



Karuna Therapeutics Announces Positive Results from Phase 3 EMERGENT-2 Trial of KarXT in Schizophrenia

August 8, 2022

Trial met primary endpoint, with KarXT demonstrating a statistically significant 9.6-point reduction in PANSS Total Score compared to placebo at Week 5 ($p < 0.0001$)

Trial also met key secondary endpoints, demonstrating statistically significant reductions in positive and negative symptoms of schizophrenia, as measured by the PANSS positive, PANSS negative and PANSS negative Marder factor subscales

KarXT was generally well tolerated, with a side effect profile substantially consistent with prior trials of KarXT in schizophrenia

The Company plans to submit a New Drug Application (NDA) with the U.S. Food & Drug Administration (FDA) in mid-2023

Conference call and webcast to take place today at 8:00 a.m. ET

BOSTON--(BUSINESS WIRE)--Aug. 8, 2022-- Karuna Therapeutics, Inc. (NASDAQ: KRTX), a clinical-stage biopharmaceutical company driven to create and deliver transformative medicines for people living with psychiatric and neurological conditions, today announced positive topline results from its Phase 3 EMERGENT-2 trial evaluating the efficacy, safety, and tolerability of its lead investigational therapy, KarXT (xanomeline-trospium), in adults with schizophrenia. The trial met its primary endpoint, with KarXT demonstrating a statistically significant and clinically meaningful 9.6-point reduction in the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo (-21.2 KarXT vs. -11.6 placebo, $p < 0.0001$) at Week 5 (Cohen's d effect size of 0.61). KarXT also demonstrated an early and sustained statistically significant reduction of symptoms, as assessed by PANSS total score, starting at Week 2 and maintained such reduction through all timepoints in the trial.

"We are thrilled that these topline results from the Phase 3 EMERGENT-2 trial confirm what was seen in our Phase 2 EMERGENT-1 trial and underscore the potential for KarXT, with its novel and unique mechanism of action, to redefine what successful treatment looks like for the 21 million people living with schizophrenia worldwide, and potentially usher in the first new class of medicine for these patients in more than 50 years," said Steve Paul, M.D., chief executive officer, president and chairman of Karuna Therapeutics. "These results represent our second positive registrational trial. We look forward to continuing to gather long-term safety data to support our submission of a New Drug Application with the U.S. Food and Drug Administration for KarXT as a treatment for schizophrenia, which we expect to occur in mid-2023."

KarXT also met key secondary endpoints in the Phase 3 EMERGENT-2 trial, demonstrating a statistically significant reduction in both positive symptoms (e.g., hallucinations or delusions) and negative symptoms (e.g., difficulty enjoying life or withdrawal from others) of schizophrenia as measured by the PANSS positive, PANSS negative and PANSS negative Marder factor subscales. Results at Week 5 include:

- 2.9-point reduction in the PANSS positive subscale with KarXT compared to placebo (-6.8 KarXT vs. -3.9 placebo, $p < 0.0001$).
- 1.8-point reduction in the PANSS negative subscale with KarXT compared to placebo (-3.4 KarXT vs. -1.6 placebo, $p = 0.0055$).
- 2.2-point reduction in the PANSS negative Marder factor subscale with KarXT compared to placebo (-4.2 KarXT vs. -2.0 placebo, $p = 0.0022$).

KarXT was generally well tolerated. Overall discontinuation rates were similar between KarXT and placebo groups (25% vs. 21%). The overall treatment-emergent adverse events (TEAEs) rate for KarXT and placebo was 75% and 58%, respectively. Discontinuation rates related to TEAEs were similar between KarXT (7%) and placebo (6%). Equal rates of serious TEAEs were observed between KarXT and placebo (2% in each group) and included suicidal ideation, worsening of schizophrenia symptoms, and appendicitis. None of the serious TEAEs were determined to be drug related. The most common TEAEs ($\geq 5\%$) in the KarXT arm were all mild to moderate in severity and included constipation, dyspepsia, nausea, vomiting, headache, increases in blood pressure, dizziness, gastroesophageal reflux disease (acid reflux), abdominal discomfort, and diarrhea. Mean blood pressure measures were similar between KarXT and placebo throughout the trial, and no syncopal events were observed. In the subset of patients with a TEAE of blood pressure increases, mean blood pressure at endpoint was similar to baseline and did not lead to trial discontinuation. Similar to prior trials, an increase in heart rate was associated with KarXT treatment and decreased in magnitude by the end of the trial. Consistent with EMERGENT-1, KarXT was not associated with common problematic side effects of current treatments, including sedation (somnolence), weight gain, and extrapyramidal symptoms.

