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

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**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): August 9, 2021**

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**TONIX PHARMACEUTICALS HOLDING CORP.**
**(Exact name of registrant as specified in its charter)**

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

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

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

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

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

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. ☐

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 |

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**Item 2.02 Results of Operations and Financial Condition**

On August 9, 2021, Tonix Pharmaceuticals Holding Corp. (the "Company") announced its operating results for the quarter ended June 30, 2021. A copy of the press release that discusses this matter is filed as Exhibit 99.01 to, and incorporated by reference in, this report.

**Item 7.01 Regulation FD Disclosure.**

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 99.02 and 99.03 hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.02 and 99.03 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

**Item 9.01 Financial Statements and Exhibits.**

(d)

| **Exhibit No.** | **Description.** |
|---|---|
| 99.01 | Press Release of the Company, dates August 9, 2021 |
| 99.02 | Corporate Presentation by the Company for August 2021 |
| 99.03 | Abbreviated Corporate Presentation by the Company for August 2021 |
| 104 | Cover Page Interactive Data File (embedded within the Inline XBRL document) |

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**SIGNATURE**

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

**TONIX PHARMACEUTICALS HOLDING CORP.**

Date: August 9, 2021

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

**Exhibit 99.01**

**Tonix Pharmaceuticals Reports Second Quarter 2021 Financial Results and Operational Highlights**

*Central Nervous System Pipeline Progressing with Two Phase 2 Studies (TNX-1300 and TNX-1900) and One Phase 3 Study (TNX-102 SL) Expected to Start This Year*

*COVID-19 Pipeline Progressing with First-in-Human Trial of TNX-2100, a Novel in vivo Skin Test for COVID-19 T cell Immunity, Expected to Start This Year*

*New Advanced Development Center, Currently Under Construction, and Planned Acquisition of Infectious Disease R&D Facility Will Expand Internal R&D and Manufacturing Capabilities for Vaccines and Antiviral Therapeutics, With Initial Focus on COVID-19*

*At June 30, 2021, Cash and Cash Equivalents Totaled Approximately $166 Million*

CHATHAM, NJ, August 9, 2021 (GLOBE NEWSWIRE) – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced financial results for the second quarter ended June 30, 2021 and provided an overview of recent operational highlights.

“Our clinical, manufacturing, and regulatory teams are advancing four programs into clinical trials by the end of 2021,” said Seth Lederman, M.D., President and Chief Executive Officer. “We look forward to initiating Phase 2 studies of TNX-1300 for cocaine intoxication and TNX-1900 for chronic migraine in the third and fourth quarters of 2021, respectively. We also expect to initiate a Phase 3 study of TNX-102 SL for PTSD outside of the U.S. and a first-in-human study of TNX-2100, a skin test diagnostic for COVID-19 T cell immunity, in the fourth quarter of 2021.”

Dr. Lederman continued, “We are expanding our R&D and manufacturing facilities. In July we announced an agreement to acquire an infectious disease research facility in Frederick, MD, and earlier this month we began construction on our Advanced Development Center (ADC) in New Bedford MA. We expect these facilities, coupled with our planned commercial scale manufacturing facility for vaccines in Hamilton, MT, will enable us to avoid future outsourcing bottlenecks and to work with greater efficiency in developing our programs for COVID-19, its variants, and other infectious diseases.”

Dr. Lederman added, “Recent reports of COVID-19 outbreaks in the U.S. and elsewhere, due primarily to the Delta variant, point to the urgent needs for more robust vaccines and more potent antiviral therapeutics. We believe the recent steps we have taken to strengthen our internal capabilities with company-controlled R&D and manufacturing facilities will accelerate our full pipeline of COVID-19 product candidates, which currently includes the TNX-1800 vaccine, TNX-3500 antiviral, TNX-2100 diagnostic, and TNX-102 SL for treating Long COVID.”

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**Recent Highlights—Key Product Candidates***

*Central Nervous System (CNS) Pipeline*

*TNX-102 SL (cyclobenzaprine HCl sublingual tablets): small molecule for the management of fibromyalgia*

- In July 2021, Tonix announced that the RALLY study, the second Phase 3 trial of TNX-102 SL 5.6 mg for fibromyalgia, stopped enrolling new participants following recommendation from a pre-planned interim analysis by the Independent Data Monitoring Committee (IDMC). Based on interim analysis results of the first 50% of targeted participants (n=337), the IDMC recommended stopping the trial for futility as TNX-102 SL was unlikely to demonstrate a statistically significant improvement in the primary endpoint of overall change from baseline in daily diary pain severity scores between those treated with TNX-102 SL 5.6 mg (2x 2.8 mg tablets) and those receiving placebo. Tonix remains blinded to the detailed interim analysis results and only received the recommendation made by the IDMC. Preliminary blinded safety data from these participants did not reveal any new safety signals, and the decision to discontinue enrolling new participants is not related to safety. The Company intends to continue studying those participants currently enrolled until completion and then proceed with a full analysis of the unblinded data, with the topline results expected to be reported in the fourth quarter of 2021, to determine the next steps in this program.

*TNX-102 SL for the treatment of Posttraumatic Stress Disorder (PTSD)*

- Tonix intends to meet with the U.S. Food and Drug Administration (FDA) to discuss potential new endpoints for the indication of treatment of PTSD in the third quarter of 2021. The Company also expects to begin enrolling a Phase 3 study of TNX-102 SL in police in Kenya in the fourth quarter of 2021.

*TNX-102 SL for the treatment of Long COVID Syndrome or Post-Acute Sequelae of COVID-19 (PASC)*

- The Company met with the FDA in the third quarter of 2021 to seek agreement on the design of a potential Phase 2 pivotal study and the overall clinical development plan for TNX-102 SL as an indicated treatment for Long COVID. Tonix expects to receive official minutes from this meeting in the third quarter of 2021.

*TNX-1300 (recombinant double mutant cocaine esterase): biologic for life-threatening cocaine intoxication*

- Tonix expects to initiate a Phase 2 open-label safety study in an emergency department setting to study TNX-1300 in the third quarter of 2021. Cocaine esterase is the most potent known catalyst for cocaine degradation. Results of a positive Phase 2 study of volunteer cocaine users in a controlled laboratory setting were reported prior to Tonix licensing the technology.

*TNX-1900 (intranasal potentiated oxytocin): small peptide for migraine, craniofacial pain, insulin resistance and related disorders*

- Tonix intends to submit an Investigational New Drug (IND) application to the FDA in the third quarter of 2021 and is targeting to start a Phase 2 study of TNX-1900 for the prophylactic treatment of chronic migraine in the U.S. in the fourth quarter of 2021. A Phase 2 trial under an investigator-initiated IND was completed in the U.S. using the TNX-1900 formulation prior to Tonix’s acquisition of the program.

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*TNX-601 CR (tianeptine oxalate and naloxone controlled-release tablets): small molecule for the treatment of major depressive disorder, PTSD and neurocognitive dysfunction associated with corticosteroid use.*

- Tonix previously completed a Phase 1 trial for formulation development outside of the U.S. Based on official minutes from a pre-IND meeting with the FDA, the Company expects to initiate a Phase 2 study for the treatment of depression in the first half of 2022, pending results of nonclinical toxicology studies and IND clearance.

*COVID-19 Pipeline*

*TNX-1800 (live virus vaccine based on Tonix's horsepox virus vector, TNX-801): COVID-19 vaccine designed as a single-administration vaccine to elicit T cell immunity*

- A Phase 1 safety study using TNX-1800 in humans is anticipated to start in the first half of 2022, pending IND clearance from the FDA and the production of cGMP material. In March 2021, positive efficacy results from a study of TNX-1800 in which non-human primates were vaccinated with TNX-1800 and challenged with live SARS-CoV-2 were reported. TNX-1800 was found to induce protection against infection in both upper and lower airways, which suggests an ability to inhibit forward transmission. The Company believes these findings also demonstrate the flexibility of the horsepox vaccine platform, and its capability to be engineered to construct new vaccines to protect against other diseases of interest in military and civilian populations.

