent allograft rejection¹

- **First Generation:** Development *halted due to thromboembolic complications (TE) – blood clots*. TE complications traced to Fc gamma receptor
- **Second Generation:** Eliminated the Fc gamma receptor (TE complication) but *potency and half life reduced which limited utility*
- **TNX-1500 Third Generation:** Re-engineered based on greater understanding of the Fc gamma receptor. Modulated the binding of FcγR while preserving FcRn function
 - Expected to deliver efficacy without compromising safety

Tonix expects to have GMP product ready in the third quarter of 2021 for TNX-1500

Selectively Modified Anti-CD40L Ab



TNX-1500 contains the full ruplizumab Fab and the engineered Fc region that modulates FcγR-binding, while preserving FcRn function.

1. Camilleri B, et al. *Exp Clin Transplant*. 2016;14(5):471-483.



Pipeline¹ Summary – by Select Therapeutic Areas

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Pain	Psychiatry	Addiction Medicine	Neurology
<ul style="list-style-type: none"> • TNX-102 SL (sublingual cyclobenzaprine) for fibromyalgia Phase 3/RELIEF Phase 3/RALLY • TNX-1900 (intranasal oxytocin) for craniofacial pain Clinical – pre-IND stage 	<ul style="list-style-type: none"> • TNX-102 SL (sublingual cyclobenzaprine) for PTSD Phase 3/RECOVERY • TNX-102 SL (sublingual cyclobenzaprine) for agitation in Alzheimer's Phase 2 ready FDA Fast Track designation • TNX-601 CR (tianeptine oxalate and naloxone) for depression and PTSD Clinical - Pre-IND stage • TNX-1600 (triple reuptake inhibitor²) for PTSD, Depression and ADHD³ Preclinical 	<ul style="list-style-type: none"> • TNX-1300 (cocaine esterase) for cocaine intoxication Phase 2 FDA Breakthrough Therapy designation • TNX-102 SL (sublingual cyclobenzaprine) for alcohol use disorder Phase 2 ready 	<ul style="list-style-type: none"> • TNX-1900 (intranasal oxytocin) for migraine Clinical – pre-IND stage • TNX-102 SL (sublingual cyclobenzaprine) for Long COVID (PASC) Clinical – pre-IND stage <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"> <p>Rare/Orphan Disease</p> </div> <ul style="list-style-type: none"> • TNX-2900 (intranasal oxytocin) for Prader-Willi syndrome Clinical – pre-IND stage

¹ Experimental new medicines and biologics, not approved for any indication

² (2S,4R,5R)-5-(((2-aminobenzo[d]thiazol-6-yl)methyl)amino)-2-((bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-yl) is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine) – licensed from Wayne State University

³ ADHD = attention deficit hyperactivity disorder

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Pipeline¹ Summary – by Select Therapeutic Areas (continued)

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Public Health	Biodefense	Transplantation/ Autoimmunity	Oncology
<ul style="list-style-type: none"> • TNX-1800 (live modified horsepox vaccine) for preventing COVID-19 Preclinical • TNX-2300 (live bovine parainfluenza vaccine) for preventing COVID-19 Preclinical • TNX-2100 (DTH skin test) for detecting exposure and T cell immunity to SARS-CoV-2 Pre-IND • TNX-3500 (sangivamycin) for COVID-19 antiviral Preclinical 	<ul style="list-style-type: none"> • TNX-801 (live horsepox vaccine) for preventing smallpox and monkeypox Preclinical • TNX-701 (oral radioprotective agent) for radioprotection Preclinical 	<ul style="list-style-type: none"> • TNX-1500 (anti-CD40-Ligand) for preventing rejection of solid organ transplants Preclinical • TNX-1500 (anti-CD40-Ligand) for treating autoimmune disease Preclinical 	<ul style="list-style-type: none"> • TNX-1700 (rTFF2²) for treatment of gastric and pancreatic cancer Preclinical

¹ Experimental new medicines and biologics, not approved for any indication

² Recombinant Trefoil Family Factor 2 – licensed from Columbia University © 2021 Tonix Pharmaceuticals Holding Corp.

