**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 17, 2020**

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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.)** |

509 Madison Avenue, Suite 1608, New York, New York 10022
**(Address of principal executive offices) (Zip Code)**

**Registrant's telephone number, including area code:** (212) 980-9155

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 |

**Item 7.01 Regulation FD Disclosure.**

Tonix Pharmaceuticals Holding Corp (the "Company") updated its investor presentations, which are used to conduct meetings with investors, stockholders and analysts and at investor and industry conferences, and which the Company intends to place on its website, which may contain nonpublic information. Copies of the presentation are filed as Exhibits 99.01, 99.02 and 99.03 hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01, 99.02 and 99.03 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

**Item 9.01 Financial Statements and Exhibits.**

(d)

| **ExhibiT No.** | **Description.** |
|---|---|
| 99.01 | Corporate Presentation by the Company for August 2020 |
| 99.02 | Corporate Presentation by the Company for August 2020 (condensed version) |
| 99.03 | Corporate Presentation by the Company for August 2020 (vaccine tutorial) |

**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 17, 2020

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

**Exhibit 99.1**

# Investor Presentation
## NASDAQ:TNXP



TONIX PHARMACEUTICALS

August 2020

**Version P0244 8-17-20 (Doc 0695)**

# 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, 2019, as filed with the Securities and Exchange Commission (the "SEC") on March 24, 2020, 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.

*Developing novel therapies for humanity*

- A clinical-stage biopharmaceutical company committed to discovering and developing innovative and proprietary new therapeutics that address the needs of patients
- We focus on developing small molecules and biologics:
  - CNS (pain, neurology, psychiatry, addiction)
  - Immunology (vaccines, immunosuppression, oncology, autoimmune disease)

# Our Pipeline – CNS Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| CNS Portfolio | TNX-102 SL[1] | **Fibromyalgia (FM) - Lead Program** | **Phase 3 – ongoing** |
| | | PTSD | Phase 3 – ongoing |
| | | Agitation in Alzheimer's | Phase 2 ready |
| | | Alcohol Use Disorder | Phase 2 ready |
| | TNX-1300[2] | Cocaine Intoxication / Overdose | Phase 2 |
| | TNX-601 CR[3] | Major depression | Phase 1 |
| | | PTSD | Phase 1 |
| | | Neurocognitive Dysfunction from Corticosteroids | Phase 1 |
| | TNX-1600[4] | Depression, PTSD and ADHD | Preclinical |
| | TNX-1900[5] | Migraine and craniofacial pain | Clinical – pre-IND[6] |

[1]TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication.
[2]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; licensed from Columbia University.
[3]TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 trial for formulation development was recently completed outside of the U.S.
[4]Assets purchased from TRImaran Pharma; license agreement with Wayne State University
[5]Assets purchased from Trigemina; license agreement with Stanford University
[6]Two ex-U.S. Phase 2 trials have been completed using TNX-1900

# Our Pipeline – Immunology Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Immunology Portfolio | **TNX-1800** | **Covid-19 vaccine – Prioritized Program[1]** | **Preclinical** |
| | TNX-2300 | Covid-19 vaccine[2] | Preclinical |
| | TNX-801 | Smallpox and monkeypox preventing vaccine[3] | Preclinical |
| | TNX-1200 | Smallpox and monkeypox preventing vaccine[4] | Preclinical |
| | TNX-1500 | Organ Transplant Rejection/Autoimmune Conditions[5] | Preclinical |
| | TNX-1700 | Gastric and pancreatic cancers[6] | Preclinical |

[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]Live attenuated vaccine based on horsepox virus
[4]Live vaccine based on vaccinia virus
[5]anti-CD40L humanized monoclonal antibody
[6]recombinant trefoil factor 2 (TFF2) based protein; licensed from Columbia University

# TNX-1800[1], a SARS-CoV-2 Vaccine Candidate



**Utilizes Tonix's proprietary horsepox virus as a vector**

- Designed to express a protein from SARS-CoV-2, the cause of COVID-19
- Collaboration with Southern Research

- **Manufacturing agreement with FUJIFILM Diosynth**
  - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
- **Key Milestones:**
  - Results from small animals and non-human primate studies, including challenge with SARS-CoV-2, due 4Q 2020
  - Phase 1 safety study in humans expected to be initiated in 2021

[1]TNX-1800 is at the pre-IND stage of development

# COVID-19 Vaccine Landscape

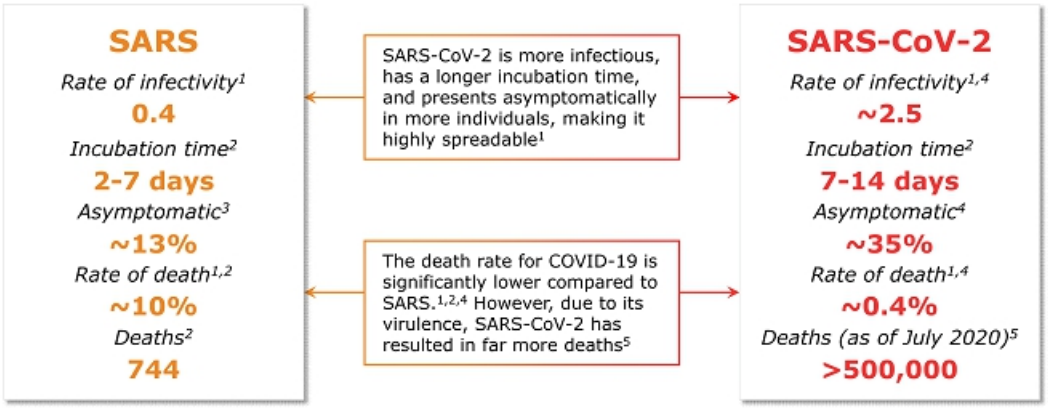


- **We expect more than one vaccine will be approved by FDA**
  - Different vaccines for different individuals
- **More than 150 vaccines in development**
  - Diversity of approaches is important since protective immunity is not yet understood
  - Technologies range from never tested before to 220 years old
  - Uncertainty exists around efficacy, durability and importantly, safety
- **Live attenuated vector systems in development include:**
  - Tonix (horsepox), Tonix (bovine parainfluenza), Merck (measles[1]- and VSV[2]-based), Zydus Cadila (measles-based)

[1]Measles-based vaccine, acquisition of Themis, collaboration with Institute Pasteur
[2]VSV = vesicular stomatitis virus; collaboration with IAVI = International AIDS Vaccine Initiative

# Unique Challenges of SARS-CoV-2






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 June 9, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html
5. Johns Hopkins University. Accessed June 11, 2020. https://coronavirus.jhu.edu/map.html