*TNX-2100 (diagnostic skin test): SARS-CoV-2 epitope peptide mixtures for intradermal administration to measure the delayed-type hypersensitivity (DTH) reaction to SARS-CoV-2*

- Tonix expects to initiate a first-in-human clinical study in the fourth quarter of 2021. TNX-2100, designed to measure functional *in vivo* T cell immunity to SARS-CoV-2, is a test comprising three different mixtures of synthetic peptides (TNX-2110, -2120 and -2130). Tonix's proposed skin test has the potential to serve as: 1) a biomarker for cellular (T-cell mediated) immunity and protective immunity; 2) a method to stratify participants in COVID-19 vaccine trials by immune status; 3) an endpoint in COVID-19 vaccine trials, and 4) a biomarker of durability of vaccine *protection.*

*TNX-3500 (sangivamycin): antiviral inhibitor of SARS-CoV-2 for the treatment of COVID-19 and potential other viral disorders*

- In April 2021, Tonix entered into an exclusive worldwide licensing agreement with OyaGen, Inc. to develop TNX-3500 (sangivamycin, formerly OYA1) for the treatment of COVID-19 and potentially other viral disorders. It has demonstrated broad-spectrum activity in laboratory-based assays against the coronaviruses SARS-CoV-2 and MERS-CoV. Tonix intends to conduct further nonclinical animal studies prior to submitting an IND and initiating a Phase 1 study.

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*Immunology Pipeline*

*TNX-1500 (anti-CD154 monoclonal antibody): third generation monoclonal antibody as first line monotherapy for preventing or treating organ transplant rejection and treating autoimmune disorders.*

- Tonix expects to start a Phase 1 study in the second half of 2022. In experiments at the Massachusetts General Hospital, a teaching hospital of Harvard Medical School, TNX-1500 product candidate is being studied as monotherapy or in combination with mycophenolate mofetil in heart and kidney organ transplants in non-human primates. Preliminary results from an ongoing experiment in heart transplants indicated that TNX-1500 appeared to have comparable efficacy to historical experiments using the chimeric mouse-human anti-CD40L monoclonal antibody (mAb) hu5c8 and no evidence of thrombosis has been observed.

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

**Recent Highlights—Facilities and Corporate**

- In August 2021, Tonix announced that it has commenced construction on its Advanced Development Center (ADC) for the development and manufacturing of Good Manufacturing Practice or GMP live-virus vaccines to support Phase 1 and 2 clinical trials. The facility is planned to be BSL-2 and expected to be operational in the first half of 2022. A groundbreaking ceremony held August 3, 2021 was attended by local, state, and federal officials, including U.S. Representative Bill Keating, Massachusetts Housing and Economic Development Secretary Mike Kennealy and New Bedford Mayor Jon Mitchell.

- In July 2021, Tonix entered into a contingent non-binding Purchase and Sales Agreement in connection with an infectious disease R&D facility in Maryland, which is expected to provide internal capacity to discover and develop vaccines and antiviral drugs against COVID-19, its variants, and other infectious diseases. The BSL-2 facility, currently owned and operated by Tonix partner Southern Research, has housed research relating to Tonix's COVID-19 vaccine candidate, TNX-1800, and to Tonix's smallpox and monkeypox candidate, TNX-801. Tonix expects the transaction to close in the fourth quarter of 2021.

- In June 2021, Tonix announced that plans were advancing to construct a commercial-scale manufacturing facility to develop and manufacture vaccines in Hamilton, Montana. Construction on the greenfield site is expected to start in 2022.

- Tonix announced its addition to both the broad-market Russell 3000® index and the small-cap Russell 2000® Index as part of the annual reconstitution of the Russell stock indexes, which was effective after the market opened on June 28, 2021. Russell indexes are widely used by investment managers and institutional investors for index funds and as benchmarks for active investment strategies.

- In July 2021, Tonix announced the appointment to its Board of Directors of Carolyn E. Taylor, who brings over 35 years of experience in corporate law, including 15 years as a partner at Covington & Burling LLP and six years as general counsel of two start-up companies.

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**Recent Highlights--Financial**

As of June 30, 2021, Tonix had $165.7 million of cash and cash equivalents, compared to $77.1 million as of December 31, 2020.

Cash used in operations was approximately $19.1 million for the three months ended June 30, 2021, compared to $10.1 million for the three months ended June 30, 2020. The increase in cash used in operations resulted primarily from an increase in research and development programs and general and administrative activities as defined below.

Second Quarter 2021 Financial Results

Research and development expenses for the second quarter of 2021 were $18.1 million, compared to $10.6 million for the same period in 2020. This increase is predominately due to increased non-clinical expenses of $7.1 million, manufacturing expenses of $2.7 million, employee-related expenses of $1.2 million and regulatory/legal expenses of $0.4 million offset by a decrease in clinical expenses of $4.1 million. We expect research and development expenses to increase during 2021 as we move our clinical development programs forward and continue to invest in our development pipeline.

General and administrative expenses for the second quarter of 2021 were $5.4 million, compared to $3.6 million for the same period in 2020. The increase in primarily due to an increase in employee-related expenses of $1.1 million, an increase in investor relations/public relations expenses of $0.2 million, an increase in financial reporting expenses of

$0.2 million and an increase in insurance premiums of $0.2 million.

Net loss available to common stockholders was $23.6 million, or $0.07 per share, basic and diluted, for the second quarter of 2021, compared to net loss of $14.2 million, or $0.23 per share, basic and diluted, for the second quarter of 2020. The basic and diluted weighted average common shares outstanding for the second quarter of 2021 was 331,281,242, compared to 62,391,006 shares for the second quarter of 2020.

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**About Tonix Pharmaceuticals Holding Corp.**

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing small molecules and biologics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is primarily composed of central nervous system (CNS) and immunology product candidates. The Company's CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL [1], is in mid-Phase 3 development for the management of fibromyalgia. Tonix's immunology portfolio includes vaccines to prevent infectious diseases and biologics to address immunosuppression, cancer, and autoimmune diseases. Tonix's lead vaccine candidate, TNX-1800 [2], is a live replicating vaccine based on the horsepox viral vector platform to protect against COVID-19, primarily by eliciting a T cell response. Tonix reported positive efficacy data from animal studies of TNX-1800 in the first quarter of 2021. TNX-801 [2], live horsepox virus vaccine for percutaneous administration, is in development to protect against smallpox and monkeypox. TNX-3500 [3] (sangivamycin) is a small molecule antiviral drug in the pre-IND stage of development.

*[1] TNX-102 SL is an investigational new drug and has not been approved for any indication.*
*[2] TNX-1800 and TNX-801 are investigational new biologics at the pre-IND stage of development and have not been approved for any indication.*
*[3] TNX-3500 is an investigational new drug at the pre-IND stage of development and has not been approved for any indication.*

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

**Forward Looking Statements**

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the development of R&D facilities, risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval, and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2020, as filed with the Securities and Exchange Commission (the "SEC") on March 15, 2021, and periodic reports filed with the SEC on or after the date thereof. All Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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**TONIX PHARMACEUTICALS HOLDING CORP.**
**CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS**
**(In Thousands, Except Share and Per Share Amounts)**
**(unaudited)**

| | Three Months Ended June 30, | | Six Months Ended June 30, | |
|---|---|---|---|---|
| | **2021** | **2020** | **2021** | **2020** |
| COSTS AND EXPENSES: | | | | |
| Research and development | $ 18,133 | $ 10,571 | $ 33,460 | $ 15,247 |
| General and administrative | 5,429 | 3,621 | 10,838 | 6,242 |
| | 23,562 | 14,192 | 44,298 | 21,489 |
| Operating Loss | (23,562) | (14,192) | (44,298) | (21,489) |
| Interest and other income, net | 9 | 13 | 92 | 37 |
| Net loss | (23,553) | (14,179) | (44,206) | (21,452) |
| Warrant deemed dividend | — | — | — | 451 |
| Preferred stock deemed dividend | — | — | — | 1,260 |
| Net loss available to common stockholders | $ (23,553) | $ (14,179) | $ (44,206) | $ (23,163) |
| Net loss per common share, basic and diluted | $ (0.07) | $ (0.23) | $ (0.14) | $ (0.54) |
| Weighted average common shares outstanding, basic and diluted | 331,281,242 | 62,391,006 | 310,807,619 | 43,209,988 |

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**TONIX PHARMACEUTICALS HOLDING CORP.**
**CONDENSED CONSOLIDATED BALANCE SHEETS**
**(in thousands)**

**(Unaudited)**

| | June 30, 2021 | December 31, 2020[1] |
|---|---|---|
| **Assets** | | |
| Cash and cash equivalents | $ 165,719 | $ 77,068 |
| Prepaid expenses and other | 11,550 | 10,921 |
| Total current assets | 177,269 | 87,989 |
| Other non-current assets | 11,896 | 10,194 |
| Total assets | $ 189,165 | $ 98,183 |
| | | |
| **Liabilities and stockholders' equity** | | |
| Total liabilities | $ 8,672 | $ 10,535 |
| Stockholders' equity | 180,493 | 87,648 |
| Total liabilities and stockholders' equity | $ 189,165 | $ 98,183 |

[1]The condensed consolidated balance sheets for the year ended December 31, 2020 has been derived from the audited financial statements but does not include all of the information and footnotes required by accounting principles generally accepted in the United States for complete financial statements.