Milestones – Recently Completed and Upcoming¹

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- ✓ 4th Quarter 2020 Positive topline data from TNX-102 SL Phase 3 F304/RELIEF study in fibromyalgia reported
- ✓ 1st Quarter 2021 Non-human primate positive efficacy data from TNX-1800 in COVID-19 models reported

Data

- 3rd Quarter 2021 Interim analysis of TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected
- 1st Quarter 2022 Topline data from TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected

Clinical Trial Initiations – 5 New Trials This Year

- 3rd Quarter 2021 Phase 2 OL safety study of TNX-1300 in ED setting for cocaine intoxication expected
- 3rd Quarter 2021 Phase 2 study of TNX-1900 for the treatment of migraine expected
- 3rd Quarter 2021 Phase 3 study of TNX-102 SL for the treatment of PTSD in Kenya expected
- 4th Quarter 2021 Phase 2 study of TNX-601 CR for the treatment of major depressive disorder expected
- 4th Quarter 2021 First-in-human clinical study of TNX-2100 for SARS-CoV-2 skin test expected
- 1st Half 2022 Phase 1 safety study of TNX-1800 for COVID-19 expected

¹ We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones.

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Management Team

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Seth Lederman, MD
President & CEO



Gregory Sullivan, MD
Chief Medical Officer



Bradley Saenger, CPA
Chief Financial Officer



Jessica Morris
Chief Operating Officer



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Thank You!



Investor Presentation

NASDAQ:TNXP

1



June 2021

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Cautionary Note on Forward-Looking Statements

2

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, risks related to failure to obtain U.S. Food and Drug Administration clearances or approvals and noncompliance with its regulations; our need for additional financing; delays and uncertainties caused by the global COVID-19 pandemic; substantial competition; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties. 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, 2020, as filed with the Securities and Exchange Commission (the "SEC") on March 15, 2021, 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.

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Tonix Pharmaceuticals: Who We Are and What We Do

Mission And Purpose

Clinical-stage biopharmaceutical company that invents, licenses, acquires and develops innovative medicines to help patients manage central nervous system (CNS) and immunology conditions

"Advancing science to improve patient care and public health"

Team of passionate professionals

Advancing innovative programs into the clinic: Phase 2 and Phase 3 clinical data are perceived as value-creating inflection points

Pipeline

Development stage: programs range from preclinical to mid-Phase 3; expect three new programs in Phase 2 by YE 2021

Therapeutic modalities: small molecules, small synthetic peptides, recombinant peptide from *E. coli*, recombinant proteins from CHO cells (monoclonal antibody, fusion protein), live virus vaccines

Route of administration: oral, sublingual, intranasal, *i.v.*, intradermal, percutaneous

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Our Pipeline – CNS Portfolio

CANDIDATES		INDICATION	STATUS
CNS Portfolio	TNX-102 SL ¹	Fibromyalgia (FM) - Lead Program	Mid-Phase 3 – ongoing
		PTSD Agitation in Alzheimer's Alcohol Use Disorder Long COVID (PASC ²)	Phase 3 ready Phase 2 ready Phase 2 ready Clinical – pre-IND ³
	TNX-1300 ⁴	Cocaine Intoxication / Overdose	Phase 2
	TNX-1900 ⁵	Migraine and Craniofacial Pain	Clinical – pre-IND ⁶
	TNX-2900 ⁷	Prader-Willi Syndrome	Clinical – pre-IND
	TNX-601 CR	Depression, PTSD, Neurocognitive Dysfunction from Steroids	Clinical – pre-IND ⁸
TNX-1600 ⁹	Depression, PTSD and ADHD	Preclinical	

¹TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication.

²Post-Acute Sequelae of COVID-19.

³Pre-IND (Investigational New Drug) meeting with the FDA scheduled for third quarter 2021 to seek agreement on design of a potential Phase 2 pivotal study.

⁴TNX-1300 (double-mutant cocaine esterase) is an investigational new biologic and has not been approved for any indication; licensed from Columbia University.

⁵Acquired from Trigemina; license agreement with Stanford University

⁶A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900; Phase 2 expected to start Q3'21

⁷Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)

⁸TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 trial for formulation development was completed outside of the U.S.; Phase 2 expected to start Q4'21

⁹Acquired from TRJmaran Pharma; license agreement with Wayne State University

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Our Pipeline – Immunology & Biodefense Portfolio

	CANDIDATES	INDICATION	STATUS
Immunology Portfolio	TNX-1800	Covid-19 vaccine – Prioritized Program¹	Phase 1, 1H 2022*
	TNX-2100	SARS-CoV-2 skin test for T cell immunity ²	First-in-human study Q4'21*
	TNX-3500	COVID-19 (SARS-CoV-2) antiviral ³	Preclinical
	TNX-2300	COVID-19 vaccine ⁴	Preclinical
	TNX-801	Smallpox and monkeypox preventing vaccine ⁵	Preclinical
	TNX-1500	Organ Transplant Rejection/Autoimmune Conditions ⁶	Preclinical
	TNX-1700	Gastric and pancreatic cancers ⁷	Preclinical
	TNX-701	Radioprotection	Preclinical