# Why Use a Horsepox Platform for a Vaccine?



## Horsepox can be engineered to express foreign genes

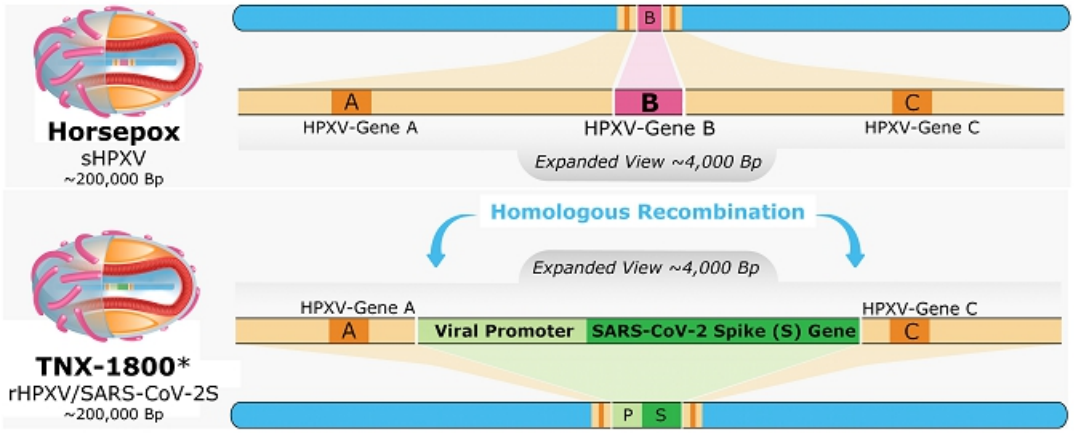
- Lack of persistence or genomic integration in the host
- Strong immunogenicity as a vaccine
- Readily manufacture at scale
- Live, attenuated vaccine – direct antigen presentation

## 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

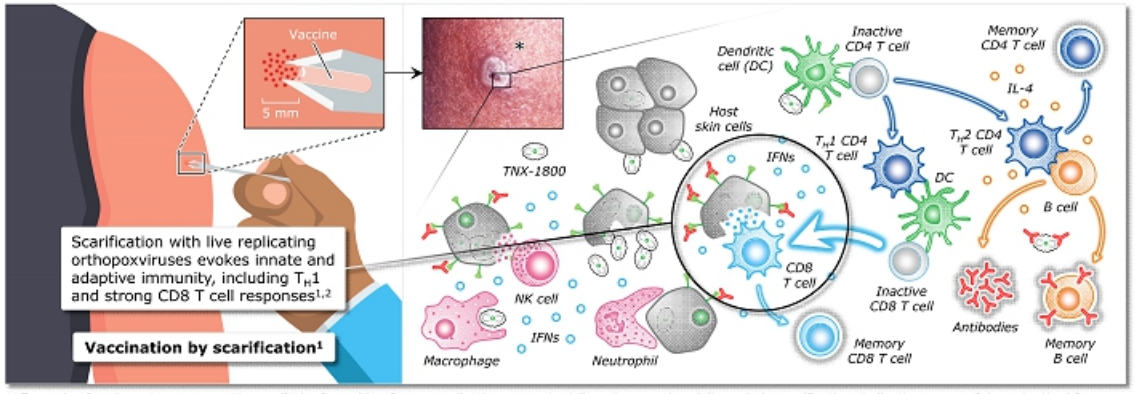





*TNX-1800 is at the pre-IND stage of development

# TNX-1800 is Designed to Induce Robust $T_H1$ Cellular Immunity






*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

# 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 Development Status



Southern Research will address two key questions:

1. Will vaccination of animals elicit an immune response to the S protein?
   - 4th Quarter 2020 –Small animal response expected[1]
2. Will immune response protect non-human primates against a challenge with SARS-CoV-2 virus?
   - 4th Quarter 2020 – Primate testing results expected[1]

Manufacturing development for GMP virus initiated

- Clinical development will require manufacturing for clinical supplies

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

# TNX-2300[1], a 2nd SARS-CoV-2 Vaccine Candidate



## 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

## Live attenuated vaccine based on bovine parainfluenza virus[1-5]

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

# 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

# Overview of TNX-102 SL*



Protectic® proprietary formulation of cyclobenzaprine that supports sublingual administration

**◇ Scientific Rationale for Protectic® Formulation ◇**

- Engenders unique pharmacokinetic and pharmacodynamic properties that emphasize sleep properties of cyclobenzaprine while minimizing undesirable properties
- Potential therapeutic value in a constellation of disorders where sleep disturbances are:
  - Co-morbid
  - Involved in the onset, progression and severity of the disease

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

# TNX-102 SL: Differentiation from Oral Formulations



| FEATURE | BENEFIT | ADVANTAGE |
|---|---|---|
| Cyclobenzaprine | 40+ years as oral medication | Established safety record |
| Formulation: Protectic® | Allows submucosal absorption | Not achievable with oral formulation |
| Administration: sublingual | Bypasses gut | Avoids first-pass metabolism; reduced formation of "activating" metabolite |
| Pharmacokinetic profile | Rapid absorption (peak at ~4 hours, low trough levels 8-24 hours) | Desired profile for nighttime action |
| Dose: low (2.8 to 5.6 mg) | Recruitment of high affinity receptors (5-$HT_{2A}$, $\alpha_1$, $H_1$) | Complimentary trimodal mechanism of action with less risk of off-target interference |

# TNX-102 SL: Results from Completed Fibromyalgia (FM) Trials



***Completed Trials in FM:***
- Phase 2 (F202 BESTFIT) – 205 patients randomized
- Phase 3 (F301 AFFIRM) – 519 patients randomized

***Topline Efficacy Results:***
- Studies did not achieve statistical significance in the primary efficacy endpoint

***More In-Depth Results:***
- Both studies showed efficacy signals justifying continued development in FM

***Safety:***
- Well tolerated; side effects consistent with known side effects of cyclobenzaprine

# TNX-102 SL 2.8 mg: Efficacy Signal in Completed FM Trials



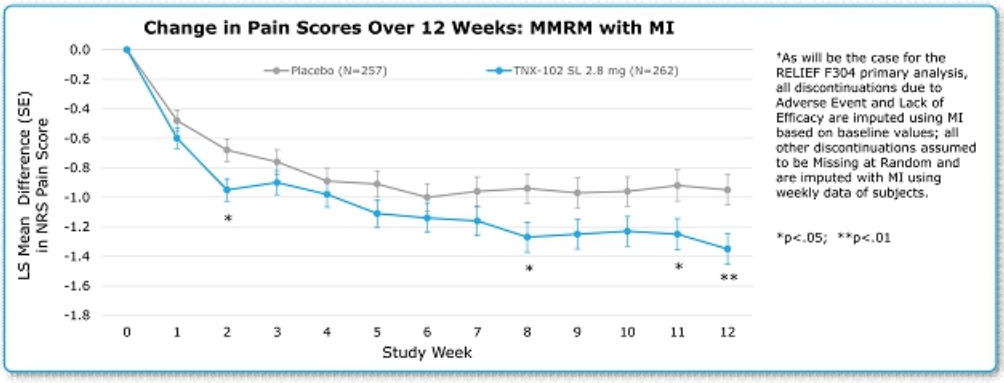
| | | Phase 2b F202 (BESTFIT)<br>*Dose: 2.8 mg* | Phase 3 F301 (AFFIRM)<br>*Dose: 2.8 mg* |
|---|---|---|---|
| **Primary Endpoint:**<br>Pain Relief at Week 12 | Pre-specified pain endpoint | Change in daily pain score (ANCOVA with JTC/MI*)<br>**Trend: p=0.172** | Responder analysis ≥30% pain reduction (Logistic regression)<br>**Trend: p=0.095** |
| | Post hoc analysis | Responder analysis ≥30% pain reduction (Logistic Regression)<br>**p=0.033** | • Imbalance in missing data and individuals with missing data treated as 'non-responder'<br>• Current FDA statistical guidance on handling missing data: analysis with MMRM with MI*<br>**p=0.005** |
| **Key Secondary Endpoints:**<br>Global improvement or improvement in symptoms and function | Patient Global Impression of Change (PGIC) | **p=0.025** | **p=0.038** |
| | Fibromyalgia Impact Questionnaire-Revised (FIQ-R) total score | **p=0.015 (ANCOVA)** | **P<0.001** |
| | PROMIS Sleep Disturbance instrument | **p=0.004 (ANCOVA)** | **P<0.001** |
| | FIQ-R Pain Item | **p=0.004** | **P<0.001** |