**Jessica Morris (corporate)**
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**Exhibit 99.02**

# Investor Presentation
## NASDAQ:TNXP



TONIX PHARMACEUTICALS

August 2021

**Version P0312 8-9-2021 (Doc 0877)**



# Cautionary Note on Forward-Looking Statements



Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, 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.

# 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 two 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



# Tonix Pipeline – CNS Portfolio



| CANDIDATES | | INDICATION | STATUS |
|---|---|---|---|
| CNS Portfolio | TNX-102 SL[1] | Fibromyalgia (FM) | Mid-Phase 3 – ongoing |
| | | Posttraumatic Stress Disorder (PTSD) | Phase 3 ready |
| | | Agitation in Alzheimer's | Phase 2 ready |
| | | Alcohol Use Disorder | Phase 2 ready |
| | | Long COVID (PASC[2]) | 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 |

[1]TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication. Long COVID/PASC program is also included in the COVID-19 Portfolio.
[2]Post-Acute Sequelae of COVID-19.
[3]Pre-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.
[4]TNX-1300 (double-mutant cocaine esterase) is an investigational new biologic and has not been approved for any indication; licensed from Columbia University.
[5]Acquired from Trigemina; license agreement with Stanford University
[6]A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900; Phase 2 expected to start Q4'21
[7]Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)
[8]TNX-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 1H 2022
[9]Acquired from TRImaran Pharma; license agreement with Wayne State University

# Tonix Pipeline – COVID-19 Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| COVID-19 Portfolio | TNX-1800 | COVID-19 vaccine[1] | Phase 1, 1H 2022* |
| | TNX-2300 | COVID-19 vaccine[2] | Preclinical |
| | TNX-102 SL | Long COVID (PASC[3]) | Clinical – pre-IND[4] |
| | TNX-2100 | SARS-CoV-2 Diagnostic for T cell immunity[5] | First-in-human study, Q4 2021* |
| | TNX-3500 | COVID-19 (SARS-CoV-2) antiviral[6] | Preclinical |

**Represents expected milestones*

[1]Live attenuated vaccine based on horsepox virus vector
[2]Live attenuated vaccine based on bovine parainfluenza virus vector; option for license with Kansas State University
[3]Post-Acute Sequelae of COVID-19
[4]Pre-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
[5]*In vivo* diagnostic: SARS-CoV-2 peptide epitope mixtures for intradermal administration to measure delayed-type hypersensitivity to SARS-CoV-2
[6]Sangivamycin, for injection



# Tonix Pipeline – Immunology & Biodefense Portfolios



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Immunology /Immuno-oncology (IO) | TNX-1500[1] | Organ Transplant Rejection/Autoimmune Conditions | Preclinical |
| | TNX-1700[2] | Gastric and pancreatic cancers | Preclinical |

| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Biodefense Portfolio | TNX-801[3] | Smallpox and monkeypox preventing vaccine | Preclinical |
| | TNX-701 | Radioprotection | Preclinical |

[1]anti-CD40L humanized monoclonal antibody
[2]Recombinant trefoil factor 2 (rTFF2) based protein; licensed from Columbia University
[3]Live attenuated vaccine based on horsepox virus

# TNX-102 SL[1]

- **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)

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





# TNX-102 SL FM Lead Program Background on Fibromyalgia

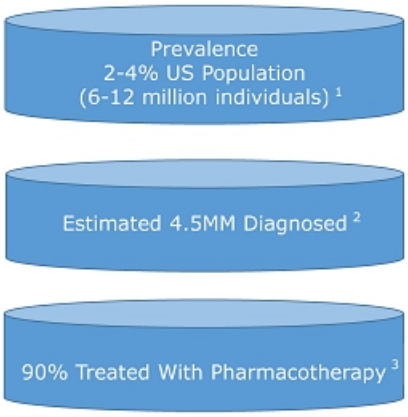
**Fibromyalgia (FM):**

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 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(5): e0138024.
3. Decision Resources, Fibromyalgia, 2012

# Challenges with Current Pharmacotherapy



### *Limitations of Current Therapies*

***Fewer than half of those treated for fibromyalgia receive relief from the three FDA-approved drugs[1]***

- 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 months[2]

***Polypharmacy***

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

***Opioid usage is not uncommon***

### *Market Dissatisfaction*

***Only 43% of patients indicated that they are satisfied with their medication for FM[5]***

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. Sarmento et al., J Opioid Manag 2019; 15(6):469-77 – 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



### *Unmet Medical Need:*

Current treatment patterns indicate that new, more effective, and better-tolerated treatments are necessary for management of FM[1]

### *Ideal Treatment Profile:*

**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**



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



***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

# Positive Phase 3 F304/RELIEF Study: Design



**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


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

**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)



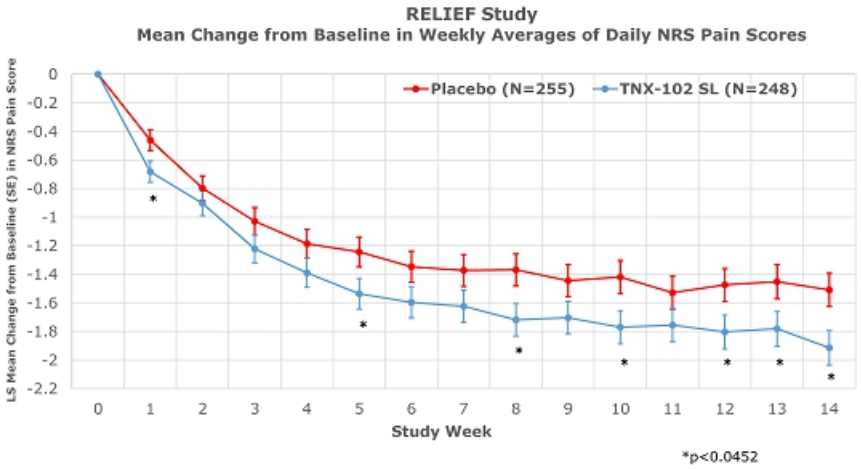
| Primary Outcome Measure at Week 14 | Placebo (N=255) | TNX-102 SL (N=248) | Treatment Difference | P value |
|---|---|---|---|---|
| | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Difference in LS Mean Change from Baseline Between TNX-102 SL and Placebo (SE) | |
| Daily Pain 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# |

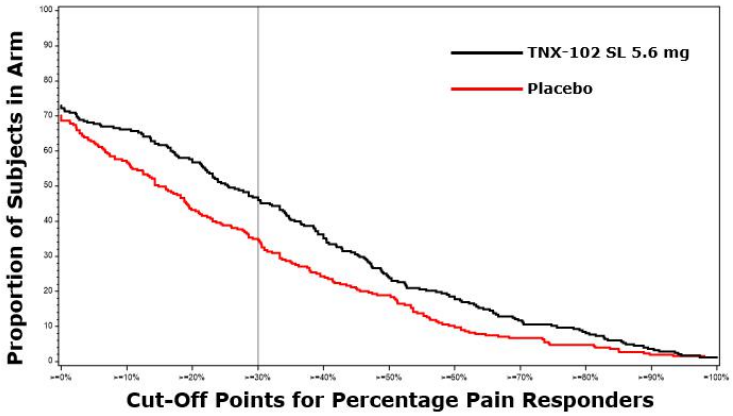
# nominally significant at p<0.0452
[1] Combined periods (pre- and post-interim analysis); responder analysis is by Logistic Regression (missing = non-responder); the five mean change analyses are by Mixed Model Repeated Measures with Multiple Imputation
Abbreviations: FIQ-R = Fibromyalgia Impact Questionnaire – 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