*Represents expected milestones

¹Live attenuated vaccine based on horsepox virus vector

²In vivo diagnostic: SARS-CoV-2 peptide epitope mixtures for intradermal administration to measure delayed-type hypersensitivity to SARS-CoV-2

³Sangivamycin, for injection

⁴Live attenuated vaccine based on bovine parainfluenza virus vector; option for license with Kansas State University

⁵Live attenuated vaccine based on horsepox virus

⁶anti-CD40L humanized monoclonal antibody

⁷Recombinant trefoil factor 2 (rTF2) based protein; licensed from Columbia University

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TNX-102 SL FM Lead Program Background on Fibromyalgia

Fibromyalgia (FM):

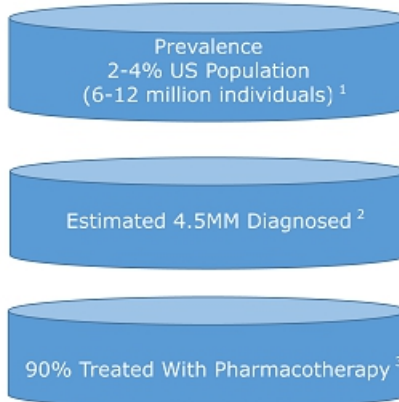
A chronic condition

Core symptoms:

- widespread pain
- sleep disturbance
- fatigue
- cognitive symptoms.

Significant disabilities (impaired daily function).

Course of disease can last decades



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

² Wallit, B., Nahin, R.L., Katz, R.S., Bergman, M.J., Wolfe, F. (2015) [The Prevalence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey](#), PLoS One; 10(9): e0138024.

³ Decision Resources, Fibromyalgia, 2012

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Challenges with Current Pharmacotherapy

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Limitations of Current Therapies

Fewer than half of those treated for fibromyalgia receive relief from the three FDA-approved drugs¹

- Lack of overall response leading to discontinuation or augmentation
- Lack of tolerability leading to discontinuation or reduction in dose (underdosing)

Current Treatment Patterns As A Result of Limitations

Switch Rates/Rotation/Discontinuation

- Over 50% of patient starting an FDA approved therapy for FM switch or discontinue therapy after 12 months²

Polypharmacy

- Average patient is using 2.6 drugs for treating their fibromyalgia, 50% of patients take 3 or more medications concomitantly³

Opioid usage is not uncommon

Market Dissatisfaction

Only 43% of patients indicated that they are satisfied with their medication for FM⁵

1. Frost and Sullivan, 2010

2. Liu et al., 2016

3. Robinson et al., 2012; prospective observational study with 1,700 participants with fibromyalgia.

4. Sarmiento et al., J Opioid Manag 2019; 15(5):460-77 – prescription opioid usage among diagnosed FM patients at one site

5. Robinson et al., 2013; prospective observational study with 1,700 participants with fibromyalgia



Fibromyalgia Unmet Need and Ideal Treatment Profile

8

Ideal Treatment Profile:

Unmet Medical Need:

Current treatment patterns indicate that new, more effective, and better-tolerated treatments are necessary for management of FM¹

Treats FM as a syndrome

- Relief from major symptoms (pain, sleep disturbances, fatigue)
- Reduces disability and improves daily living (global function)

Well tolerated with low discontinuation

- Low systemic side-effects
- No daytime somnolence
- No weight gain or impact on sexual function

Suitable for chronic use

- Not scheduled
- Non opioid
- Non abuse potential

Source: 1. Yang, et al, 2016



TNX-102 SL: Engineered to Treat FM

This unique formulation of cyclobenzaprine has been designed to optimize delivery and absorption, while minimizing the potential residual effects of oral formulations of cyclobenzaprine.

Innovative and proprietary Protectic® delivery technology

- Overcomes mucosal absorption barrier
- Allows sublingual (SL) administration to achieves relevant systemic drug exposure
- Stable SL tablet formulation

• Benefits of sublingual delivery

- Rapid drug exposure following nighttime administration
- Lower daytime exposure
- Avoids first-pass metabolism
 - Reduces risk of pharmacological interference from major metabolite

No recognized abuse or dependency concerns



Phase 3 F304/RELIEF Study: Design

General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia
- Adaptive Design: one unblinded interim analysis based on 50% of randomized participants

TNX-102 SL once-daily at bedtime
5.6 mg (2 x 2.8 mg tablets)¹ N= 248

Placebo once-daily at bedtime
N= 255

14 weeks

Primary endpoint (Week 14):

