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Tonix Pharmaceuticals Announces Results of Pre-IND Meeting with FDA on TNX-601 CR for the Treatment of Major Depressive Disorder

Company Expects to Initiate a Phase 2 Clinical Trial in the Fourth Quarter of 2021, Pending Results of Toxicology Studies

CHATHAM, N.J., March 22, 2021 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced that it has received the official minutes from a Type B pre-investigational new drug (IND) meeting with the U.S. Food and Drug Administration (FDA) on its development plan for TNX-601 CR (tianeptine oxalate and naloxone controlled-release) tablet for the treatment of major depressive disorder (MDD). Tonix's TNX-601 CR is a novel oral formulation which is being developed as a potential treatment for MDD, posttraumatic stress disorder, and neurocognitive dysfunction associated with corticosteroid use. Tianeptine sodium (amorphous) immediate release (IR) has been available in Europe and many countries in Asia and Latin America for the treatment of depression for more than three decades, first marketed in France in 1989.

Based on the official minutes, Tonix expects to submit the IND to conduct a human abuse potential study and meet with FDA's controlled substances staff (CSS) to reach agreement on the details of the abuse potential study. Pending the results of the human abuse potential study and the results of ongoing nonclinical toxicology studies, Tonix expects to be in a position to initiate a Phase 2 study for the treatment of MDD in the fourth quarter of 2021.

"We are pleased with the results of the FDA meeting on developing TNX-601 CR for the treatment of MDD and we look forward to advancing its clinical development," said Seth Lederman, M.D., President and Chief Executive Officer of Tonix Pharmaceuticals. "Tianeptine products have been approved in Europe and other countries around the world and marketed as prescriptions drugs for treating depression for more than 3 decades. We believe that with respect to tianeptine, TNX-601 CR would meet the bioequivalence standard for daily dosing of these immediate release (IR) products. No tianeptine-containing product has been approved by the FDA. TNX-601 CR's proposed mechanism of action is distinct from any approved antidepressant in the U.S."

"TNX-601 CR is designed for once daily dosing, which is believed to provide an adherence advantage relative to the three times per day dosing of the immediate-release sodium salt products available in Europe and other jurisdictions around the world," said Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals. "The efficacy of tianeptine sodium IR

is comparable to both selective serotonin inhibitor (SSRI) and tricyclic antidepressants[1,2] while being associated with a lower incidence of sexual dysfunction than either class[3]. And unlike SSRIs, tianeptine is not associated with adverse effects on libido[4]. Given tianetptine's unique metabolic pathway, we believe that TNX-601 CR has a reduced risk of drug-drug interactions compared to SSRIs[5]. Tianeptine's antidepressant activity is believed to relate to indirect modulation of the glutamatergic system. While it does not have measurable interactions with the NMDA, AMPA or kainate receptors, tianeptine is known to modulate AMPA receptor trafficking and to promote synaptic plasticity in the hippocampus under conditions of stress or corticosteroid use."

Dr. Sullivan continued, "We are excited to bring to the clinic the discoveries and observations of the late Professor Bruce McEwen (1938-2020) of Rockefeller University in New York City who noted that tianeptine's ability in animal models, 'to restore normal neuroplasticity… and to reverse stress-induced impairments in synaptic glutamate transmission… is crucial in virtually all key functions perturbed in depressed states'."[6]

Tonix has added naloxone to the TNX-601 CR tablet as a deterrent to parenteral abuse, because tianeptine is a weak mu-opioid receptor agonist and has been linked to illicit misuse at much higher doses than those reported to be effective in the treatment of MDD[7]. In patients who were prescribed tianeptine for depression, the French Transparency Committee found an incidence of abuse of approximately 1 case per 1,000 patients treated[8]. Clinical trials have shown that cessation of a therapeutic course of tianeptine did not result in dependence or withdrawal symptoms following 6-weeks[2,3,9–11], 3-months[12], or 12-months[13] of treatment.

[1]Jeon, H. J., et al. *J. Clin. Psychopharmacol.* **2014**, *34* (2), 218–225.
[2]Emsley, R., et al. *J. Clin. Psychiatry* **2018**, *79* (4)
[3]Bonierbale M, et al. *Curr Med Res Opin* **2003**, *19*(2):114-124.
[4]Costa e Silva, J. A., et al. *Neuropsychobiology* **1997**, *35* (1), 24–29.
[5]Wagstaff, A. J. et al. *CNS Drugs* **2001**, *15* (3), 231–259.
[6]McEwen, B. S., et al. *Mol. Psychiatry* **2010**, *15* (3), 237–249.
[7]Lauhan, R., et al. *Psychosomatics* **2018**, *59* (6), 547–553.
[8]Haute Authorite de Sante; Transparency Committee Opinion. Stablon 12.5 Mg, Coated Tablet, Re-Assessment of Actual Benefit at the Request of the Transparency Committee. December 5, 2012.
[9]Guelfi, J. D., et al. *Neuropsychobiology* **1989**, *22* (1), 41–48.
[10]Invernizzi, G. et al., *Neuropsychobiology* **1994**, *30* (2–3), 85–93.
[11]Lepine, J. P., et al. *Hum. Psychopharmacol.* **2001**, *16* (3), 219–227.
[12]Guelfi, J. D. et al., *Neuropsychobiology* **1992**, *25* (3), 140–148.
[13]Lôo, H. et al., *Br. J. Psychiatry. Suppl.* **1992**, No. 15, 61–65.