*MI=multiple imputation; JTC = jump to control; MMRM = Multiple measures repeated models

# Results from F301 (AFFIRM) Using Current FDA Statistical Guidance on Handling of Missing Data



- A retrospective analysis conducted using Mean Pain Analysis, MMRM with MI† demonstrated a significant effect on pain, even though the dose was 2.8 mg

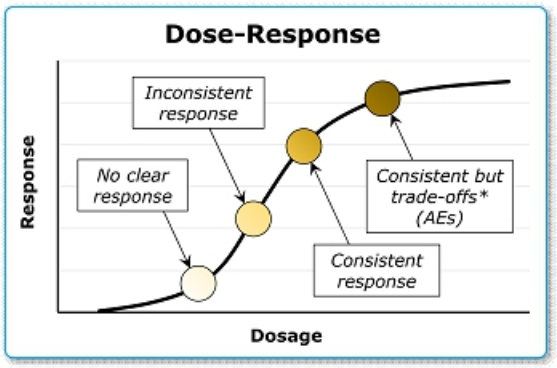


# Where Are We on the Dose-Response Curve?



**Basic Pharmacology**

- Dose can make the difference in the strength of the response




*Trade off's are increases in adverse events, side-effects and drug-drug interactions

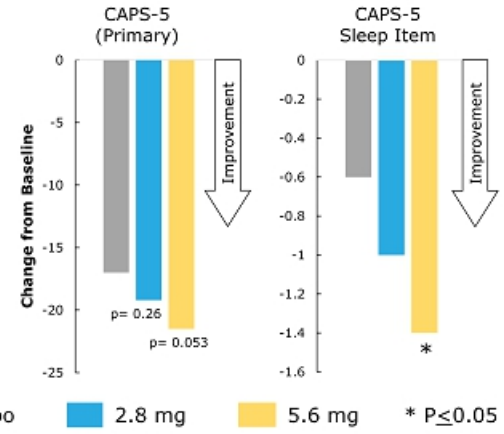
# Dose Response from Phase 2 PTSD Study*



## Consistent Dose-response Across Primary and Key Secondary Endpoints at Week 12

- Clinician Administered PTSD Scale for DSM-5 (CAP-5)

* Phase 2 study (AtEase), a randomized, placebo-controlled study of 231 patients with PTSD at 25 U.S. clinical sites, receiving a sublingual dose of either 2.8 mg TNX-102 SL (n=90) or 5.6 mg TNX-102 SL (n=49) compared to placebo (n=92)

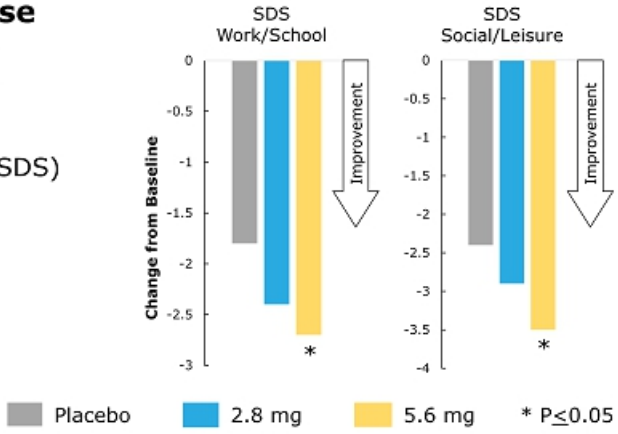


# Dose Response from Phase 2 PTSD Study



## Consistent Dose-response Across Primary and Key Secondary Endpoints at Week 12

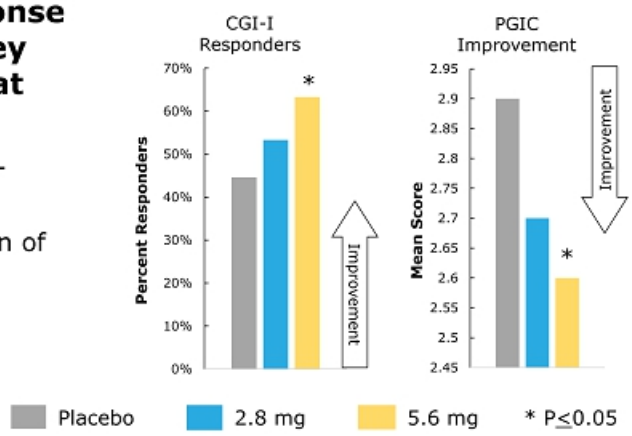
- Sheehan Disability Score (SDS)



# Dose Response from Phase 2 PTSD Study



- **Consistent Dose-response Across Primary and Key Secondary Endpoints at Week 12**
  - Clinical Global Impression-Improvement (CGI-I)
  - Patients' Global Impression of Change (PGIC)




Placebo 2.8 mg 5.6 mg * P≤0.05

# Effect of Dose on Adverse Events (AEs) in the P201/AtEase and P301/HONOR PTSD Studies



**Dose-related AEs:**

- AE profiles are comparable between FM and PTSD studies at 2.8 mg
- No serious and unexpected AEs in PTSD at either 2.8 or 5.6 mg doses
- No unique systemic AEs observed for 5.6 mg dose (but generally, a modest increase in frequency)
- Severity and incidence of oral hypoesthesia (oral numbness) are not dose related

| | | P201 | | | P301 | |
|---|---|---|---|---|---|---|
| | | Placebo (N=94) | 2.8 mg (N=93) | 5.6 mg (N=50) | Placebo (N=134) | 5.6 mg (N=134) |
| **Systemic Adverse Event * #** | Somnolence | 6.4% | 11.8% | 16.0% | 9.0% | 15.7% |
| | Dry Mouth | 10.6% | 4.3% | 16.0% | | |
| | Headache | 4.3% | 5.4% | 12.0% | | |
| | Insomnia | 8.5% | 7.5% | 6.0% | | |
| | Sedation | 1.1% | 2.2% | 12.0% | | |
| **Local Administration Site Reaction * #** | Hypoaesthesia oral | 2.1% | 38.7% | 36.0% | 1.5% | 37.3% |
| | Paresthesia oral | 3.2% | 16.1% | 4.0% | 0.7% | 9.7% |
| | Glossodynia | 1.1% | 3.2% | 6.0% | | |
| | Product Taste Abnormal | | | | 3.0% | 11.9% |

*Only adverse events (AEs) are listed that are at a rate of ≥ 5% in any TNX-treated group

*No values in a row for either study means the AE in the active group(s) in that study was at a rate of <5%

# TNX-102 SL 5.6 mg for Fibromyalgia: Phase 3 F304/RELIEF Study Design



## General study characteristics:

- Randomized, double-blind, placebo-controlled study in fibromyalgia in approximately 40 U.S. sites (N=470)
- Adaptive Design: one unblinded interim analysis based on 50% of randomized participants