- Daily diary pain severity score change from baseline

Key Secondary endpoints (Week 14):

Symptom Relief

- PROMIS Sleep Disturbance instrument T-score
- PROMIS Fatigue instrument T-score
- FIQ-R Symptom Domain score

Global function

- PGIC responder analysis
- FIQ-R Function Domain score

Pivotal efficacy study to support NDA approval

¹Two week run in at 2.8 mg dose at bedtime, followed by 12 weeks at 5.6 mg dose

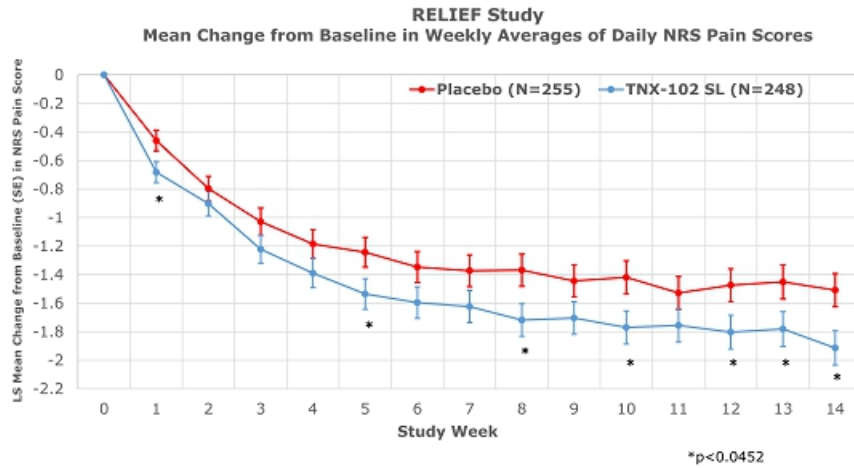
F304/RELIEF Study Topline Primary Efficacy Endpoint

Positive outcome for primary endpoint (daily pain) at Week 14

Primary Outcome Measure at Week 14	Placebo (N=255)	TNX-102 SL (N=248)	Treatment Difference	P value
LS Mean Change from Baseline ¹ (SE)	-1.5 (0.12)	-1.9 (0.12)	-0.4 (0.16)	0.010*

Statistical Method: Mixed Model Repeated Measures analysis with Multiple Imputation
 *p<0.0452 (requisite p-value hurdle for full study after Interim Analysis)
¹ Same primary endpoint analysis for FDA approvals of Cymbalta® and Lyrica® in fibromyalgia
 Abbreviations: LS = least squares; NRS = numeric rating scale; SE = standard error

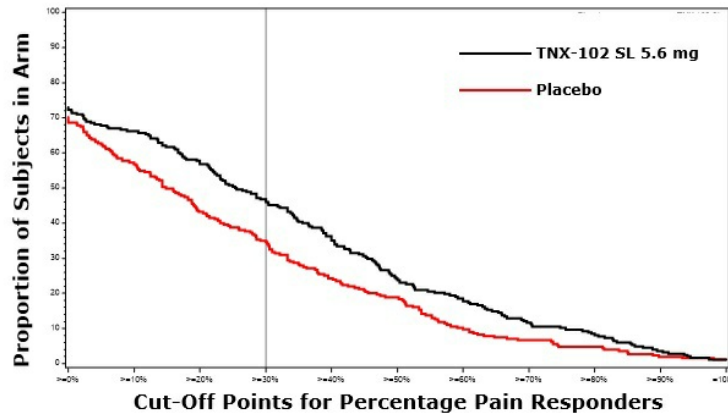
F304/RELIEF Study: Primary Efficacy Endpoint Results (continued)





F304/RELIEF Study: Continuous Responder Analysis (CRA) Graph

- The CRA graph allows one to see the proportion of responders over an entire range of cut-off points
- For example, >=30% improvement in pain is considered clinically meaningful in pain studies
- Looking at that vertical line at >=30% and visualizing a horizontal line to the y-axis tells you the proportion of each arm that achieved that level of pain improvement or better (47% for TNX-102 SL and 35% for placebo)
- It can be seen that TNX-102 SL separates from placebo, always at a higher proportion, up to about >=95% improvement



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F304/RELIEF Study: Key Secondary Efficacy Endpoints

Outcome Measure at Week 14	Intent-to-Treat Analysis ¹	P-value
Non-Specific		
Patient Global Impression of Change	Responder Analysis: Proportion "Much Improved" or "Very Much Improved"	0.058
Fibromyalgia Syndrome-Related		
FIQ-R Symptom Domain	Mean Change from Baseline	0.007 [#]
FIQ-R Function Domain	Mean Change from Baseline	0.009 [#]
PROMIS Fatigue	Mean Change from Baseline	0.018 [#]
Daily Sleep Quality Diary, NRS	Mean Change from Baseline	<0.001 [#]
PROMIS Sleep Disturbance	Mean Change from Baseline	<0.001 [#]

