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Tonix Pharmaceuticals Announces Clinical Proof-of-Concept Study of TNX-1900 (Intranasal Potentiated Oxytocin)

Intranasal Oxytocin Blocks the Release of CGRP in Animal Models

Intranasal Oxytocin is the Core Technology of TNX-1900 for Migraine

Oxytocin Treatment Affects a Pathway that is Distinct from the Recently Available CGRP Migraine Treatment Drug Class

CHATHAM, N.J., May 22, 2023 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP), a clinical-stage biopharmaceutical company, today announced that it has entered into a research collaboration agreement to evaluate the effect of TNX-1900 (intranasal potentiated oxytocin) on capsaicin- or electrical stimulation-induced forehead dermal blood flow in healthy female human volunteers. Dr. Antoinette Maassen van den Brink, Professor of Neurovascular Pharmacology, Erasmus University Medical Center, will serve as principal investigator for the study.

“Collaborating with Professor Maassen van den Brink is an exciting opportunity to learn about the potential for TNX-1900 for treating migraine, facial pain and other related conditions,” said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. “In animal studies, intranasal oxytocin blocks the release of calcitonin gene-related peptide (CGRP) release from trigeminal neurons.[1] CGRP is released from trigeminal neurons during a migraine attack and several CGRP inhibitors are approved for the treatment of migraine. Both a CGRP inhibitor and a triptan have been successfully tested in the model and have been found to inhibit the forehead dermal blood flow response to capsaicin in migraineurs and healthy volunteers, respectively.[2,3] We look forward to learning the results of TNX-1900 in this proof-of-concept study. Together with other studies, the results will guide future development of this potential non-addictive treatment for migraine and other painful conditions.”

Dr. Maassen van den Brink, the principal investigator of the study said, “The signaling pathways that mediate migraine and facial pain are becoming understood. Oxytocin represents a potential new therapeutic option, targeting a pathway in migraine that is distinct from the recently available CGRP inhibitor migraine treatment drug class.”

In February 2023, Tonix initiated enrollment in its Phase 2 PREVENTION study of TNX-1900 for chronic migraine. The Company expects topline results in the fourth quarter of this year.

About Migraine

Migraine is a neurovascular condition that typically manifests in a throbbing moderate to severe headache which lasts at least four hours, often on one side of the head and aggravated by routine physical activity. It can also be accompanied by nausea, vomiting, visual disturbances, and sensitivity to bright light and loud noises.[4] Epidemiological studies indicate that globally, approximately 1.2 billion individuals suffer from migraines annually.[5] In the U.S., approximately 39 million Americans suffer from migraines and among these individuals, approximately four million experience chronic migraines (15 or more headache days per month, at least eight of which are migraines).[5] The current FDA approved drugs for migraine prevention in chronic migraine include Botox® (onabotulinumtoxin), and the anti-CGRP/CGRP-receptor monoclonal antibodies Aimovig® (erenumab), Vyepti® (eptinezumab), Ajovy® (fremanezumab) and Emgality® (galcanezumab).

About TNX-1900

TNX-1900 (intranasal potentiated oxytocin) is a proprietary formulation of oxytocin in development as a candidate for prevention of chronic migraine and other conditions. In 2020, TNX-1900 was acquired from Trigemina, Inc. who had licensed the technology underlying the composition and method from Stanford University. TNX-1900 is a drug-device combination product, based on an intranasal actuator device that delivers oxytocin into the nasal cavity. Oxytocin is a naturally occurring human peptide hormone that also acts as a neurotransmitter in the brain. Oxytocin has no recognized addiction potential. It has been observed that low oxytocin levels in the body are associated with increases in migraine headache frequency, and that increased oxytocin levels are associated with fewer migraine headaches. Certain other chronic pain conditions are also associated with decreased oxytocin levels. Migraine attacks are caused, in part, by the activity of pain-sensing trigeminal neurons which, when activated, release calcitonin gene-related peptide (CGRP) which binds to receptors on other nerve cells and starts a cascade of events that is believed to result in migraine. Oxytocin when delivered via the nasal route, concentrates in the trigeminal system[6] resulting in binding of oxytocin to receptors on neurons in the trigeminal system, inhibiting the release of CGRP and transmission of pain signals returning from the site of CGRP release.[1] Blocking CGRP release is a distinct mechanism compared with CGRP receptor antagonist and anti-CGRP antibody drugs, which block the binding of CGRP to its receptor, or bind to the peptide CGRP. With TNX-1900, the addition of magnesium to the oxytocin formulation enhances oxytocin receptor binding[7] as well as its inhibitory effects on trigeminal neurons and resultant craniofacial analgesic effects, as demonstrated in animal models.[8] Intranasal oxytocin has been shown to be well tolerated in several clinical trials in both adults and children[9]. Targeted nasal delivery results in low systemic exposure and lower risk of non-nervous system, off-target effects, which could potentially occur with systemic CGRP receptor antagonists and anti-CGRP (receptor) antibodies[10]. For example, CGRP has roles in dilating blood vessels in response to ischemia, including in the heart. The Company believes nasally targeted delivery of oxytocin could translate into selective blockade of CGRP release from neurons 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 rapidly reversible, in contrast to monthly or quarterly dosing, as is the case with anti-CGRP antibodies, giving physicians and their patients greater control. In addition to chronic migraine, TNX-1900 will be developed for treatment of episodic migraine, craniofacial pain conditions, binge eating disorder, and insulin resistance. Tonix also has a

license with the University of Geneva to use TNX-1900 for the treatment of insulin resistance and related conditions.

Tonix Pharmaceuticals Holding Corp.*

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

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

[1]Tzabazis A, et al. Cephalalgia. 2016. 36(10):943-50.

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erenumab. J Neurol Neurosurg Psychiatry. 2022 Aug;93(8):911-912.

[3]Ibrahimi K, et al. A human trigeminovascular biomarker for antimigraine drugs: A randomized double-blind, placebo-controlled, crossover trial with sumatriptan. Cephalalgia. 2017 Jan;37(1):94-98.

[4]The International Classification of Headache Disorders, 3rd Edition. Cephalalgia. 2018. 38(1):1-211

[5]Burch et al., Migraine: Epidemiology, Burden, and Comorbidity, Neurol Clin 37 (2019):631–649

[6]*Yeomans DC, et al. Transl Psychiatry. 2021. 11(1):388.*
[7]*Antoni FA and Chadio SE. Biochem J. 1989. 257(2):611-4.*
[8]*Cai Q, et al., Psychiatry Clin Neurosci. 2018. 72(3):140-151.*
[9]*Yeomans, DC et al. 2017. US patent US2017368095*
[10]*MaassenVanDenBrink A, et al. Trends Pharmacol Sci. 2016. 37(9):779-788*

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, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the “SEC”) on March 13, 2023, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

Contacts

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

Maddie Stabinski (media)
Russo Partners
madeline.stabinski@russopartnersllc.com
(212) 845-4273

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

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