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Tonix Pharmaceuticals Announces Enrollment Initiated in Mass General Brigham Phase 2 Investigator-Initiated Study of TNX-1900 (Intranasal Potentiated Oxytocin) for Bone Health in Children with Autism Spectrum Disorder

Children with Autism Spectrum Disorder are at Risk for Low Bone Density

Preliminary Data Suggest that the Administration of Oxytocin May Favorably Impact Bone Formation and Strength

Recent Meta-Analysis Reported that Plasma Oxytocin Levels Tend to be Lower in Children with Autism Spectrum Disorder than Controls[1]

CHATHAM, N.J., Nov. 13, 2023 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a biopharmaceutical company with marketed products and a pipeline of development candidates, today announced that the first participant was enrolled in an investigator-initiated Phase 2 study of TNX-1900 (intranasal potentiated oxytocin) for improving bone health in children with autism spectrum disorder (ASD), named the BOX study, at Massachusetts General Hospital (MGH). The aim of this Department of Defense-funded study is to investigate the efficacy and safety of TNX-1900 as a novel therapeutic agent to increase bone density and improve bone structure and strength in children with ASD. Tonix is providing active drug and placebo for the BOX study as part of a drug donation agreement with MGH. MGH is the sponsor of the trial, which is being conducted under an investigator-initiated investigational new drug (IND) application.

“Low bone density in ASD is a serious problem,” said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. “Intranasal potentiated oxytocin is a potential treatment option that addresses the biology of bone loss specific to ASD which is different from osteoporosis in post-menopausal women. Intranasal oxytocin has a long history of being tested for the treatment of ASD, but results have been inconsistent. Tonix’s magnesium-potentiated intranasal oxytocin is designed to improve consistency in clinical effects, because it reduces the ‘high-dose’ inhibition seen in the ‘inverted U’ dose response in animals.”[2]

Madhusmita Misra, M.D., MPH, Chief, Division of Pediatric Endocrinology, Department of Pediatrics, Mass General for Children, and principal investigator of the study said, “The

childhood and adolescent years are critical for bone mass accrual towards achievement of peak bone mass, a key determinant of future bone health and fracture risk. Preliminary data show that over a four-year period, children with ASD fail to catch-up with typically developing children for bone health measures despite optimizing calcium and vitamin D intake[3]. The difference between these groups often becomes more drastic over time."

Elizabeth A. Lawson, M.D., M.M.Sc., Director, Interdisciplinary Oxytocin Research Program in the Neuroendocrine Unit, Department of Medicine, MGH, who is a co-investigator on the study continued, "Preclinical studies indicate that, in addition to its known central prosocial effects,[4] oxytocin is an important mediator of bone homeostasis, promoting bone formation over resorption.[5-7] Pilot data indicate strong associations between low levels of oxytocin and worse bone health in both sexes and across clinical populations, supporting the critical role of oxytocin in bone metabolism."[8-11]

"Preclinical studies and some clinical trials have shown prosocial effects of oxytocin in individuals with autism," reported Ann Neumeyer, M.D., Medical Director of Lurie Center for Autism, Department of Pediatrics and Neurology, Mass General for Children and also a co-investigator. "This research study will further investigate effects of oxytocin on social impairment associated with autism as a secondary outcome."[12]

Dr. Lederman continued, "Given the increasing prevalence of ASD in children and its association with impaired bone health, lower oxytocin levels in those with ASD than neurotypical controls, and preclinical data showing that oxytocin can favorably impact bone health, a study examining the role of oxytocin in improving bone health in children with ASD is both timely and essential."

The Phase 2 investigator-initiated BOX study is a randomized, placebo-controlled study to evaluate the effects of twice daily administration of TNX-1900 on bone measures in children with ASD. Study subjects, ages six to 18 years old, will be randomized 1:1 to receive TNX-1900 twice per day or placebo for 12 months in the double-blind phase, followed by a six-month open label phase during which all study subjects will receive TNX-1900 twice daily. The primary endpoint is the difference between TNX-1900 compared to placebo groups in 12-month change in whole body less head bone mineral density Z-scores. A Z-score compares one's bone density to the average bone density of age and gender matched controls.

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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 within the central nervous system (CNS). 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 headache. Oxytocin when delivered via the nasal route, concentrates in the trigeminal system[1] 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.[2] 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 formulation enhances oxytocin receptor binding[3] as well as oxytocin's inhibitory effects on trigeminal neurons and resultant craniofacial analgesic effects, as demonstrated in animal models[4]. Intranasal oxytocin has been shown to be well tolerated in several clinical trials in both adults and children[5]. Targeted nasal delivery results in low systemic exposure and lower risk of non-CNS, off-target effects, which could potentially occur with systemic CGRP antagonists such as anti-CGRP antibodies[6]. 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 patients greater control. In addition to chronic migraine, TNX-1900 will be developed for treatment of episodic migraine, binge eating disorder, and craniofacial pain conditions. Tonix also has a license with the University of Geneva for the use of TNX-1900 in the treatment of insulin resistance and related conditions.

About TNX-2900

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.

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Tonix Pharmaceuticals Holding Corp.*

Tonix is a biopharmaceutical company focused on commercializing, developing, discovering and licensing therapeutics to treat and prevent human disease and alleviate suffering. Tonix Medicines, our commercial subsidiary, markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg under a transition services agreement with Upsher-Smith Laboratories, LLC from whom the products were acquired on June 30, 2023. Zembrace SymTouch and Tosymra are each indicated for the treatment of acute migraine with or without aura in adults. Tonix's development portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS development portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead development CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia, having completed enrollment of a potentially confirmatory Phase 3 study in the third quarter of 2023, with topline data expected in late December 2023. TNX-102 SL is also being developed to treat fibromyalgia-type Long COVID, a chronic post-acute COVID-19 condition, and topline results were reported in the third quarter of 2023. TNX-1900 (intranasal potentiated oxytocin), is in development as a preventive treatment in chronic migraine, and enrollment has completed in a Phase 2 proof-of-concept study with topline data expected in early December 2023. TNX-1900 is also being studied in binge eating disorder, pediatric obesity and social anxiety disorder by academic collaborators under investigator-initiated INDs. 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 fourth quarter of 2023. Tonix's rare disease development 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 development 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 was initiated in the third quarter of 2023. Tonix's infectious disease pipeline includes TNX-801, a vaccine in development to prevent smallpox and mpox. TNX-801 also serves as the live virus vaccine platform or recombinant pox vaccine platform for other infectious diseases, including TNX-1800, in development as a vaccine to protect against COVID-19. During the fourth quarter of 2023, TNX-1800 was selected by the U.S. National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Project NextGen for inclusion in Phase 1 clinical trials. The infectious disease development portfolio also includes TNX-3900 and TNX-4000, which are classes of broad-spectrum small molecule oral antivirals.

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

Zembrace SymTouch and Tosymra are registered trademarks of Tonix Medicines. Intravail is a registered trademark of Aegis Therapeutics, LLC, a wholly owned subsidiary of Neurelis, Inc. All other marks are property of their respective owners.

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, including the intended use of proceeds from the public offering and other statements that are predictive in nature. 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; risks related to the failure to successfully market any of our products; 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.

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