# 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






# Adverse Events*(AEs) in F304/RELIEF Study



**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

# Safety and Tolerability in F304/RELIEF Study



- 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



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



## 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 participants [1]

**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***

[1]Pending agreement from FDA on statistical analysis plan
[2]Two 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

**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) include[1]:**

- 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
- Clinical phase of interim cohort completed

**Topline results expected in 1st quarter 2022**

**Potential pivotal efficacy study to support NDA approval**

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



| | |
|---|---|
| **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<br>•European Patent Office (EPO) issued European Patent No. 2968992 in December 2019 (validated in 37 countries). Opposition filed in October 2020 by Hexal AG<br>• China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019<br>•Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018<br>•8 granted patents (Indonesia, Saudi Arabia, New Zealand, Australia, Mexico, Taiwan, Israel, South Africa)<br>•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<br>• 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<br>• Australian Patent Office issued Australian Patent No. 2013274003 in October 2018 and Patent No. 2018241128 in September 2020<br>• JPO issued Japanese Patent No. 6259452 in December 2017<br>• 20 patent applications pending (1 being allowed in Mexico) |



# TNX-102 SL for Long COVID (PASC)



**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 fog[3]
- Like fibromyalgia, is experienced by women at a higher rate, approximately four times more, than that of men[4]
- Long COVID is a chronic disabling condition that is expected to result in a significant global economic burden[5]
- 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 December[6]

*[1]Feb. 24, 2021 - White House COVID-19 Response Team press briefing; Feb 25, 2021 - policy brief from the World Health Organization on long COVID*
*[2]Nalbandian, Ani, et al. "Post-acute COVID-19 syndrome." Nature Medicine (2021): 1-15.*
*[3]Clauw DJ, et al. Pain. 2020 Aug; 161(8): 1694–1697.*
*[4]Cox, 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*
*[5]Briggs, Andrew, and Anna Vassall. "Count the cost of disability caused by COVID-19." (2021): 502-505.*
*[6]The 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.*

# Opportunities to Expand TNX-102 SL to Other Indications



**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-1800[1]

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

- **Targeted Indication**: COVID-19 vaccine

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

# TNX-1800[1]: 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 undetectable[2] CoV-2 by PCR in upper and lower airways[3]
- **Manufacturing agreement with FUJIFILM Diosynth**
  - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
  - Expect GMP[4] clinical supply to be ready for human trials targeted to begin in 1st half of 2022[5]

[1]TNX-1800 (horsepox/Cov-2 spike live vaccine) is at the pre-IND stage of development
[2]Less than 1,000 genomes by PCR
[3]Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage
[4]Good Manufacturing Practice = GMP
[5]We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones



# 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?

**Effect on forward transmission (spread of infection to others)**
- Concerns about whether vaccinated people can be infectious to others

**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 | Unknown for variants like delta | 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, LNP[1]-encapsulated CoV-2 Spike ["Spike"] mRNA) EUA[2]
  - Pfizer & BioNTech (LNP-encapsulated Spike mRNA) EUA
- **Subunit**
  - Sanofi/GSK (recombinant Spike protein with adjuvant[3]) In Phase 3
  - Novavax (NVX-CoV2373, recombinant Spike protein with adjuvant[4]) 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 measles[5]-encoding Spike) Terminated Jan '21 - Phase 1[6]
  - Merck (V591, pseudo-typed VSV[7]-encoding Spike) Terminated Jan '21 - Phase 1[6]

[1]Lipid Nanoparticle = "LNP"
[2]Emergency Use Authorization = "EUA"
[3]GSK adjuvant AS03 contains squalene, DL-α-tocopherol and polysorbate
[4]Novavax adjuvant Matrix-M1 contains saponin extracted from the Quillaja saponaria Molina tree



[5]Measles-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
[7]VSV = 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 Diseases[1]



- **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

[1]For example, the eradication of smallpox, containment of measles, mumps, and rubella

# TNX-1800[1]: Engineered for Long-term Immunity



**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 vaccine[2]
- 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

[1]TNX-1800 (horsepox/Cov-2 spike live vaccine) is at the pre-IND stage of development
[2]Brinkmann A et al, Genome Biology (2020) 21:286 https://doi.org/10.1186/s13059-020-02202-0



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



**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 (≥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 (≤1:10 titer).
- Level of neutralizing anti-CoV-2 antibody production was similar between the low and high dose TNX-1800 groups ($1 \times 10^6$ Plaque Forming Units [PFU]) and $3 \times 10^6$ 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.

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



**CHALLENGE WITH SARS-COV-2:**

- Six days after challenge with SARS-CoV-2, TNX-1800 vaccinated animals had undetectable[1] SARS-CoV-2 in upper or lower airways[2].

**DOSE:**

- Supports the expectation that TNX-1800 at the low dose of 1 x $10^6$ 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.

[1]Less than 1,000 genomes by PCR
[2]Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage



# Why Use a Horsepox Platform for a Vaccine?



## Horsepox can be engineered to express foreign genes

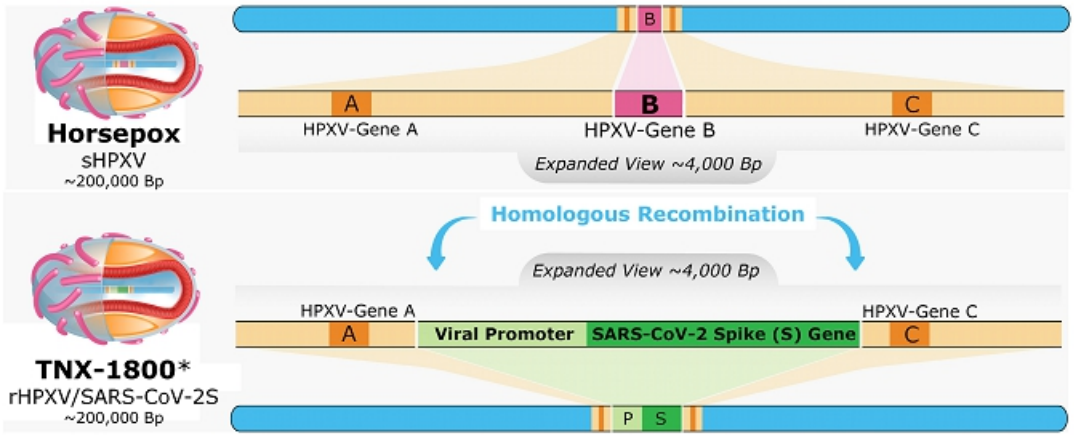
- Lack of persistence or genomic integration in the host
- Strong immunogenicity as a vaccine
- Readily manufacture at scale
- Live, attenuated vaccine – direct antigen presentation

## 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

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



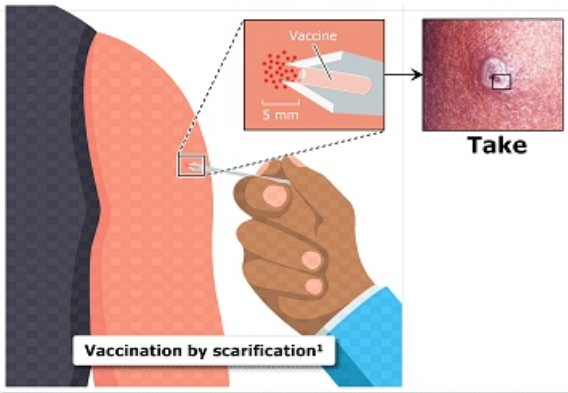



*TNX-1800 is at the pre-IND stage of development



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








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

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

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

# Unique Challenges of SARS-CoV-2



| SARS | | SARS-CoV-2 |
|---|---|---|
| *Rate of death*[1,2] **~10%** | 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 deaths[5] | *Rate of death*[1,4] **0.003% - 5.4%** |
| *Deaths*[2] **744** | | *Deaths (as of July 2021)*[5] **>4.2M** |
| *Rate of infectivity*[1] **0.4** | SARS-CoV-2 is more infectious, has a longer incubation time, and presents asymptomatically in more individuals, making it highly spreadable[1] | *Rate of infectivity*[1,4] **~2.5** |
| *Incubation time*[2] **2-7 days** | | *Incubation time*[2,4] **6-14 days** |
| *Asymptomatic*[3] **~13%** | | *Asymptomatic*[4] **~40%** |

