November 23, 2021

Tonix Pharmaceuticals Announces FDA Clearance of the IND for Potentiated Intranasal Oxytocin (TNX-1900) for the Prevention of Migraine Headache in Chronic Migraineurs

Approximately Four Million in U.S. Suffer from Chronic Migraine

Development of TNX-1900 Also Planned for Treatment of Episodic Migraine, Craniofacial Pain and Insulin Resistance

CHATHAM, N.J., Nov. 23, 2021 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced the U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug (IND) Application to support the initiation of a Phase 2 study of TNX-1900* (intranasal potentiated oxytocin) for the prevention of migraine headache in chronic migraineurs. The program is expected to qualify for the 505(b)(2) pathway for FDA approval, which is available to new formulations of an approved drug.

“We are excited to have received the FDA’s IND clearance to begin clinical trials for TNX-1900 in prevention of migraine headaches in chronic migraineurs,” said Seth Lederman, M.D., President and CEO of Tonix. “An estimated four million individuals in the United States suffer from chronic migraine. We believe that by engaging and stimulating oxytocin receptors in the trigeminal ganglia, TNX-1900 has the potential to help chronic migraine sufferers. TNX-1900 contains magnesium, which potentiates the action of oxytocin at oxytocin receptors in animal models. We expect to begin enrollment in the TNX-1900 Phase 2 study in the second half of 2022.” Dr. Lederman added, “We also plan to develop TNX-1900 for craniofacial pain as well as insulin resistance. A related intranasal potentiated oxytocin product candidate, TNX-2900*, is under development for the treatment of Prader-Willi syndrome.”

**TNX-1900 and TNX-2900 are investigational new drugs and have not been approved for any indication.*

About Migraine

Migraine is a neurological condition that manifests in throbbing headache, often on one side of the head, that lasts at least four hours. It can also be accompanied by nausea, vomiting, visual disturbances, and sensitivity to bright light, strong smells, and loud noises[1]. Epidemiological studies indicate that globally, approximately 1.2 billion individuals suffer from

migraines annually.[2] 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).[2]

About TNX-1900

TNX-1900 (intranasal potentiated oxytocin) is a proprietary formulation of oxytocin in development as a candidate for prophylaxis of chronic migraine and for the treatment of craniofacial pain, insulin resistance and related conditions. In 2020, TNX-1900 was acquired from Trigemina, Inc. and licensed from Stanford University. TNX-1900 is a drug-device combination product, based on an intranasal actuator device that delivers oxytocin into the nose. Oxytocin is a naturally occurring human hormone that acts as a neurotransmitter in the brain. Oxytocin has no recognized addiction potential. It has been observed that low oxytocin levels in the body can lead to increase in migraine headache frequency, and that increased oxytocin levels can relieve 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 nerve cells which, when activated, release of CGRP which binds to receptors on other nerve cells and starts a cascade of events that is believed to result in headache. Oxytocin when delivered via the nasal route, concentrates in the trigeminal system[3] resulting in binding of oxytocin to receptors on neurons in the trigeminal system, inhibiting transmission of pain signals and the release of CGRP.[4] Blocking CGRP release is a distinct mechanism compared with CGRP antagonist and anti-CGRP antibody drugs, which block the binding of CGRP to its receptor. With TNX-1900, the addition of magnesium to the oxytocin formula enhances oxytocin receptor binding[5] as well as its effects on trigeminal neurons and craniofacial analgesic effects in animal models[7]. Intranasal oxytocin has been well tolerated in several clinical trials in both adults and children[6]. 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 antagonists such as anti-CGRP antibodies[8]. For example, CGRP has roles in dilating blood vessels in response to ischemia, including in the heart. We believe nasally 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, as is the case with anti-CGRP antibodies, giving physicians and their patients greater control. We intend to initiate a Phase 2 study in chronic migraine in the second half of 2022. We also plan to develop TNX-1900 for treatment of episodic migraine, craniofacial pain and insulin resistance. Tonix has a license with the University of Geneva to use TNX-1900 for the treatment of insulin resistance and related conditions. TNX-2900* is another intranasal potentiated oxytocin-based therapeutic candidate, being developed for the treatment of Prader-Willi syndrome, or PWS. The technology for TNX-2900 was licensed from the French National Institute of Health and Medical Research. PWS, an orphan condition, is a rare genetic disorder of failure to thrive in infancy, associated with uncontrolled appetite later in childhood.

[1]https://www.mayoclinic.org/diseases-conditions/migraine-headache/symptoms-causes/syc-20360201

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

[3]Yeomans DC, et al. *Transl Psychiatry*. 2021. 11(1):388.
[4]Tzabazis A, et al. *Cephalalgia*. 2016. 36(10):943-50.
[5]Antoni FA and Chadio SE. *Biochem J.* 1989. 257(2):611-4.
[6]Yeomans, DC et al. 2017. US patent US2017368095
[7]Cai Q, et al., *Psychiatry Clin Neurosci*. 2018. Mar;72(3):140-151.
[8]MaassenVanDenBrink A, et al. *Trends Pharmacol Sci.* 2016. 37(9):779-788

About Tonix Pharmaceuticals Holding Corp.

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing therapeutics and diagnostics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is primarily composed of immunology and central nervous system (CNS) product candidates. Tonix's immunology portfolio includes COVID-19-related product candidates to prevent and treat COVID-19, to treat Long COVID as well as to detect functional T cell immunity to SARS-CoV-2. 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] (cyclobenzaprine HCl sublingual tablets), is in mid-Phase 3 development for the management of fibromyalgia. TNX-1300[2] is a biologic designed to treat cocaine intoxication that is expected to start a Phase 2 trial before year end. Tonix's lead vaccine candidate for COVID-19, TNX-1800[3], is a live replicating vaccine based on Tonix's recombinant pox vaccine (RPV) platform to protect against COVID-19, primarily by eliciting a T cell response. Tonix expects to start a Phase 1 study in humans in the second half of 2022. Tonix is developing TNX-2100[4], an *in vivo* diagnostic to measure the presence of functional T cell immunity to SARS-CoV-2 and intends to initiate a first-in-human clinical study in the first quarter of 2022. TNX-3500[5] (sangivamycin) is a small molecule antiviral drug to treat acute COVID-19 and is in the pre-IND stage of development. Finally, TNX-102 SL is a small molecule drug being developed to treat Long COVID, a chronic post-COVID condition, and is also in the pre-IND stage. Tonix expects to conduct a Phase 2 study in Long COVID in the first half of 2022. Tonix's immunology portfolio also includes biologics to address immunosuppression, cancer, and autoimmune diseases.

[1]TNX-102 SL is an investigational new drug and has not been approved for any indication.
[2]TNX-1300 is an investigational new biologic at the pre-IND stage of development and has not been approved for any indication.
[3]TNX-1800 is an investigational new biologic and has not been approved for any indication. TNX-1800 is based on TNX-801, live horsepox virus vaccine for percutaneous administration, which is in development to protect against smallpox and monkeypox. TNX-801 is an investigational new biologic and has not been approved for any indication.
[4]TNX-2100 is an investigational new biologic and has not been approved for any indication
[5]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, 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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Source: Tonix Pharmaceuticals Holding Corp.