## 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:

- Patient Global Impression of Change (PGIC): Proportion of patients with a rating of "very much improved" or "much improved"
- Fibromyalgia Impact Questionnaire – Revised (FIQR): Symptoms Domain

**Interim analysis results expected September 2020**

**Topline results expected 4Q 2020**

**Potential 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

*PROMIS = Patient Reported Outcome Measurement Information System

# TNX-102 SL 5.6 mg for Fibromyalgia: Phase 3 F304/RELIEF Study Status



- **Key changes to protocol from previous Phase 3 trial in FM**
  - Exclusive use of higher dose of 5.6 mg (2 x 2.8 mg)
  - Primary endpoint: mean pain improvement
  - Analysis: MMRM with MI
- **Clear guidance from FDA to advance fibromyalgia program using higher dose (5.6 mg)**
- **Long-term safety of 5.6 mg dose from PTSD studies expected to support FM NDA**
- **Study is progressing on schedule**
  - First participant enrolled in the new Phase 3 RELIEF study in December 2019
  - Completed enrollment in July 2020
  - Interim analysis results expected September 2020; topline results expected 4Q 2020 if no delays
  - Potential pivotal efficacy study to support NDA approval

# TNX-102 SL 5.6 mg for Fibromyalgia : New Phase 3 F306/Rally Study



- **Plan to initiate a 2nd potentially pivotal Phase 3 trial, F306 or the RALLY study, of TNX-102 SL for the management of fibromyalgia**
- **Expect the FDA to require two registration-quality clinical studies to support marketing approval**
- **RALLY trial design will be very similar to F304 / RELIEF study**
  - Exclusive use of higher dose of 5.6 mg (2 x 2.8 mg)
  - Primary endpoint: mean pain improvement
  - Analysis: MMRM with MI
- **Expect to enroll first participant in 3Q 2020**

# Highlights of Lead Programs[1]



- **TNX-102 SL for fibromyalgia (FM)**
  - Phase 3 clinical development – RELIEF study fully enrolled
  - Sublingual cyclobenzaprine tablets at higher dose of 5.6 mg
  - Milestones:
    - 3rd Quarter 2020 – Enrollment in new Phase 3 Rally study expected to begin[5]
    - September 2020 – Interim analysis results expected from RELIEF study[5]
    - 4th Quarter 2020 - Topline data expected from RELIEF study[5]
- **TNX-1800 potential vaccine for COVID-19[2]**
  - Preclinical stage
  - Live virus vaccine designed on our horsepox vaccine platform[4] to express the SARS-CoV-2 Spike (S) protein
  - Milestones:
    - 4th Quarter 2020 –Small animal response results expected[4]
    - 4th Quarter 2020 – Primate testing results expected[4]
    - 2021 – Initiation of Phase 1 human safety study expected[4]

[1] Experimental new medicines and biologics, not approved for any indication
[2] Collaboration with Southern Research
[3] TNX-801 is unmodified horsepox virus, which is in development as a vaccine to protect against smallpox and monkeypox
[4] We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones

# 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-102 SL: Potential Treatment for Agitation in Alzheimer's Disease (AAD)



**Agitation is one of the most distressing and debilitating of the behavioral complications of Alzheimer's disease**

- Includes emotional lability, restlessness, irritability and aggression[1]

**Link between disturbed sleep and agitation in Alzheimer's[1-3]**

- Agitation is commonly diurnal (e.g., "sundowning")

**Prevalence**

- Agitation is likely to affect more than half of the 5.3 million Americans who currently suffer from moderate to severe Alzheimer's disease; expected to nearly triple by 2050[4]

**Significant unmet need** with no FDA approved drugs for the treatment of AAD

**Proposed Phase 2 study can potentially serve as a pivotal efficacy study to support NDA approval[5]**

[1]Rosa, K.et al. (2015). *American Journal of Alzheimer's Disease & Other Dementias, 30*:78
[2]Shih, Y. H., et al. (2017). *Journal of the American Medical Directors Association, 18*, 396.
[3]Canevelli, M., et al. (2016). *Frontiers in medicine, 3*.
[4]The Alzheimer's Association, 2017 Alzheimer's Disease Facts and Figures: https://www.alz.org/facts/
[5]FDA comments on final protocol received October 2018

# TNX-102 SL: Potential Treatment for Alcohol Use Disorder (AUD)



**AUD is a chronic relapsing brain disease**

- Characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using

**Sleep disturbance is extremely common in alcohol recovery**[1]

- Significantly impacts daytime cognition, mood, and ability to participate in alcohol treatment, and is associated with increased risk of relapse

**Prevalence**

- An estimated 36 million adults in the U.S. have AUD[2]

**Three FDA-approved medications**

- Remains an unmet need due to compliance and safety issues

**FDA cleared Tonix's IND application for initiation of a Phase 2 proof-of-concept study**

- Program expected to qualify for 505(b)(2) pathway for FDA approval

[1]Arnedt et al, J Addict Dis. 2007 ; 26(4): 41–54
[2]Grant et al, JAMA Psychiatry 2015; 72(8): 757-766; www.census.gov

# 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 Rickett Benckiser (TNX-1300 was formerly RBP-8000)[3]**

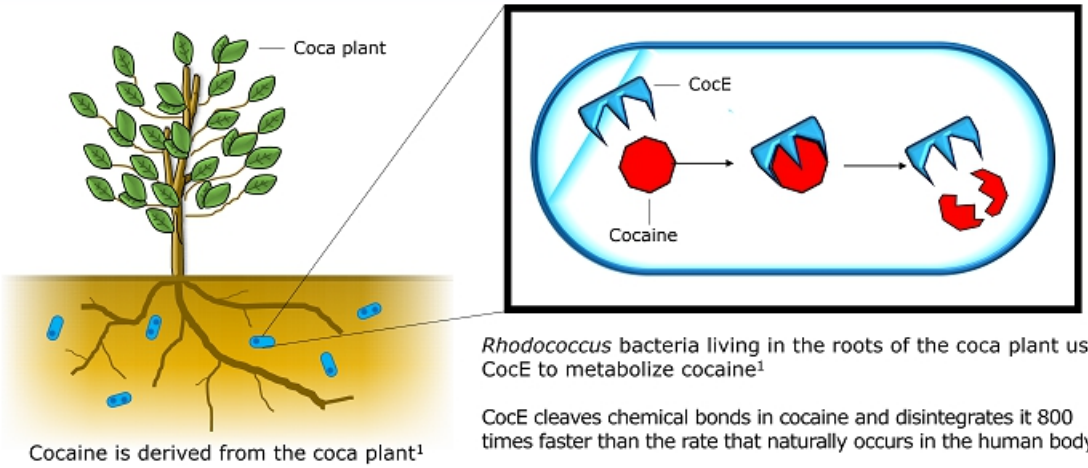
- Volunteer cocaine abusers received cocaine 50 mg *i.v.* infusion over 10 minutes
- TNX-1300 given one minute after completion of cocaine infusion
  - Rapidly reversed the physiologic effects of cocaine; cocaine plasma exposures dropped by 90% within two minutes
  - Well tolerated with the most frequently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