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 July 2021. https://coronavirus.jhu.edu/map.html



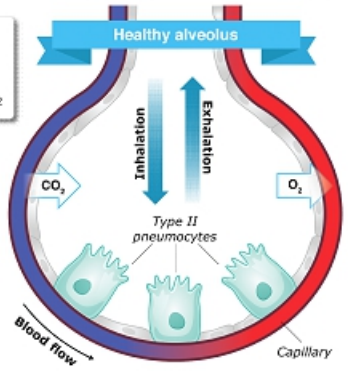
# Infection of Type II Pneumocytes Can Lead to Lethal Respiratory Illness

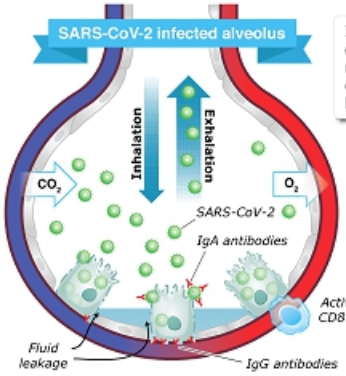


**SARS-CoV-2 Infects Type II Pneumocytes in Lung Alveoli**[1]

Type II pneumocytes in the alveoli secrete pulmonary surfactants that are necessary for effective gas exchange.[2]

These cells also serve as progenitor cells for repairing damaged alveoli.[2]




In COVID-19, infection of type II pneumocytes results in impaired gas exchange and fluid leakage into alveoli.[3]

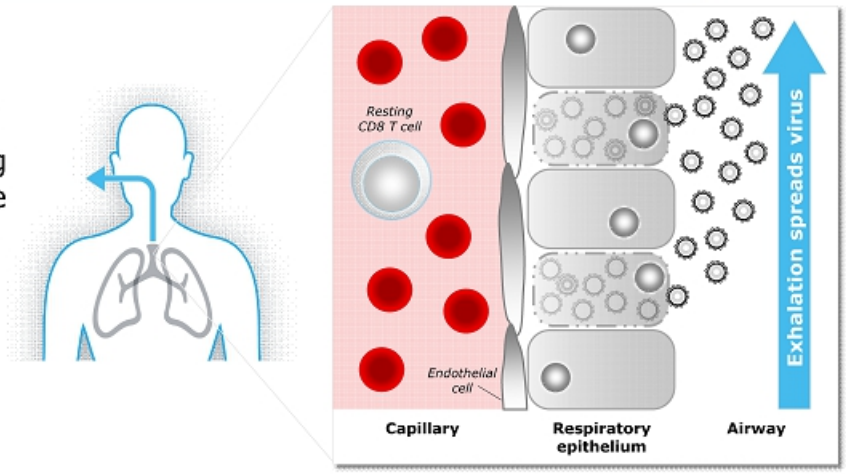
Strong antibody responses to SARS-CoV-2 are linked to more severe disease and fatality.[4]

1. Knudsen L, et al. *Histochem Cell Biol.* 2018;150(6):661-676.
2. Mason RJ. *Am J Physiol Lung Cell Mol Physiol.* 2020;319(1):115-120.
3. Xu Z, et al. *Lancet Respir Med.* 2020;8(4):420-422.
4. Lee WS, et al. *Nat Microbiol.* 2020;5:1185-1191.

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



- 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



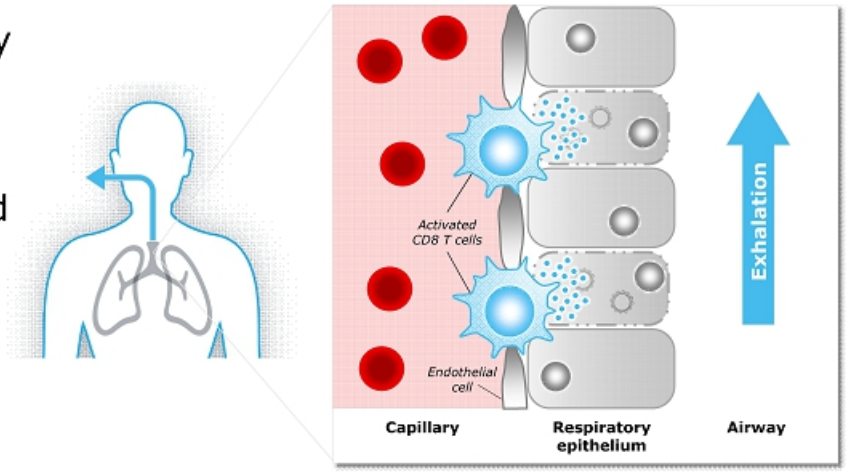

Ber-Dn YM, et al. eLife. 2020;9:e57309.



# CoV-2 Specific T Cells Kill the Virus Factories



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




Ber-Dn YM, et al. eLife. 2020;9:e57309.

# Contrasting T cell and Antibody Immunity



- **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



# TNX-1800: Potential Development and Uses



- **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-2100[1] skin test may be used to stratify for T cell immunity

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

# COVID-19 Vaccine Platform: Planned Internal Development and Manufacturing Capabilities



**Infectious Disease R&D Center (RDC) – Frederick, MD**

- Function: Accelerated development of vaccines and antiviral drugs against COVID-19, its variants and other infectious diseases
- Description: ~48,000 square feet, BSL-2, currently operated by Southern Research
- Status: Acquisition expected to close in the fourth quarter of 2021

**Advanced Development Center (ADC) – New Bedford, MA**

- Function: Development and clinical scale manufacturing of live-virus vaccines to support Phase 1 and Phase 2 trials
- Description: ~45,000 square feet, under construction, planned BSL-2
- Status: Expected to be operational in first half 2022

**Commercial Manufacturing Center (CMC) – Hamilton, MT**

- Function: Commercial scale manufacturing of live-virus vaccines
- Description: ~44 acre green field site, planned BSL-2
- Status: Planning for initiation of construction in 2022





# TNX-3500[1]

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

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

# TNX-3500[1]: SARS-CoV-2 Antiviral for the Treatment of COVID-19



**TNX-3500 (sangivamycin) – potential monotherapy antiviral[2]**

- 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 studies[3]
- 65 times more potent than remdesivir in inhibiting SARS-CoV-2 in cell culture infectivity studies (dose to achieve $IC_{90}$)[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 $IC_{90}$
- 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

[1]TNX-3500 is in the pre-IND stage of development and has not been approved for any indication.
[2]Bennett, RP et al., *Viruses*. 2020 13(1):52. doi: 10.3390/v13010052.
[3]Cavins JA et al., *Cancer Chemotherapy Reports*. 1967. 51(4)
[4]Data on file, live virus BSL-4 testing conducted by NIAID in collaboration with OyaGen





# TNX-2300[1]

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

[1]TNX-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



## 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-2300[1] drives expression of CoV-2 spike and CD40-L

## Live attenuated vaccines based on bovine parainfluenza virus[2-6]

- 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

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





# TNX-2100[1]

- **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

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

# TNX-2100[1]: Potential Skin Test to Measure SARS-CoV-2 Exposure and T Cell Immunity



## 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
- DTH to SARS-CoV-2 spike protein has been shown in COVID-convalescent and vaccinated individuals[3,4]

## Potentially scalable test for widespread use

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

*[1]TNX-2100 is in the pre-IND stage of development and has not been approved for any indication.*
*[2]Intracellular cytokine staining (ICS) measured by flow cytometry after in vitro stimulation of purified peripheral blood mononuclear cells*
*[3]Barrios, Y et al. Clinical Immunol. (2021) 226:108730*
*[4]Barrios, Y et al. Vaccines (2021) 9:575*



# TNX-2100: Potential Uses and Development Plans



## 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

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

# TNX-1300[1]

- **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**

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



# TNX-1300* for the Treatment of Cocaine Intoxication



**Recombinant protein that degrades cocaine in the bloodstream[1]**

- 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 plants[2]
- 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]**

