Karuna Therapeutics Announces The Lancet Publication of Data from Phase 3 EMERGENT-2 Trial Evaluating KarXT in Schizophrenia

December 14, 2023

KarXT demonstrated statistically significant and clinically meaningful improvements in positive and negative symptoms of schizophrenia compared to placebo, as measured by primary and secondary endpoints

KarXT was generally well tolerated and not associated with many adverse events typically associated with current antipsychotics, including somnolence, weight gain and extrapyramidal symptoms

New Drug Application for KarXT for the treatment of schizophrenia in adults was recently accepted with a Prescription Drug User Fee Act (PDUFA) action date of September 26, 2024

If approved, KarXT, a dual M1/M4 muscarinic agonist, would represent the first new pharmacological approach to treating schizophrenia in several decades

BOSTON--(BUSINESS WIRE)--Dec. 14, 2023-- Karuna Therapeutics, Inc. (NASDAQ: KRTX), a biopharmaceutical company driven to discover, develop, and deliver transformative medicines for people living with psychiatric and neurological conditions, today announced that results from the Phase 3 EMERGENT-2 trial of KarXT (xanomeline-trospium) in adults with schizophrenia were published in The Lancet. The manuscript shares KarXT data showcasing a clinically meaningful and statistically significant reduction in positive and negative symptoms of schizophrenia among adult patients experiencing acute psychosis, alongside a distinct tolerability profile.

“Having such robust data showcased in one of the world’s most prestigious medical journals attests to the potential of KarXT’s novel mechanism of action to redefine the treatment landscape for the millions grappling with schizophrenia’s disabling symptoms,” said Steve Paul, M.D., president of research and development and chief scientific officer of Karuna Therapeutics and co-author on the manuscript. “The data published in our manuscript continue to reinforce our confidence in KarXT as we look ahead to the results of our ongoing trials, including EMERGENT-4 and EMERGENT-5, which will provide a longer-term view of the efficacy and safety of KarXT in people living with schizophrenia.”

The Phase 3 EMERGENT-2 trial was a double-blind, placebo-controlled, five-week inpatient trial that enrolled 252 adults with schizophrenia in the United States. Participants were randomized 1:1 to receive a twice-daily, flexible dose of KarXT or placebo. In the trial, KarXT demonstrated a statistically significant and clinically meaningful 9.6-point reduction in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo (-21.2 KarXT vs. -11.6 placebo, $p<0.0001$) at week 5, the primary outcome measure of the study. Results published in *The Lancet* also include data for all the pre-specified secondary outcome measures: change in PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, Clinical Global Impression-Severity score, and percentage of participants achieving a ≥30% reduction from baseline to week 5 in PANSS total score, where KarXT demonstrated statistically significant reductions compared to placebo at week 5 ($p<0.05$) on each endpoint.

KarXT was generally well tolerated, with overall discontinuation rates similar to placebo (KarXT 25% vs. placebo 21%). Discontinuation rates due to treatment-emergent adverse events (TEAEs) were also similar between KarXT and placebo (7% vs. 6%, respectively). The most common KarXT TEAEs (≥5% and at least twice the rate of placebo) were constipation, dyspepsia, nausea, vomiting, hypertension, dizziness, and gastroesophageal reflux disease (acid reflux). The majority of common TEAEs occurred in the first two to three weeks of treatment, were transient, and resolved before the end of the trial (week 5). The data from EMERGENT-2 suggests that KarXT may have a distinctive safety and tolerability profile, as it was not associated with many of the adverse events typically associated with current antipsychotic treatments, including somnolence, weight gain and extrapyramidal motor symptoms.

“Coming off the heels of our NDA acceptance of KarXT for the treatment of schizophrenia, this publication in *The Lancet* further validates KarXT’s potential as an alternative to currently available treatment options that block dopamine receptors,” said Inder Kaul, MD, MPH, senior vice president of clinical development at Karuna Therapeutics and lead author of the manuscript. “For the first time in decades, a potential new therapeutic option presents the possibility of treating schizophrenia symptoms, perhaps without the burden of many of the side effects commonly associated with current antipsychotics.”

“New treatments and novel mechanisms are urgently needed for people with schizophrenia because many don’t respond to their therapy and others only have a partial improvement in symptoms or intolerable side effects,” said Rishi Kakar, M.D., chief scientific officer and medical director of Segal Trials, an author of the manuscript, and lead investigator of the Phase 3 EMERGENT-2 trial. “The antipsychotic activity and differentiated safety and tolerability profile demonstrated in EMERGENT-2, and the other completed EMERGENT trials, provide hope to the healthcare community and patients that KarXT may provide a much-needed new way to treat those living with schizophrenia.”

The published manuscript, titled “Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline–trospium) in schizophrenia (EMERGENT-2): results from a randomized, double-blind, placebo-controlled, flexible-dose phase 3 trial in the United States,” is available online and will appear in the print issue of The Lancet at a later date.

About KarXT
KarXT (xanomeline-trospium) is an investigational muscarinic antipsychotic in development for the treatment of schizophrenia and psychosis related to Alzheimer’s disease. Through its novel mechanism of action, KarXT acts as a dual M1/M4 muscarinic acetylcholine receptor agonist in the central nervous system, which is thought to improve positive, negative, and cognitive symptoms of schizophrenia. Unlike existing treatments, KarXT does not directly block dopamine receptors, representing a potential new approach to treating schizophrenia.

About Schizophrenia
Schizophrenia is a persistent and often disabling mental illness impacting how a person thinks, feels, and behaves, and affects nearly 24 million

people worldwide, including 2.8 million people in the U.S. It is characterized by three symptom domains: positive symptoms (hallucinations and delusions), negative symptoms (difficulty enjoying life and withdrawal from others), and cognitive impairment (deficits in memory, concentration, and decision-making). In part due to limitations with current treatments, people living with schizophrenia often struggle to maintain employment, live independently, and manage relationships. While current treatments can be effective in managing select symptoms, approximately 30% of people do not respond to therapy, with an additional 50% experiencing only a partial improvement in symptoms or unacceptable side effects.

About Karuna
Karuna Therapeutics is a biopharmaceutical company driven to discover, develop, and deliver transformative medicines for people living with psychiatric and neurological conditions. At Karuna, we understand there is a need for differentiated and more effective treatments that can help patients navigate the challenges presented by serious mental illness. Utilizing our extensive knowledge of neuroscience, we are harnessing the untapped potential of the brain in pursuit of novel pathways to develop medicines that make meaningful differences in peoples' lives. For more information, please visit www.karunatx.com.

Forward-Looking Statements
This press release contains forward looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding our goals to develop and commercialize our product candidates, and other statements identified by words such as "could," "expects," "intends," "may," "plans," "potential," "should," "will," "would," or similar expressions and the negatives of those terms. Forward-looking statements are not promises or guarantees of future performance and are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in such forward-looking statements. These factors include risks related to our limited operating history, our ability to obtain necessary funding, our ability to generate positive clinical trial results for our product candidates and other risks inherent in clinical development, the timing and scope of regulatory approvals, changes in laws and regulations to which we are subject, competitive pressures, our ability to identify additional product candidates, risks relating to business interruptions, and other risks set forth under the heading "Risk Factors" of our Annual Report on Form 10-K for the year ended December 31, 2022 and in our subsequent filings with the Securities and Exchange Commission. Our actual results could differ materially from the results described in or implied by such forward-looking statements. Forward-looking statements speak only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise these forward-looking statements.

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