# Psychiatry, Immunology and Oncology Preclinical Pipeline[1]



| Pipeline Product | Indication(s) | Category |
|---|---|---|
| **TNX-1600**<br>Triple reuptake inhibitor[2] | **Daytime treatment for Depression, PTSD and ADHD[3]** | **Psychiatry** |
| **TNX-1500**<br>Anti-CD154 monoclonal antibody | **Prevention and treatment of organ transplant rejection**<br>**Treatment of autoimmune conditions** | **Transplant**<br>**Autoimmunity** |
| **TNX-1700**<br>rTFF2[4] | **Treatment for gastric and pancreatic cancers** | **Oncology** |

[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
[4] Recombinant Trefoil Family Factor 2 – licensed from Columbia University

# Pipeline Summary – by Select Therapeutic Areas



## Pain

- **TNX-102 SL (sublingual cyclobenzaprine) for fibromyalgia**
  Phase 3/RELIEF
- **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) for depression and PTSD**
  Phase 2-ready
- **TNX-1600 (triple reuptake inhibitor) for PTSD, Depression and ADHD**
  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

# Pipeline 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

**Biodefense**

- **TNX-801 (live horsepox vaccine) for preventing smallpox and monkeypox**
  Preclinical
- **TNX-1200 (live vaccinia vaccine) for preventing smallpox and monkeypox**
  Preclinical
- **TNX-701 (oral radioprotective agent) for radioprotection**
  Preclinical

# Tonix Financial Overview



| NASDAQ: TNXP | |
|---|---|
| Cash and cash equivalents, June 30, 2020 | $55.0 million |
| Net proceeds from common stock offering - July 15, 2020 | $9.6 million |
| Warrant exercises subsequent to June 30, 2020 | $2.4 million |
| Average Daily Volume (3-month average) | 25.6 million |
| Common Stock outstanding as of August 7th, 2020 | 130.3 million |

# Milestones – Recently Completed and Upcoming[1]



| | |
|---|---|
| ☑ 3rd Quarter 2020 | IND application cleared by FDA for initiation of Phase 2 POC study of TNX-102 SL for AUD |
| ❑ **September 2020** | **Interim analysis results from TNX-102 SL Phase 3 F304/RELIEF study in fibromyalgia expected** |
| ❑ **3rd Quarter 2020** | **Enrollment in second potentially pivotal pivotal Phase 3 trial, the RALLY study, for TNX-102 SL for the management of fibromyalgia expected to begin** |
| ❑ **4th Quarter 2020** | **Topline data from TNX-102 SL Phase 3 F304/RELIEF study in fibromyalgia expected** |
| ❑ **4th Quarter 2020** | **Small animal data from TNX-1800 in COVID-19 model expected** |
| ❑ **4th Quarter 2020** | **Primate data from TNX-1800 in COVID-19 model expected** |
| ❑ **2021** | **Initiation of Phase 1 safety study of TNX-1800 for COVID-19 expected** |

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

# Management Team



**Seth Lederman, MD**
President & CEO

TARGENT X | Fusilev (levoleucovorin) for injection | vela

**Gregory Sullivan, MD**
Chief Medical Officer

Columbia University Department of Psychiatry | New York State Psychiatric Institute

**Bradley Saenger, CPA**
Chief Financial Officer

Shire | VERTEX | Steward | pwc

**Jessica Morris**
Chief Operating Officer

Deutsche Bank | svb Silicon Valley Bank | American Capital

TONIX PHARMACEUTICALS

# *Thank You!*

**Exhibit 99.2**

# Investor Presentation
## NASDAQ:TNXP



TONIX PHARMACEUTICALS

August 2020

**Version P0241 (Doc 0692)**

# 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, 2019, as filed with the Securities and Exchange Commission (the "SEC") on March 24, 2020, 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 Financial Overview



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| Common Stock outstanding as of August 7th, 2020 | 130.3 million |

# Tonix Pharmaceuticals: Lead Programs[1]



- **TNX-102 SL for fibromyalgia (FM)**
  - Phase 3 clinical development – RELIEF study enrolling
  - Sublingual cyclobenzaprine tablets at higher dose of 5.6 mg
  - Milestones:
    - Sept 2020 – Optional interim analysis results expected[5]
    - 4Q2020 – Topline data expected[5]
- **TNX-1800 potential vaccine for COVID-19[2,3]**
  - Preclinical stage
  - Live virus vaccine designed elicit predominately T cell response for durable immunity - horsepox platform[4] to express the SARS-CoV-2 Spike (S) protein
  - Milestones:
    - 4Q2020 – Small animal response expected[5]
    - 4Q2020 – Primate testing results expected[5]

[1] Experimental new medicines and biologics, not approved for any indication
[2] Collaboration with Southern Research
[3] COVID-19 = Coronavirus disease 2019
[4] TNX-801 is unmodified horsepox virus, which is in development as a vaccine to protect against smallpox and monkeypox
[5] We cannot predict whether the global COVID-19 pandemic will impact the timing of these milestones

# Our Pipeline – CNS Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| CNS Portfolio | **TNX-102 SL[1]** | **Fibromyalgia (FM) - Lead Program** | **Phase 3 – ongoing** |
| | | PTSD | Phase 3 – ongoing |
| | | Agitation in Alzheimer's | Phase 2 ready |
| | | Alcohol Use Disorder | Pre-IND[2] |
| | TNX-1300[3] | Cocaine Intoxication / Overdose | Phase 2 |
| | TNX-601 CR[4] | Major depression | Phase 1 |
| | | PTSD | Phase 1 |
| | | Neurocognitive Dysfunction from Corticosteroids | Phase 1 |
| | TNX-1600 | Depression, PTSD and ADHD | Preclinical |
| | TNX-1900 | Migraine and craniofacial pain | Clinical – pre-IND[5] |

[1]TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is an investigational new drug and has not been approved for any indication.
[2]Pre-Investigational New Drug (IND) meeting completed in October 2019 with FDA. Upon receiving FDA clearance of an IND application, it will be Phase 2 POC ready as it is expected to qualify for the 505(b)(2) pathway for approval,
[3]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.
[4]TNX-601 CR is in the pre-IND stage in the U.S.; a Phase 1 trial for formulation development was recently completed outside of the U.S.
[5]Two ex-U.S. Phase 2 trials have been completed using TNX-1900

# Our Pipeline – Immunology Portfolio



| | CANDIDATES | INDICATION | STATUS |
|---|---|---|---|
| Immunology Portfolio | **TNX-1800** | **Covid-19 vaccine – Prioritized Program** | **Preclinical** |
| | TNX-801 | Smallpox and monkeypox preventing vaccine | Preclinical |
| | TNX-1200 | Smallpox and monkeypox preventing vaccine | Preclinical |
| | TNX-1500 | Organ Transplant Rejection/Autoimmune Conditions | Preclinical |
| | TNX-1700 | Gastric and pancreatic cancers | Preclinical |

# Fibromyalgia Landscape



- **Neurobiological disorder characterized by chronic widespread pain, non-restorative sleep, fatigue, diminished cognition[1]**
  - Recognized as a *bona fide* condition relatively recently (1980s)

- **Affects ~6-12 million adults (>90% women) in the U.S.[2]**
  - FM drugs from Pfizer (Lyrica®) and Lilly (Cymbalta®) were blockbusters with significant investment in direct-to-consumer advertising

- **Despite FDA-approved drugs, FM remains an unmet need**
  - Majority of patients do not respond or cannot tolerate therapy due to side effects[3]
  - Substantial off-label use of narcotic painkillers and prescription sleep aids[4]