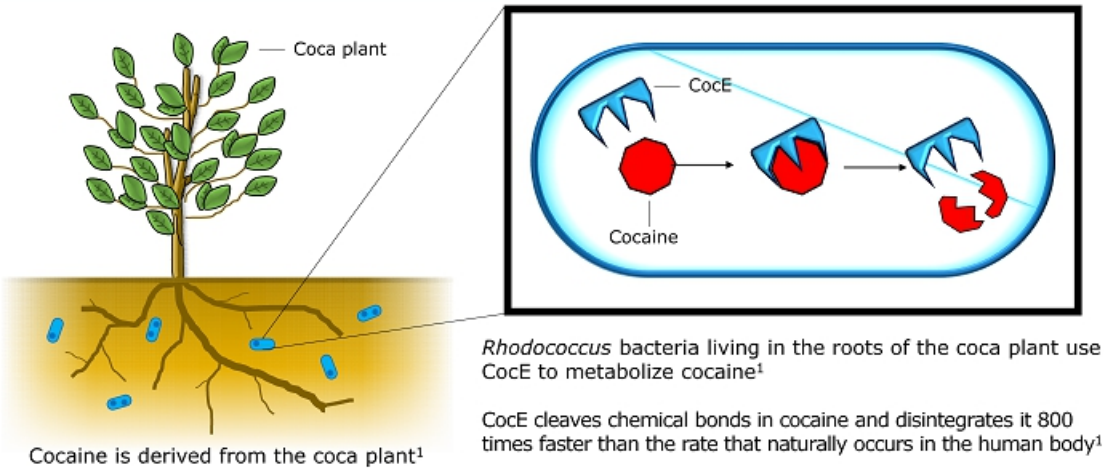
- Volunteer cocaine abusers received cocaine 50 mg *i.v.* infusion over 10 minutes
- TNX-1300 given one minute after completion of cocaine infusion
  - Rapidly reversed the physiologic effects of cocaine; cocaine plasma exposures dropped by 90% within two minutes
  - Well tolerated with the most frequently 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.

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






Cocaine is derived from the coca plant[1]

*Rhodococcus* bacteria living in the roots of the coca plant use CocE to metabolize cocaine[1]

CocE cleaves chemical bonds in cocaine and disintegrates it 800 times faster than the rate that naturally occurs in the human body[1]

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



# TNX-1300 Development Plan



- **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

# TNX-1900[1]

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

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



# 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 receptor[1]

**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

# TNX-1900 for the Treatment of Migraine – Prevalence



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

**Migraine is the second leading cause of years lived with disability[1]**

**In U.S., the estimated cost of all migraine headaches was $78 billion in 2014[2]**

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

**Chronic migraine (≥ 15 headaches / month ) effects about 1-2% of individuals[3]**

- 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 receptor[4]

[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, Cephalagia, 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



**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**

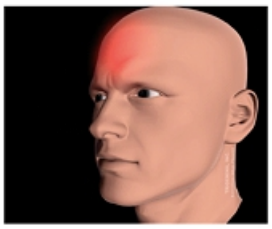
TNX-1900 believed to partially block release of CGRP in the trigeminal nerve

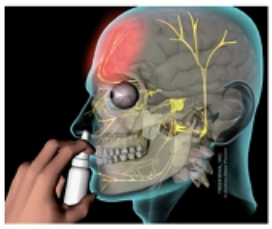
Proprietary Nasal to Brain Delivery

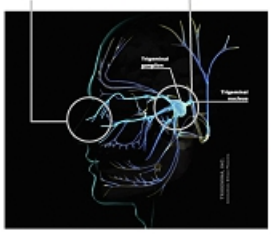
Permeates nasal mucosa

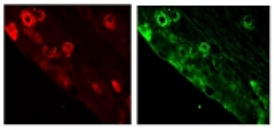
Transported to trigeminal system and brain

Oxytocin Receptors Co-Localize with CGRP in most Trigeminal Ganglia Neurons



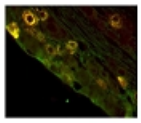






Oxytocin Receptors CGRP

Overlay of Oxytocin Receptors and CGRP Staining



HEAD PAIN | PATIENT USES TNX-1900 | TARGETED DELIVERY

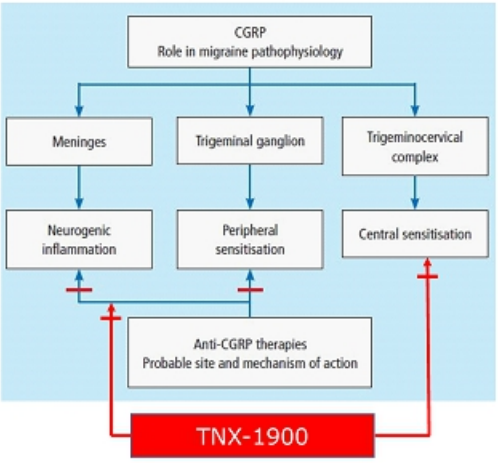
Abbrev. CGRP, calcitonin gene-related peptide

# 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-glial 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



**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 fourth 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





# TNX-2900[1]

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

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

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



**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 obesity[1]**

- 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**

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





# TNX-601 CR[1]

- **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

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

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



**Proprietary new controlled release formulation for once-daily dosing**

- Pending toxicology results, and IND clearance, Phase 2 study expected to start in 1H 2022
- 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.*



# TNX-601 CR: A Potential Treatment for Depression



**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

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



## 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" study[1]
- 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

[1]Pending a meeting and agreement on study design with FDA controlled substances staff (CSS)



# TNX-601 CR Intellectual Property – U.S. Protection expected until 2037



| | |
|---|---|
| **Composition of matter (crystalline oxalate salt) and method of use:**<br>**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.<br>•USPTO Provisional patent filed March 2021<br>•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:**<br>**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<br>• 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)<br>• Canadian Patent Office issued Canadian Patent No. CA 2,723,688 in June 2018 for treating cognitive impairment associated with corticosteroid treatment<br>• 1 patent application pending (United States) |

# TNX-1500[1]

- **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

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





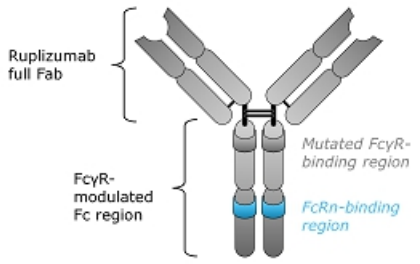
# TNX 1500, a New CD40 Ligand (CD40L) Antibody, for the Prevention of Allograft Rejection

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 rejection[1]

- **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

Phase 1 study expected to start 2H 2022

**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.

# Pipeline[1] Summary – by Select Therapeutic Areas



## Pain

- **TNX-102 SL (sublingual cyclobenzaprine) for fibromyalgia**
  Phase 3/RELIEF
  Phase 3/RALLY
- **TNX-1900 (intranasal oxytocin) for craniofacial pain**
  Clinical – pre-IND stage

## Psychiatry

- **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 inhibitor[2]) for PTSD, Depression and ADHD[3]**
  Preclinical

## Addiction Medicine

- **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

## Neurology

- **TNX-1900 (intranasal oxytocin) for migraine**
  Clinical – pre-IND stage
- **TNX-102 SL (sublingual cyclobenzaprine) for Long COVID (PASC)**
  Clinical – pre-IND stage

## Rare/Orphan Disease

- **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-ol) is an inhibitor of reuptake of three monoamine neurotransmitters (serotonin, norepinephrine and dopamine) – licensed from Wayne State University
[3] ADHD = attention deficit hyperactivity disorder



# Pipeline[1] Summary – by Select Therapeutic Areas (continued)



## Public Health

- **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

## Biodefense

- **TNX-801 (live horsepox vaccine) for preventing smallpox and monkeypox**
  Preclinical
- **TNX-701 (oral radioprotective agent) for radioprotection**
  Preclinical

## Transplantation/ Autoimmunity

- **TNX-1500 (anti-CD40-Ligand) for preventing rejection of solid organ transplants and autoimmune disease**
  Preclinical

## Oncology

- **TNX-1700 (rTFF2[2]) 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

# Milestones – Recently Completed and Upcoming[1]



| | |
|---|---|
| ☑ 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 |
| ☑ 3rd Quarter 2021 | Interim analysis of TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia reported |

**Data**

| | |
|---|---|
| ❑ **4th Quarter 2021** | **Topline data from TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected** |

**Clinical Trial Initiations – Four New Trials This Year**

| | |
|---|---|
| ❑ **3rd Quarter 2021** | **Phase 2 OL safety study of TNX-1300 in ED setting for cocaine intoxication expected** |
| ❑ **4th Quarter 2021** | **Phase 2 study of TNX-1900 for the treatment of migraine expected** |
| ❑ **4th Quarter 2021** | **Phase 3 study of TNX-102 SL for the treatment of PTSD in Kenya 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** |
| ❑ **1st Half 2022** | **Phase 2 study of TNX-601 CR for the treatment of major depressive disorder expected** |
| ❑ **2nd Half 2022** | **Phase 1 study of TNX-1500 for prevention of allograft rejection expected** |

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



# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT X · Fusilev (levoleucovorin) for injection · vela

**Gregory Sullivan, MD**
Chief Medical Officer

**Bradley Saenger, CPA**
Chief Financial Officer

Shire · VERTEX · Steward · pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank · svb Silicon Valley Bank · American Capital

TONIX PHARMACEUTICALS

# *Thank You!*

**Exhibit 99.03**

# Investor Presentation
## NASDAQ:TNXP



TONIX PHARMACEUTICALS

August 2021

**Version P0311 8-9-2021 (Doc 0876)**



# Cautionary Note on Forward-Looking Statements



Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, 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.