About Depression

According to the National Institute of Mental Health, depression affects approximately 17 million adults in the U.S.[1] have had at least one major depressive episode, with approximately 2.5 million adults treated with adjunctive therapy.[2,3] Depression is a condition

characterized by symptoms such as a depressed mood or loss of interest or pleasure in daily activities most of the time for two weeks or more, accompanied by appetite changes, sleep disturbances, motor restlessness or retardation, loss of energy, feelings of worthlessness or excessive guilt, poor concentration, and suicidal thoughts and behaviors. These symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The majority of people who suffer from depression do not respond adequately to initial antidepressant therapy.[4]

[1]National Institute of Mental Health. (2017). Major Depression. Retrieved from http://www.nimh.nih.gov/health/statistics/major-depression.shtml
[2]IMS NSP, NPA, NDTI MAT-24-month data through Aug 2017.
[3]PLOS One, Characterization of Treatment Resistant Depression Episodes in a Cohort of Patients from a US Commercial Claims Database, Oct 2013, Vol 8, Issue 10.
*[4]Rush AJ, et al. (2007) Am J. Psychiatry 163:11, pp. 1905-1917 (STAR*D Study).*

About TNX-601 CR

TNX-601 CR is a novel oral formulation of tianeptine oxalate designed for once-daily daytime dosing that is in the pre-IND (Investigational New Drug) stage of development for the treatment of MDD. Tianeptine sodium (amorphous) immediate release was first marketed for depression in France in 1989 and has been available for decades in Europe, Russia, Asia, and Latin America for the treatment of depression. Tianeptine sodium has an established safety profile from decades of use in these jurisdictions. Currently there is no tianeptine-containing product approved in the U.S. and no controlled release tianeptine product approved in any jurisdiction. Tonix discovered a novel oxalate salt of tianeptine that may provide improved stability, consistency, and manufacturability compared to known forms of tianeptine. Tianeptine is believed to work in depression as a modulator of the glutamatergic system. Tianeptine modulates the glutamatergic system indirectly since it does not interact with NMDA, AMPA or kainate receptors. In animals, tianeptine has been shown to reverse the adverse neuroplastic changes that are observed during periods of stress and elevated corticosteroid exposure. Tianeptine and its MC5 metabolite are weak mu-opioid receptor (MOR) agonists. Tonix has added naloxone to the TNX-601 CR tablet as a deterrent to parenteral abuse as tianeptine has been linked to illicit misuse at much higher doses than the reported therapeutic dose in the treatment of MDD. Neither tianeptine nor MC5 have been shown to bind other neurotransmitter receptors. Tianeptine's reported pro-cognitive and anxiolytic effects as well as its ability to attenuate the neuropathological effects of excessive stress responses suggest that it may be used to treat post-traumatic stress disorder by a different mechanism of action than TNX-102 SL.

Tonix Pharmaceuticals Holding Corp.

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing small molecules and biologics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is primarily composed of central nervous system (CNS) and immunology product candidates. The CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL[1], is in mid-Phase 3 development for the management of fibromyalgia, and positive data on the RELIEF Phase 3 trial were recently reported. The Company expects interim data from a second Phase 3 study, RALLY, in the

third quarter of 2021[2] and topline data in the fourth quarter of 2021. The immunology portfolio includes vaccines to prevent infectious diseases and biologics to address immunosuppression, cancer, and autoimmune diseases. Tonix's lead vaccine candidate, TNX-1800[3], is a live replicating vaccine based on the horsepox viral vector platform to protect against COVID-19, primarily by eliciting a T cell response. Tonix reported positive efficacy data from animal studies of TNX-1800 in the first quarter of 2021. TNX-801[3], live horsepox virus vaccine for percutaneous administration, is in development to protect against smallpox and monkeypox.

[1]TNX-102 SL is an investigational new drug and has not been approved for any indication.
[2]Pending agreement from FDA on statistical analysis plan.
[3]TNX-1800 and TNX-801 are investigational new biologics and have 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.

Contacts

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

Olipriya Das, Ph.D. (media)

Russo Partners
Olipriya.Das@russopartnersllc.com
(646) 942-5588

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

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