[#] nominally significant at p<0.0452

¹ Combined periods (pre- and post-interim analysis); responder analysis is by Logistic Regression (missing = non-responder); the five mean change analyses are by Mixed Model Repeated Measures with Multiple Imputation
Abbreviations: FIQ-R = Fibromyalgia Impact Questionnaire - Revised; NRS = numeric rating scale; PROMIS = Patient-Reported Outcomes Measurement Information System

*TNX-102 SL is in clinical stage of development and not approved for any indication

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Adverse Events*(AEs) in F304/RELIEF Study

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Those AEs reported at rate of greater than 5% in either treatment arm

Systemic Adverse Events	Placebo N=255	TNX-102 SL 5.6 mg N=248
Somnolence/Sedation	1.2%	5.6%
Local Administration Site Reactions		
Tongue/mouth numbness	0.8%	17.3%
Tongue/mouth pain/discomfort	2.0%	11.7%
Taste impairment	0.4%	6.5%
Tongue/mouth tingling	0.4%	5.6%

* Table reports only AEs at rate of greater than 5% in either treatment arm

Discontinuation rate due to adverse events: 8.9% TNX-102 SL compared to 3.9% for placebo

No serious and unexpected AEs in RELIEF related to TNX-102 SL

- Systemic AEs comparable with prior studies
- Oral AEs similar to prior studies with TNX-102 SL, although tongue/mouth numbness at about half the rate in RELIEF

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Approved Fibromyalgia Pharmacotherapies

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Pfizer

- Drug: Lyrica® or pregabalin (U.S. patent expired in 2018)
- Approved: 2004
- Mechanism: modulates nerve impulses involved in the transmission of pain through selective binding to the alpha2-delta protein of the voltage-gated calcium channels in CNS tissues
- Peak Sales: Approximately \$5 billion (including all approved indications)

Lilly

- Drug: Cymbalta® or duloxetine (U.S. patent expired 2014)
- Approved: 2004
- Mechanism: serotonin and norepinephrine reuptake inhibitor (SNRI)
- Peak Sales: Approximately \$5 billion (including all approved indications)

Abbvie (developed by Forest Laboratories)

- Drug: Savella® or milnacipran (on patent)
- Approved: 2009
- Mechanism: serotonin and norepinephrine reuptake inhibitor (SNRI)
- Peak Sales: Approximately \$130 million (approved for fibromyalgia indication only)

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TNX-102 SL Intellectual Property – U.S. Protection expected until 2035

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Composition of matter (eutectic): Protection expected to 2034/2035

- United States Patent and Trademark Office (USPTO) issued United States Patent No. 9636408 in May 2017, Patent No. 9956188 in May 2018, Patent No. 10117936 in November 2018, and Patent No. 10864175 on December 2020
- European Patent Office (EPO) issued European Patent No. 2968992 in December 2019 (validated in 37 countries). Opposition filed in October 2020 by Hexal AG
- China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019
- Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018
- 8 granted patents (Indonesia, Saudi Arabia, New Zealand, Australia, Mexico, Taiwan, Israel, South Africa)
- 11 patent applications pending (1 being allowed in Canada)

Composition of matter (sublingual): Protection expected to 2033

- New Zealand Intellectual Property Office issued New Zealand Patent No. 631144 in March 2017 and Patent No. 726488 in January 2019
- Taiwanese Intellectual Property Office issued Taiwanese Patent No. I590820 in July 2017, Patent No. I642429 in December 2018 and Patent No. I683660 in February 2020
- Australian Patent Office issued Australian Patent No. 2013274003 in October 2018 and Patent No. 2018241128 in September 2020
- JPO issued Japanese Patent No. 6259452 in December 2017
- 20 patent applications pending (1 being allowed in Mexico)

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TNX-102 SL for FM: Next Steps

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2nd Phase 3 study, RALLY (F306)

- Same protocol design as RELIEF study but with 200 more patients
- Enrollment began in September 2020
- Interim cohort recruited in March 2021
- Interim analysis results expected in 3rd quarter 2021¹
- Topline results expected in 1st quarter 2022

Following positive results from RALLY, an NDA could potentially be filed in 2022

- Long term safety exposure studies completed in PTSD patients expected to support the FM NDA
- GMP manufacturing processes mature and 36-month stability established