# 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 two 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



# Tonix Pipeline – CNS Portfolio



| CANDIDATES | | INDICATION | STATUS |
|---|---|---|---|
| CNS Portfolio | TNX-102 SL[1] | Fibromyalgia (FM) | Mid-Phase 3 – ongoing |
| | | Posttraumatic Stress Disorder (PTSD) | Phase 3 ready |
| | | Agitation in Alzheimer's | Phase 2 ready |
| | | Alcohol Use Disorder | Phase 2 ready |
| | | Long COVID (PASC[2]) | 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 |

[1]TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication. Long COVID/PASC program is also included in the COVID-19 Portfolio.
[2]Post-Acute Sequelae of COVID-19.
[3]Pre-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.
[4]TNX-1300 (double-mutant cocaine esterase) is an investigational new biologic and has not been approved for any indication; licensed from Columbia University.
[5]Acquired from Trigemina; license agreement with Stanford University
[6]A Phase 2 trial under an investigator-initiated IND has been completed in the U.S. using TNX-1900; Phase 2 expected to start Q4'21
[7]Co-exclusive license agreement with French National Institute of Health and Medical Research (Inserm)
[8]TNX-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 1H 2022
[9]Acquired from TRImaran Pharma; license agreement with Wayne State University

# Tonix Pipeline – COVID-19 Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| COVID-19 Portfolio | TNX-1800 | COVID-19 vaccine[1] | Phase 1, 1H 2022* |
| | TNX-2300 | COVID-19 vaccine[2] | Preclinical |
| | TNX-102 SL | Long COVID (PASC[3]) | Clinical – pre-IND[4] |
| | TNX-2100 | SARS-CoV-2 Diagnostic for T cell immunity[5] | First-in-human study, Q4 2021* |
| | TNX-3500 | COVID-19 (SARS-CoV-2) antiviral[6] | Preclinical |

**Represents expected milestones*

[1]Live attenuated vaccine based on horsepox virus vector
[2]Live attenuated vaccine based on bovine parainfluenza virus vector; option for license with Kansas State University
[3]Post-Acute Sequelae of COVID-19
[4]Pre-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
[5]*In vivo* diagnostic: SARS-CoV-2 peptide epitope mixtures for intradermal administration to measure delayed-type hypersensitivity to SARS-CoV-2
[6]Sangivamycin, for injection



# Tonix Pipeline – Immunology & Biodefense Portfolios



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Immunology /Immuno-oncology (IO) | TNX-1500[1] | Organ Transplant Rejection/Autoimmune Conditions | Preclinical |
| | TNX-1700[2] | Gastric and pancreatic cancers | Preclinical |

| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Biodefense Portfolio | TNX-801[3] | Smallpox and monkeypox preventing vaccine | Preclinical |
| | TNX-701 | Radioprotection | Preclinical |

[1]anti-CD40L humanized monoclonal antibody
[2]Recombinant trefoil factor 2 (rTFF2) based protein; licensed from Columbia University
[3]Live attenuated vaccine based on horsepox virus

# TNX-102 SL FM Lead Program
# Background on Fibromyalgia



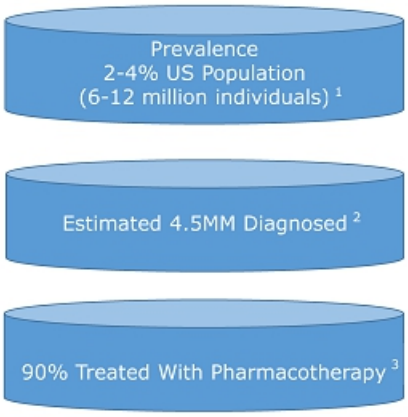
**Fibromyalgia (FM):**

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 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(5): e0138024.
3. Decision Resources, Fibromyalgia, 2012



# Challenges with Current Pharmacotherapy



## *Limitations of Current Therapies*

***Fewer than half of those treated for fibromyalgia receive relief from the three FDA-approved drugs[1]***
- 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 months[2]

***Polypharmacy***
- Average patient is using 2.6 drugs for treating their fibromyalgia, 50% of patients take 3 or more medications concomitantly[3]

***Opioid usage is not uncommon***

## *Market Dissatisfaction*

***Only 43% of patients indicated that they are satisfied with their medication for FM[5]***

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. Sarmento et al., J Opioid Manag 2019; 15(6):490-77 – 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



***Unmet Medical Need:***

Current treatment patterns indicate that new, more effective, and better-tolerated treatments are necessary for management of FM[1]

***Ideal Treatment Profile:***

**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**

[1]Two 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



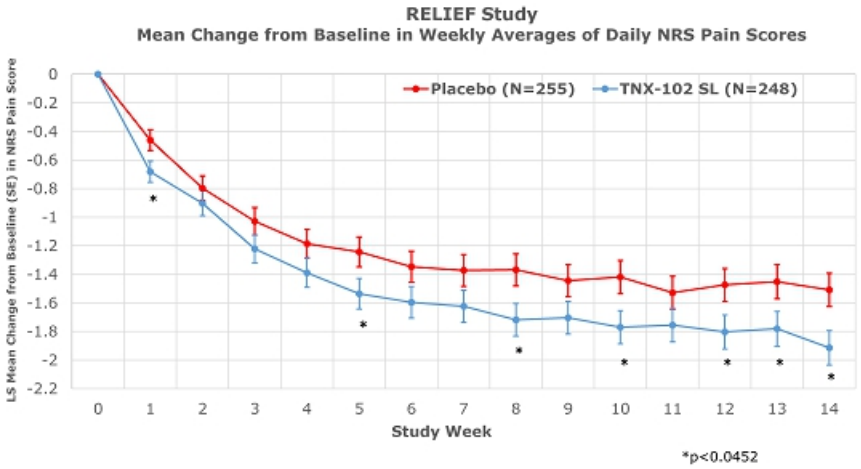
**Positive outcome for primary endpoint (daily pain) at Week 14**

| 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)



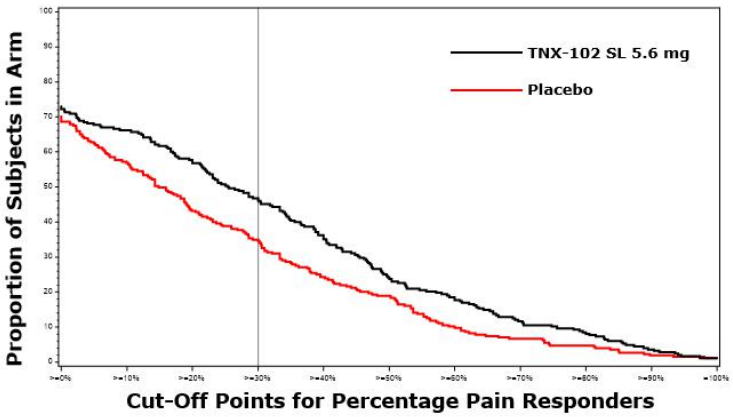





# F304/RELIEF Study: Continuous Responder Analysis (CRA) Graph



- 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



# 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



# Adverse Events*(AEs) in F304/RELIEF Study



**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

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



| | |
|---|---|
| **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<br>•European Patent Office (EPO) issued European Patent No. 2968992 in December 2019 (validated in 37 countries). Opposition filed in October 2020 by Hexal AG<br>• China National Intellectual Property Administration issued Chinese Patent No. ZL 201480024011.1 in April 2019<br>•Japanese Patent Office (JPO) issued Japanese Patent No. 6310542 in March 2018<br>•8 granted patents (Indonesia, Saudi Arabia, New Zealand, Australia, Mexico, Taiwan, Israel, South Africa)<br>•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<br>• 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<br>• Australian Patent Office issued Australian Patent No. 2013274003 in October 2018 and Patent No. 2018241128 in September 2020<br>• JPO issued Japanese Patent No. 6259452 in December 2017<br>• 20 patent applications pending (1 being allowed in Mexico) |