[1] Phillips K & Clauw DJ, Best Pract Res Clin Rheumatol 2011;25:141; [2] American Chronic Pain Association (www.theacpa.org, 2019);[3] Market research by Frost & Sullivan, commissioned by Tonix , 2011; [4] Patient Trends: Fibromyalgia", Decision Resources, 2011

# Fibromyalgia Program Goals



- **TNX-102 SL is a non-opioid, centrally acting analgesic**
  - Potential to provide a new therapeutic option for the management of fibromyalgia
- **Treatment objective: restore functionality and quality of life**
  - Potential to broadly improve symptoms with acceptable tolerability
- **Tonix's proprietary sublingual formulation allows for dosing convenience (one pill taken daily at bedtime)**
  - Designed to emphasize sleep properties of TNX-102 SL while decreasing undesirable day time side effects

# TNX-102 SL 2.8 mg: Treatment Activity in Completed FM Trials



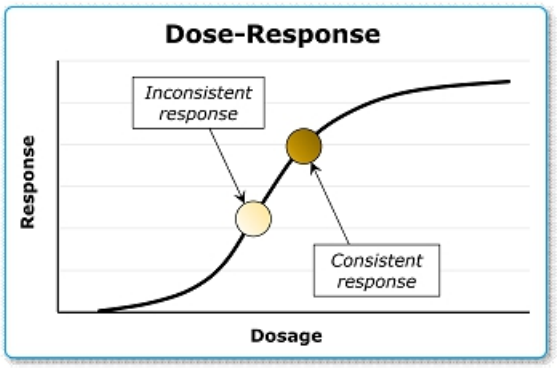
| | | Phase 2b F202 (BESTFIT) *Dose: 2.8 mg* | Phase 3 F301 (AFFIRM) *Dose: 2.8 mg* |
|---|---|---|---|
| **Primary Endpoint:** Pain Relief at Week 12 | Change in Mean Pain | ✗ | ✓ |
| | 30% Responder Analysis | ✓ | ✗ |
| **Key Secondary Endpoints:** Global improvement or improvement in symptoms and function | Patient Global Impression of Change (PGIC) | ✓ | ✓ |
| | Fibromyalgia Impact Questionnaire-Revised (FIQ-R) total score | ✓ | ✓ |
| | PROMIS Sleep Disturbance instrument | ✓ | ✓ |
| | FIQ-R Pain Item | ✓ | ✓ |
| ***Safety:*** Well tolerated; side effects consistent with known side effects of cyclobenzaprine | | | |

✓ represents a p value < .05
✗ represents a p value > .05

# Where Are We on the Dose-Response Curve?



- Dose can make the difference in the consistency and strength of the response
- Tonix believes the dose used in the Phase 2b and first Phase 3 studies was potentially too low leading to inconsistent responses




*Trade off's are increases in adverse events, side-effects and drug-drug interactions

# TNX-102 SL:
# On-going Phase 3 Study in FM (F304/RELIEF)



- **Key changes to protocol from previous Phase 3 trial in FM**
  - Exclusive use of higher dose of 5.6 mg (2 x 2.8 mg)
  - Primary endpoint: mean pain improvement (vs. responder analysis)
- **Potential pivotal efficacy study to support NDA approval**
  - Long-term safety of 5.6 mg dose from PTSD studies expected to support FM NDA
- **Study is progressing ahead of schedule**
  - Achieved 50% enrollment in April 2020

# Fibromyalgia Next Steps



- **Upcoming milestones (before year end)**
  - Phase 3 interim analysis results expected September 2020
  - Topline Phase 3 results expected 4Q20
- **TNX-102 SL is a new, differentiated product candidate**
  - Sleep quality mechanism of action
- **Established but unsatisfied patient population**
  - 6-12 M U.S. patients
  - Widespread off-label opiate use

# Opportunities to Expand to Other Indications



**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

# COVID-19 Vaccine Landscape



- **We expect more than one vaccine will be approved by FDA**
  - Different vaccines for different individuals
- **More than 125 vaccines in development**
  - Diversity of approaches is important since protective immunity is not yet understood
- **Only ~4 live replicating vector systems in development**
  - Tonix (horsepox), Merck (measles[1]- and VSV[2]-based), Zydus Cadila (measles-based)

[1]Measles-based vaccine, acquisition of Themis, collaboration with Institute Pasteur
[2]VSV = vesicular stomatitis virus; collaboration with IAVI = International AIDS Vaccine Initiative

# Where Do We Go From Here?



- **Goal: Effective COVID-19 vaccines**
  - So we can return to work and school

- **Need #1 Quickly available vaccines**
  - Even if they offer only temporary immunity -- several now in human trials

- **Need #2 Vaccines providing long-term immunity**
  - Durable immunity for years
  - Blocking of forward transmission
  - Expect longer development and testing timelines

# Live, Replicating Virus Vaccines for Other Infectious Diseases[1]



- **Long term, durable immunity**
  - 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: COVID-19 Vaccine Engineered for Long-term Immunity



- **Based on viral vaccine developed more than 200 years ago by Edward Jenner for a smallpox vaccine**
  - Eradicated smallpox
  - T cell eliciting immunity
  - Single dose immunity without adjuvants
  - Manufacturable in scale on existing systems
  - Glass-sparing packaging owing to small unit dose

- **One of 4 known live replicating virus vaccine vectors under development for COVID-19**
  - Tonix, Merck, Zydus Cadila
  - Expected to provide $T_H1$ immunity

# TNX-1800: Development Status for COVID-19 Vaccine



- **Development collaboration with Southern Research**
  - Study of human immunity in convalescent volunteers
  - Animal testing
- **Manufacturing agreement with FUJIFILM Diosynth**
  - Development for Good Manufacturing Practice (GMP) manufacturing for human trials
- **Key Milestones: Results from animal studies due 4Q20**
  - Small animals and non-human primate studies, including challenge with CoV-2

# Expected Near-Term Milestones



- ❑3Q20 **TNX-102 SL Phase 3 interim analysis in fibromyalgia**
- ❑4Q20 **TNX-1800 small animal data in COVID-19 model**
- ❑4Q20 **TNX-1800 primate data in COVID-19 model**
- ❑4Q20 **TNX-102 SL Phase 3 top-line data in fibromyalgia**

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

TONIX PHARMACEUTICALS

# *Thank You!*

**Exhibit 99.3**

# COVID-19 Vaccines: Challenges and Opportunities



TONIX PHARMACEUTICALS

August 2020
NASDAQ: TNXP

**Version P0240 (Doc 0691)**

# Cautionary Note on Forward-Looking Statements



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# Seth Lederman, MD



Currently, CEO of Tonix Pharmaceuticals, Dr. Lederman began his career in research in the early days of the AIDS crisis and studied the entry of HIV into cells at the molecular and cell biological levels. Dr. Lederman is a co-inventor of the horsepox vaccine vector on which Tonix's current COVID-19 vaccine, TNX-1800 is based. Previously, Dr. Lederman served as an Associate Professor at Columbia University from 1996 until 2017. He joined the faculty of Columbia University's College of Physicians and Surgeons in 1985, became Assistant Professor of Medicine in 1988, and Associate Professor with tenure in 1996 and Director of the Laboratory of Molecular Immunology in 1997. From 1988 to 2002, Dr. Lederman directed basic science research at Columbia in molecular immunology, infectious diseases and the development of therapeutics for autoimmune diseases. Dr. Lederman is author of numerous scientific articles, and inventor of technologies recognized by a number of issued patents. His fundamental work on the CD40-Ligand (CD154) elucidated the molecular basis of T cell helper function and has led to the development of therapeutic candidates for autoimmune diseases and organ transplant rejection in collaboration with Biogen and UCB. In addition to his research, Dr. Lederman served as attending physician in the Edward Daniels Arthritis and Autoimmunity Clinic on the Medical Service at Columbia Presbyterian Hospital from 1988-1996. Dr. Lederman earned an AB from Princeton in Chemistry cum laude in 1979 and an MD from Columbia University's College of Physicians and Surgeons in 1983. Dr. Lederman trained in internal medicine and rheumatology at Columbia's Presbyterian Hospital. He was an NIH Physician-Scientist 1985-1990 at Columbia.