¹Pending agreement from FDA on statistical analysis plan

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TNX-102 SL for Long COVID (PASC)

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Long COVID or Post-acute Sequelae of COVID-19 (PASC)

- Symptoms can include fatigue, sleep disorders, pain, fevers, shortness of breath, cognitive impairment described as "brain fog", gastrointestinal symptoms, anxiety, and depression
- Can persist for months and can range in severity from mild to incapacitating
- Occurs in more than 30% of patients.²
- While typically associated with moderate or severe COVID-19, Long COVID can occur after mild COVID-19 or even after asymptomatic SARS-CoV-2 infection

Long COVID Overlap with Fibromyalgia

- Long COVID has been compared to fibromyalgia because of the common symptoms of sleep disturbance, persistent pain, fatigue, and brain fog³
- Like fibromyalgia, is experienced by women at a higher rate, approximately four times more, than that of men⁴
- Long COVID is a chronic disabling condition that is expected to result in a significant global economic burden⁵
- In response to the urgent need for therapies that address PASC, Congress awarded \$1.15 billion to the National Institutes of Health to study Long COVID last December⁶

¹Feb. 24, 2021 - White House COVID-19 Response Team press briefing; Feb 25, 2021 - policy brief from the World Health Organization on long COVID

²Haibandian, Ani, et al. "Post-acute COVID-19 syndrome." *Nature Medicine* (2021): 1-15.

³Clew D, et al. *Pain*. 2020 Aug; 161(8): 1694-1697.

⁴Cox, D. "Why are women more prone to long Covid?" *The Guardian*. 13 Jun 2021 <https://www.theguardian.com/society/2021/jun/13/why-are-women-more-prone-to-long-covid>

⁵Briggs, Andrew, and Anna Vassili. "Count the cost of disability caused by COVID-19." (2021): 502-505.

⁶The NIH provision of Title III Health and Human Services, Division H--Coronavirus Response and Relief Supplemental Appropriations Act, 2021, of H.R. 133, The Consolidated Appropriations Act of 2021. The bill was enacted into law on 27 December 2020, becoming Public Law 116-260.

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COVID-19 Vaccines with Emergency Use Authorization (EUA): Still Uncertainty

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Durability of protection

- Are vaccinated people protected one year later?
- Need for annual vaccinations with mRNA vaccines? Will annual boosters work?
- Durable protection is associated with T cell response

Detecting and mitigating vaccine failure

- Need a strategy for identifying individuals at risk after vaccination and second line vaccines

No biomarker of protection

- No test to establish vaccine protection

Current and future variants

- Unknown effectiveness of existing vaccines



TNX-1800¹: a COVID-19 Vaccine Candidate

21

- **Utilizes Tonix’s proprietary horsepox virus as a vector**
 - Encodes a protein from SARS-CoV-2, the cause of COVID-19
 - Developed in collaboration with University of Alberta, Canada
- **Animal testing with Southern Research Institute**
 - Non-human primate immune response positive results reported in 4th quarter 2020
 - Non-human primate CoV-2 challenge testing positive data reported in 1st quarter 2021
 - TNX-1800 vaccinated animals had undetectable² CoV-2 by PCR in upper and lower airways³
- **Manufacturing agreement with FUJIFILM Diosynth**
 - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
 - Expect GMP⁴ clinical supply to be ready for human trials targeted to begin in 1st half of 2022⁵

¹TNX-1800 (horsepox/CoV-2 spike live vaccine) is at the pre-IND stage of development

²Less than 1,000 genomes by PCR

³Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage

⁴Good Manufacturing Practice = GMP

⁵We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones



Potential Profile of TNX-1800 Compared to EUA Covid-19 Vaccines

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Criteria	EUA Vaccines	TNX-1800
Number of shots	One – two	One
Duration	Unknown	Years / decades
Boosters	Unknown	Not required
Protection from variants	Unknown	Likely provides protection
Forward Transmission	Probably prevents (for PFE)	Likely prevents
Biomarker	None	Yes - "Take"
Manufacturing	Complex	Conventional
Glass sparing packaging	No	Yes
Shipping and storage	Cold Chain	Standard refrigeration
Protection from smallpox	No	Yes



TNX-3500¹: SARS-CoV-2 Antiviral for the Treatment of COVID-19

23

TNX-3500 (sangivamycin) – potential monotherapy antiviral²

- Licensed from OyaGen, April 2021
- Demonstrated broad spectrum antiviral (nanomolar activity against SARS-CoV-2, MERS, Ebola, and Lassa)
- Demonstrated human tolerability for chronic dosing from US National Cancer Institute studies³
- 65 times more potent than remdesivir in inhibiting SARS-CoV-2 in cell culture infectivity studies (dose to achieve IC₉₀)⁴

Potential COVID-19 combination therapy with remdesivir

- TNX-3500 antiviral effect is additive when combined with remdesivir and reduces the amount of each drug necessary for an IC₉₀
- Combination therapies for other viruses have reduced the emergence of drug resistant viral strains

Development plans

- 2nd quarter 2021: Plan to initiate animal pharmacokinetic and efficacy studies

¹TNX-3500 is in the pre-IND stage of development and has not been approved for any indication.