# TNX-102 SL for FM: Next Steps



**2nd Phase 3 study, RALLY (F306)**

- July 2021: Tonix stopped-enrollment in the RALLY study following an unblinded, pre-planned interim analysis by the Independent Data Monitoring Committee (IDMC)
- Based on interim analysis results of the first 50% (n=337) enrolled participants, the IDMC recommended stopping the trial as TNX-102 SL is unlikely to demonstrate a statistically significant improvement in the primary endpoint.
- Tonix will allow currently enrolled participants (n= 514) to complete the treatment period
- 4th quarter 2021: topline results expected, following completion of study for currently enrolled participants

**Following analysis of results from the full RALLY study, Tonix will determine next steps for this program**

# TNX-102 SL for Long COVID (PASC)



**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 fog[3]
- Like fibromyalgia, is experienced by women at a higher rate, approximately four times more, than that of men[4]
- Long COVID is a chronic disabling condition that is expected to result in a significant global economic burden[5]
- 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 December[6]

*[1]Feb. 24, 2021 - White House COVID-19 Response Team press briefing; Feb 25, 2021 - policy brief from the World Health Organization on long COVID*
*[2]Nalbandian, Ani, et al. "Post-acute COVID-19 syndrome." Nature Medicine (2021): 1-15.*
*[3]Clauw DJ, et al. Pain. 2020 Aug; 161(8): 1694–1697.*
*[4]Cox, 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*
*[5]Briggs, Andrew, and Anna Vassall. "Count the cost of disability caused by COVID-19." (2021): 502-505.*
*[6]The 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.*



# 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?

**Effect on forward transmission (spread of infection to others)**

- Concerns about whether vaccinated people can be infectious to others

**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-1800[1]: 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 undetectable[2] CoV-2 by PCR in upper and lower airways[3]
- **Manufacturing agreement with FUJIFILM Diosynth**
  - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
  - Expect GMP[4] clinical supply to be ready for human trials targeted to begin in 1st half of 2022[5]

[1]TNX-1800 (horsepox/Cov-2 spike live vaccine) is at the pre-IND stage of development
[2]Less than 1,000 genomes by PCR
[3]Upper airway = oropharyngeal swabs; Lower airway = tracheal lavage
[4]Good Manufacturing Practice = GMP
[5]We 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



| 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 | Unknown for variants like delta | 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 |

# COVID-19 Vaccine Platform: Planned Internal Development and Manufacturing Capabilities



## Infectious Disease R&D Center (RDC) – Frederick, MD

- Function: Accelerated development of vaccines and antiviral drugs against COVID-19, its variants and other infectious diseases
- Description: ~48,000 square feet, BSL-2, currently operated by Southern Research
- Status: Acquisition expected to close in the fourth quarter of 2021

## Advanced Development Center (ADC) – New Bedford, MA

- Function: Development and clinical scale manufacturing of live-virus vaccines to support Phase 1 and Phase 2 trials
- Description: ~45,000 square feet, under construction, planned BSL-2
- Status: Expected to be operational in first half 2022

## Commercial Manufacturing Center (CMC) – Hamilton, MT

- Function: Commercial scale manufacturing of live-virus vaccines
- Description: ~44 acre green field site, planned BSL-2
- Status: Planning for initiation of construction in 2022



# TNX-3500[1]: SARS-CoV-2 Antiviral for the Treatment of COVID-19



## TNX-3500 (sangivamycin) – potential monotherapy antiviral[2]

- 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 studies[3]
- 65 times more potent than remdesivir in inhibiting SARS-CoV-2 in cell culture infectivity studies (dose to achieve $IC_{90}$)[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 $IC_{90}$
- Combination therapies for other viruses have reduced the emergence of drug resistant viral strains

## Development plans

- 3rd quarter 2021: plan to initiate animal studies

[1]TNX-3500 is in the pre-IND stage of development and has not been approved for any indication.
[2]Bennett, RP et al., *Viruses*. 2020 13(1):52. doi: 10.3390/v13010052.
[3]Cavins JA et al., *Cancer Chemotherapy Reports*. 1967. 51(4)
[4]Data on file, live virus BSL-4 testing conducted by NIAID in collaboration with OyaGen

# TNX-2100[1]: Potential Skin Test to Measure SARS-CoV-2 Exposure and T Cell Immunity



**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
- DTH to SARS-CoV-2 spike protein has been shown in COVID-convalescent and vaccinated individuals[3,4]

**Potentially scalable test for widespread use**

- Adaptive Biotech's T Detect™ COVID received FDA EUA – based on genetic analysis of T cell receptors
- Other tests[2] 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

*[1]TNX-2100 is in the pre-IND stage of development and has not been approved for any indication.*
*[2]Intracellular cytokine staining (ICS) measured by flow cytometry after in vitro stimulation of purified peripheral blood mononuclear cells*
*[3]Barrios, Y et al. Clinical Immunol. (2021) 226:108730*
*[4]Barrios, Y et al. Vaccines (2021) 9:575*



# TNX-1300: Cocaine Esterase (CocE)



**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

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



**Intranasal oxytocin(OT) has potential utility in treating migraine[1]**

- 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 a preservative-free intranasal formulation of magnesium and OT**

- Magnesium is known to potentiate the binding of oxytocin to its receptor[2]

**Initiation of Phase 2 study for treatment of chronic migraine anticipated in 4th quarter 2021**

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



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



**Prader-Willi syndrome is the most common genetic cause of life-threatening childhood obesity[1]**

- 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**

[1]Foundation 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)



**Proprietary new controlled release formulation for once-daily dosing**

- Pending toxicology results, and IND clearance, Phase 2 study expected to start in 1H 2022
- 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



**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

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

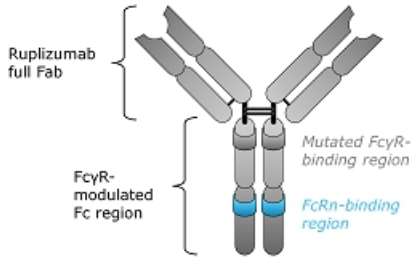


The CD40-CD40L pathway is a pivotal immune system modulator and is a well-established and very promising treatment target to more safely prevent allograft rejection[1]

- **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

Phase 1 study expected to start 2H 2022

**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.



# Milestones – Recently Completed and Upcoming[1]



| | |
|---|---|
| ☑ 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 |
| ☑ 3rd Quarter 2021 | Interim analysis of TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia reported |

**Data**

| | |
|---|---|
| ❑ **4th Quarter 2021** | **Topline data from TNX-102 SL Phase 3 F306/RALLY study in fibromyalgia expected** |

**Clinical Trial Initiations – Four New Trials This Year**

| | |
|---|---|
| ❑ **3rd Quarter 2021** | **Phase 2 OL safety study of TNX-1300 in ED setting for cocaine intoxication expected** |
| ❑ **4th Quarter 2021** | **Phase 2 study of TNX-1900 for the treatment of migraine expected** |
| ❑ **4th Quarter 2021** | **Phase 3 study of TNX-102 SL for the treatment of PTSD in Kenya 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** |
| ❑ **1st Half 2022** | **Phase 2 study of TNX-601 CR for the treatment of major depressive disorder expected** |
| ❑ **2nd Half 2022** | **Phase 1 study of TNX-1500 for prevention of allograft rejection expected** |

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

# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT | Fusilev (levoleucovorin) for injection | vela

**Gregory Sullivan, MD**
Chief Medical Officer

**Bradley Saenger, CPA**
Chief Financial Officer

Shire | VERTEX | Steward | pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank | svb Silicon Valley Bank | American Capital





TONIX PHARMACEUTICALS

# *Thank You!*