# What Is the Goal of Vaccination?



- **Vaccination instructs the immune system how to respond *rapidly* upon reinfection[1-3]**
  - A typical infection is a *race* between the virus and the immune response
  - Vaccination gives the body a "head start"
- **Most vaccines against viruses protect against *serious illness*, not *infection*[2,3]**
  - Different vaccines work in different ways
  - How an effective vaccine protects against disease depends on the nature of the virus[2,3]
- **Blocking *forward transmission* (spread of infection) is essential for public health[4]**

1. Centers for Disease Control and Prevention. Accessed June 9, 2020. https://www.cdc.gov/vaccines/pubs/pinkbook/prinvac.html
2. Plotkin SA. *Vaccines*. 2008;47(3):401-409.
3. Plotkin SA. *Clin Vaccine Immunol*. 2010;17(7):1055-1065.
4. Hardt K, et al. *Vaccine*. 2016;34(52):6691-6699.

# Immune Memory



- **<u>*Recognizes*</u> the offending pathogen or toxin**
  - T cells recognize fragments of pathogens on the surfaces of infected cells
  - Antibodies recognize the pathogens directly

- **Recalls the <u>*type of immune response*</u> elicited**
  - <u>*For better:*</u> Protective responses are repeated on re-exposure
  - <u>*For worse:*</u> Non-productive responses are repeated (*e.g.,* allergic responses become established patterns )

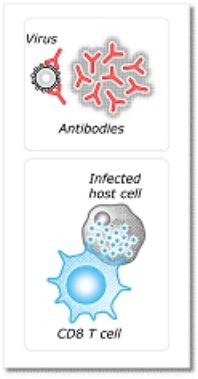
- **Vaccines are designed to teach the body both <u>*recognition*</u> and a protective <u>*type of immune response*</u>**

# The Roles of Antibodies and Cellular Immunity in Vaccines



- **Antibody immunity**
  - Recognizes pathogens directly
  - Antibodies can prevent infection (in lab experiments)
  - Typical clinical test for exposure to a virus

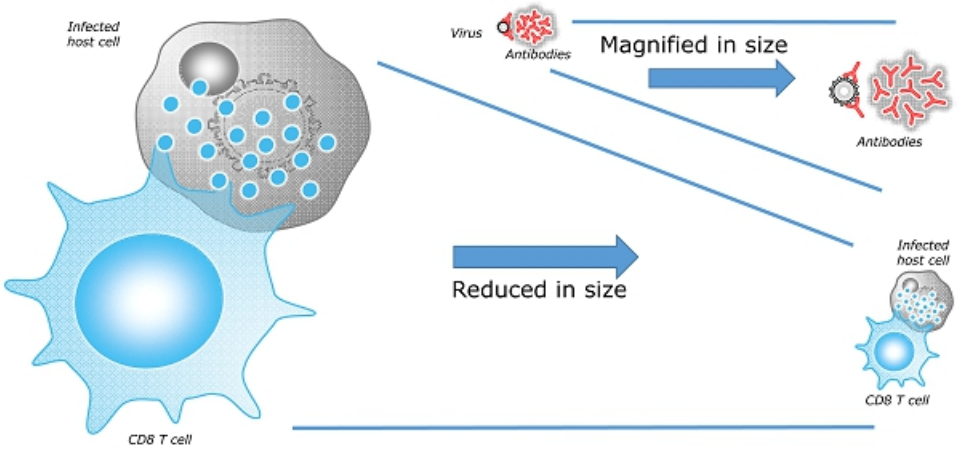
- **T cell immunity**
  - Recognizes fragments of pathogens on the surfaces of infected cells, not pathogens directly
  - Kills/destroys vaccine factories (i.e., infected cells)
  - Key to limiting disease severity and controlling infection once replication has been established.[1]
  - Lab test – ***NOT*** a clinical test




1. Plotkin SA. *Clin Vaccine Immunol.* 2010;17(7):1055-1065.

# Scale: T cells are Much Larger than Antibodies and Viruses





# 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

# Distinct, Non-Overlapping Roles for T cells and Antibodies in Viral Immunity



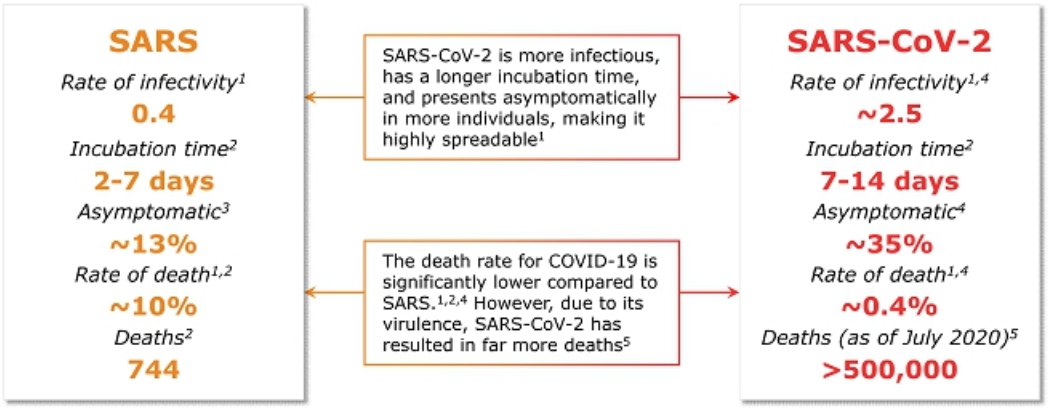
| | Antigens Recognized | | Effector Functions | |
|---|---|---|---|---|
| | Infected cells | Viruses directly | Kill infected cells | Block entry |
| T cells | + | - | + | - |
| Antibodies | - | + | - | + |

| | Actions in Infected Hosts | | Effect on transmission | |
|---|---|---|---|---|
| | Clear infection | Decrease tissue spread | Block forward transmission | Potential $T_H2$ chronicity |
| T cells | + | - | + | - |
| Antibodies | - | + | - | + |

[1]Intracellular pathogens include intracellular bacteria and protozoa
[2]Extracellular pathogens include worms and toxins

# Unique Challenges of SARS-CoV-2






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.
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# COVID-19: Reason for Optimism?