²Bennett, RP et al., *Viruses*. 2020 13(1):52. doi: 10.3390/v13010052.

³Cavins JA et al., *Cancer Chemotherapy Reports*. 1967. 51(4)

⁴Data on file, live virus BSL-4 testing conducted by NIAID in collaboration with OyaGen

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TNX-2100¹: Potential Skin Test to Measure SARS-CoV-2 Exposure and T Cell Immunity

24

TNX-2100 (SARS-CoV-2 epitope peptide mixtures for intradermal administration)

- Designed to elicit delayed-type hypersensitivity (DTH) in individuals who have been exposed to SARS-CoV-2 or who have been successfully vaccinated
- Potential to measure the presence and strength of functional *in vivo* T cell immunity

Potentially scalable test for widespread use

- Adaptive Biotech's T Detect™ COVID received FDA EUA – based on genetic analysis of T cell receptors
- Other tests² for T cell immunity to SARS-CoV-2 require specialized laboratories and are not amenable to standardization

Development plans

- 4th quarter 2021: Plan to initiate first-in-human clinical testing pending clearance of IND

¹TNX-2100 is in the pre-IND stage of development and has not been approved for any indication.

²Intracellular cytokine staining (ICS) measured by flow cytometry after *in vitro* stimulation of purified peripheral blood mononuclear cells

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TNX-1300: Cocaine Esterase (CocE)

25

CocE is the most potent known catalyst for cocaine degradation

- Natural bacterial CocE is unstable at body temperature

Thermostable bacterial CocE (active for ~6 hours at body temperature)

- Targeted mutations stabilize CocE
- Natural bacterial CocE is unstable at body temperature

Phase 2 open-label safety study of TNX-1300 in emergency department setting for cocaine intoxication)

- Initiation of enrollment anticipated 3rd quarter 2021

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TNX-1900 (Intranasal Potentiated Oxytocin) for the Treatment of Migraine

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Intranasal oxytocin(OT) has potential utility in treating migraine¹

- Intranasal (*i.n.*) OT reaches the trigeminal ganglion
- Preclinical evidence of OT blocking CGRP release and suppressing pain transmission
- CGRP antagonists and antibodies approved for the treatment of migraine
- Association of low oxytocin levels during and preceding migraine episodes

TNX-1900 is an intranasal formulation of magnesium and OT

- Magnesium is known to potentiate the binding of oxytocin to its receptor²

Initiation of Phase 2 study for treatment of chronic migraine anticipated in 3rd quarter 2021

1. Tzabazis et al., 22017
2. Antoni and Chadio, 1989

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TNX-2900 (*i.n.* Potentiated OT) for the Treatment of Prader-Willi Syndrome

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Prader-Willi syndrome is the most common genetic cause of life-threatening childhood obesity¹

- Results in lack of suckling in infants and, in children and adults, severe hyperphagia, an overriding physiological drive to eat, leading to severe obesity and other complications associated with significant mortality
- No approved treatment for either the suckling deficit in babies or the obesity and hyperphagia in older children associated with Prader-Willi syndrome.
- Orphan disease occurring in approximately one in 15,000 births

Intranasal OT has been shown to improve suckling in newborn animals but also suppresses feeding behaviors in adult animal models

- Tonix's patented potentiated oxytocin formulation is believed to increase specificity for OT receptors relative to vasopressin receptors

Tonix intends to submit applications to the FDA for Orphan Drug and Fast Track designations for TNX-2900

¹Foundation for Prader-Willi Research (fpwr.org).



TNX-601 CR* (Tianeptine Oxalate and Naloxone HCl Controlled Release) Tablets for the Treatment of Major Depressive Disorder (MDD)

28

Proprietary new controlled release formulation for once-daily dosing

- Expect to open IND with a Human Abuse Potential study pending IND clearance
- Pending toxicology results, expect to start Phase 2 study in 4Q 2021
- Suitability for once-daily dosing established in Phase 1 pharmacokinetic study, completed outside of the U.S.
 - Well tolerated in study and side effects were consistent with the known safety profile of tianeptine sodium
- Tianeptine sodium immediate release is approved and marketed outside of the U.S. for three times a day dosing for the treatment of depression
 - Once-daily dosing for TNX-601 CR believed to have an adherence advantage over three times a day dosing with tianeptine sodium

Proprietary new oxalate salt with improved pharmaceutical properties

- Tianeptine oxalate is crystalline, while tianeptine sodium is amorphous

Issued patents directed to tianeptine and tianeptine oxalate

- **Composition of Matter:** Issued US patent directed to oxalate salt, U.S. Patent No. 10,449,203 and 10,946,027
- **Method of Use:** Issued European patent directed to methods of treating cognitive impairment associated with corticosteroid treatment, European Patent No. 3246031

*TNX-601 CR (tianeptine oxalate and naloxone HCl controlled release tablets) is in the pre-IND stage in the U.S. and has not been approved for any indication.

TNX-601 CR: A Potential Treatment for Depression

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TNX-601 CR's proposed mechanism of action is completely distinct from any approved antidepressant in the U.S.

- Antidepressant activity is believed to relate to indirect modulation of the glutamatergic system
 - Known to modulate AMPA receptor trafficking and to promote synaptic plasticity in the hippocampus under conditions of stress or corticosteroid use.
- Tianeptine sodium is reported to have prominent anti-anxiety effects in depression with a low incidence of sexual side effects
- TNX-601 CR leverages the established efficacy and safety of tianeptine sodium IR as a treatment for depression outside of the U.S.
- Johnson and Johnson acquired TransForm in 2005 to develop a CR version of tianeptine for the US

Significant interest and need for new treatments, particularly for medicines that modulate the glutamatergic system

- Majority suffering from depression do not have an adequate response to initial antidepressant therapy
- Recently Spravato® (esketamine) a glutamine system modulator was approved for the treatment of depression with Breakthrough Therapy designation

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TNX-1500, a New CD40 Ligand (CD40L) Antibody, for the Prevention of Allograft Rejection

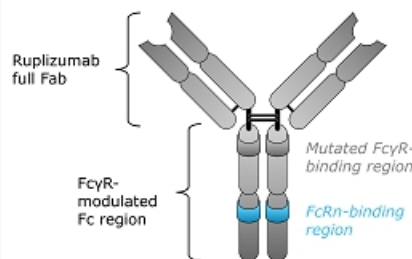
30

The CD40-CD40L pathway is a pivotal immune system modulator and is a well-established and very promising treatment target to more safely prevent allograft rejection¹

- **First Generation:** Development *halted due to thromboembolic complications (TE) – blood clots*. TE complications traced to Fc gamma receptor
- **Second Generation:** Eliminated the Fc gamma receptor (TE complication) but *potency and half life reduced which limited utility*
- **TNX-1500 Third Generation:** Re-engineered based on greater understanding of the Fc gamma receptor. Modulated the binding of FcγR while preserving FcRn function
 - Expected to deliver efficacy without compromising safety

Tonix expects to have GMP product ready in the 3rd quarter of 2021 for TNX-1500

Selectively Modified Anti-CD40L Ab



TNX-1500 contains the full ruplizumab Fab and the engineered Fc region that modulates FcγR-binding, while preserving FcRn function.

1. Camilleri B, et al. *Exp Clin Transplant*. 2016;14(5):473-483.

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Milestones – Recently Completed and Upcoming¹

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- ✓ 4th Quarter 2020 Positive topline data from TNX-102 SL Phase 3 F304/RELIEF study in fibromyalgia reported
- ✓ 1st Quarter 2021 Non-human primate positive efficacy data from TNX-1800 in COVID-19 models reported

Data

- 3rd Quarter 2021 Interim analysis of TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected
- 1st Quarter 2022 Topline data from TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected

Clinical Trial Initiations – 5 New Trials This Year

- 3rd Quarter 2021 Phase 2 OL safety study of TNX-1300 in ED setting for cocaine intoxication expected
- 3rd Quarter 2021 Phase 2 study of TNX-1900 for the treatment of migraine expected
- 3rd Quarter 2021 Phase 3 study of TNX-102 SL for the treatment of PTSD in Kenya expected
- 4th Quarter 2021 Phase 2 study of TNX-601 CR for the treatment of major depressive disorder expected
- 4th Quarter 2021 First-in-human clinical study of TNX-2100 for SARS-CoV-2 skin test expected
- 1st Half 2022 Phase 1 safety study of TNX-1800 for COVID-19 expected

¹ We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones.

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Thank You!