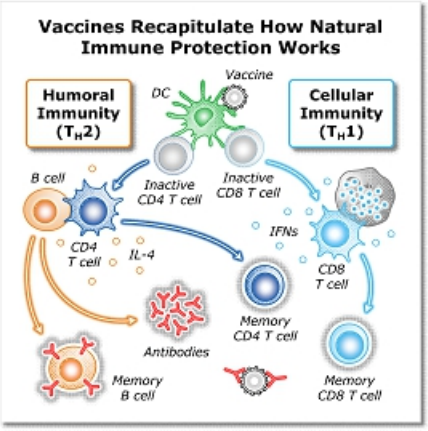


- **Most people recover, which suggests:**
  - Vaccines can be designed that safely mimic infection
  - Herd immunity can be achieved by vaccination
- **Vaccine developers can learn from individuals who recover**
  - Study their immunity in detail for a blueprint of a successful immune response
  - Potential to block forward transmission (contagion) by infected people
- **Comparison to HIV: protective immunity is unknown**
  - No vaccine developed after 35 years

# Successful Vaccines Recapitulate Optimal Immune Responses to Infection



- **Successful vaccines recapitulate how natural immune protection works**
  - Exploit elements of protective responses from survivors
- **The most effective immune response varies by pathogen**
  - Must be considered when designing a vaccine[1,2]
- **Understanding protective immunity is required for vaccine design and testing**
  - Need to learn what constitutes "healthy" or "unhealthy" immune responses to SARS-CoV-2

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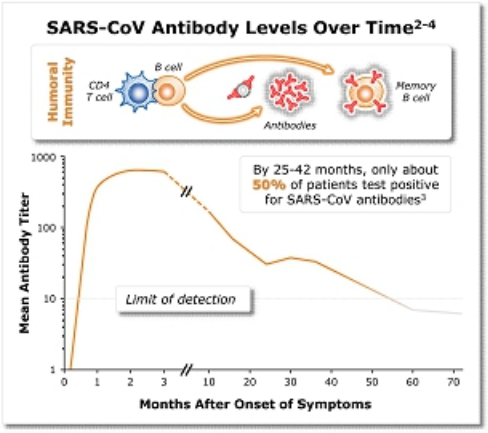
# Humoral Immunity May Only Be Protective Against SARS-CoV for a Limited Duration



- High levels of virus-specific antibodies are found in recovered SARS patients, though these decline rapidly[1-3]
- Virus-specific memory B-cell responses are undetectable by 6 years after recovery from SARS[4]
- In about 60% of patients, virus-specific memory CD8 T cells remain detectable and responsive to SARS-CoV antigen for at least 6 years[4]

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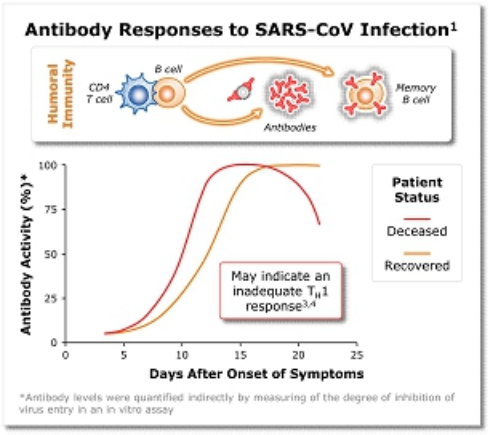
# Over-Active Humoral Immunity May Be Damaging in SARS-CoV Infection



- Patients with early, strong humoral responses against SARS-CoV had worse outcomes, with disease severity correlated to $T_H2$ cytokine patterns[1-3]
- Over-active antibody responses may effectively clear virus, but can also worsen disease by[4-6]:
  - Promoting excessive inflammation in the lungs that causes tissue damage
  - Increasing viral infectivity and enabling further spread of infection through antibody-dependent enhancement (ADE)

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# Live, Replicating Virus Vaccines for Other Infectious Diseases[1]



- **Long term, durable immunity**
  - 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

# Live Replicating Vaccines Induce T Helper 1 ($T_H1$) Polarization of Immunity



**Initial exposure to a vaccine or pathogen pushes immunity towards one of two mutually exclusive responses[1]**

- **$T_H1$ is T cell predominant – "cell mediated immunity"**
  - Effective against viruses, intracellular bacteria and protozoa
- **$T_H2$ is antibody predominant – "humoral immunity"**
  - Effective against bacteria and other extracellular parasites including worms

[1]Note: The CoV-2 antibody test is expected to be "positive" in either $T_H1$ or $T_H2$ responses

# $T_H1$ Polarization is Typically Effective Against Viruses



## FDA's guidance on COVID-19 vaccines recognizes $T_H1$ responses[1]

- $T_H1$ inducing vaccines may go to First-in-Human studies without certain animal testing

## An inappropriate $T_H2$ immune response to a virus can lead to bad outcomes

- Serious disease
- Chronic, persistent infection and inflammation

[1]FDA guidance for Industry "Development and Licensure of Vaccines to Prevent COVID-19" – July 2020 - Page 8, Section D. – 4th bullet point: "COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to [First in human] FIH trials without first completing postvaccination challenge studies in appropriate animal models, provided adequate risk mitigation strategies are put in place in the FIH trials" https://www.fda.gov/media/139638/download.

# Types of Pathogen and Effective Immune Responses



| | | | Type of Pathogen | |
|---|---|---|---|---|
| | | | Intra-cellular (Viruses[1]) | Extra-cellular (Bacteria[2]) |
| **T-Helper Polarization** | **Predominant Immunity** | | | |
| $T_H1$ | T cells | | + | - |
| $T_H2$ | Antibodies | | - | + |

**T cells recognize digested fragments ("antigens") on pathogens on the surfaces of infected cells**

[1]Intracellular pathogens include intracellular bacteria and protozoa
[2]Extracellular pathogens include worms and toxins

# Vaccine Type and Expected Immunity



| | Type of Vaccine | | | |
|---|---|---|---|---|
| | Subunit | DNA/RNA | Non-Replicating | Live Replicating |
| **Probability of Expected Polarization** | | | | |
| $T_H1$ | Unlikely | Unknown | Unknown | Likely |
| $T_H2$ | Likely | Unknown | Unknown | Unlikely |

**DNA/RNA vaccines and non-replicating vaccines are relatively novel: probability of T cell polarizations can be affected by other factors**

- Different subtypes of vaccines
- Type of antigen expressed (e.g., a cell surface antigen can bias towards $T_H2$ response)

# 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 to 220 years old

- **Live attenuated vector systems in development include:**
  - Tonix (horsepox), Tonix (bovine parainfluenza), Merck (measles[1]- and VSV[2]-based), Zydus Cadila (measles-based)

[1]Measles-based vaccine, acquisition of Themis, collaboration with Institute Pasteur
[2]VSV = vesicular stomatitis virus; collaboration with IAVI = International AIDS Vaccine Initiative

# Where Do We Go From Here?



- **Goal: Effective COVID-19 vaccines**
  - So we can return to work and school

- **Need #1 Quickly available vaccines**
  - Even if they offer only temporary immunity -- several now in human trials

- **Need #2 Vaccines providing long-term immunity**
  - Durable immunity for years
  - Blocking of forward transmission
  - Expect longer development and testing timelines

# TNX-1800[1]: COVID-19 Vaccine Engineered for Long-term Immunity



- **Based on viral vaccine developed more than 200 years ago by Edward Jenner for a smallpox vaccine**
  - Eradicated smallpox
  - T cell eliciting immunity
  - Single dose immunity without adjuvants
  - Manufacturable in scale on existing systems
  - Glass-sparing packaging owing to small unit dose

[1]TNX-1800 is at the pre-IND stage of development

TONIX PHARMACEUTICALS

# *Thank You!*