"Despite the number of available treatment options, there continues to be a tremendous unmet need in the treatment of schizophrenia, placing an immense burden on both patients and their caregivers," said Rishi Kakar, M.D., chief scientific officer, Segal Trials and lead investigator of the Phase 3 EMERGENT-2 trial. "These data build on the growing body of clinical evidence supporting the potential of KarXT as a new and differentiated approach for schizophrenia, demonstrating notable improvements across both positive and negative symptoms, while not being associated with common problematic side-effects of current therapies, such as weight gain, sedation and movement disorders. This unique profile of KarXT has the potential to provide a new meaningful treatment option for our patients and their families beyond the current standard of care."

The EMERGENT program consists of the completed positive Phase 2 EMERGENT-1 and Phase 3 EMERGENT-2 trials, as well as three ongoing trials evaluating the acute efficacy and long-term safety of KarXT (EMERGENT-3, EMERGENT-4, and EMERGENT-5). Topline data from the Phase 3 EMERGENT-3 trial are expected in the first quarter of 2023. The data from our EMERGENT program will be used to support submission of an NDA

with the U.S. FDA for KarXT as a treatment for schizophrenia, which is expected in mid-2023. Additional analysis of data from the Phase 3 EMERGENT-2 trial is ongoing, with plans to present these results at future medical meetings.

Conference Call and Webcast Information

Karuna will hold a webcast and conference call this morning at 8:00 a.m. ET to share results from an interim analysis of its Phase 3 EMERGENT-2 trial of KarXT for the treatment of schizophrenia.

A live webcast of the presentation will be available on the Investor Relations page of Karuna's website at investors.karunatx.com. A replay of the webcast will also be archived for up to 30 days on Karuna's website following the conference.

About the Phase 3 EMERGENT-2 Trial

The Phase 3 EMERGENT-2 trial is a double-blind, placebo-controlled, five-week, inpatient trial evaluating the efficacy, safety, and tolerability of our lead investigational therapy, KarXT, as compared to placebo in adults with schizophrenia in the United States. The primary endpoint was change from baseline in Positive and Negative Syndrome Scale (PANSS) total score, a scale for measuring schizophrenia symptom severity, of KarXT compared to placebo at Week 5. Key secondary endpoints included change from baseline in PANSS positive, PANSS negative and PANSS negative Marder factor subscale of KarXT compared to placebo at Week 5.

A total of 252 adults (between the ages of 18-65 years) with a confirmed diagnosis of schizophrenia who were experiencing symptoms of psychosis enrolled in the trial. Patients were randomized 1:1 to receive either a flexible dose of KarXT (n=126) or placebo (n=126) two times a day (BID) for five weeks. On Days 1-2, patients received a dose of 50/20 KarXT (50mg xanomeline/20mg trospium) BID or matching placebo. On Day 3, patients escalated to a dose of 100/20 BID, and starting on Day 8, patients could increase to 125/30 BID based on tolerability. In the trial, 81% of patients on KarXT compared to 90% on placebo titrated to the highest dose level (125/30).

About KarXT

KarXT (xanomeline-trospium) is an oral, investigational M1/M4-preferring muscarinic agonist in development for the treatment of psychiatric and neurological conditions, including schizophrenia and psychosis in Alzheimer's disease. Comprised of muscarinic agonist xanomeline and muscarinic antagonist trospium, it is designed to preferentially stimulate muscarinic receptors in the central nervous system. KarXT is the first potential medicine of its kind with a truly new and unique dual mechanism that does not rely on the dopaminergic or serotonergic pathway to treat symptoms of serious mental illness. This approach has the potential to provide a differentiated therapy, and, if approved, to beneficially impact the lives of millions of people with serious mental illness.

About Schizophrenia

Schizophrenia is a chronic and often debilitating mental illness that impacts how one thinks, feels, and behaves. It is characterized by positive symptoms (hallucinations and delusions), negative symptoms (difficulty enjoying life and withdrawal from others), and cognitive impairment. Together these symptoms can severely impact quality of life and productivity, with only 10% of people gainfully employed and many struggling to meet adult milestones – such as living independently. The life expectancy of people living with schizophrenia is reduced by 10-20 years compared to the general population. Schizophrenia affects approximately 21 million people worldwide and is most commonly treated with antipsychotics. Unfortunately, many people with schizophrenia continue to experience limited efficacy or problematic side effects while on antipsychotic therapy, and up to 74% of patients discontinue medication before 18 months. When schizophrenia treatment is discontinued, it can lead to impacts on health including relapse, hospitalization, and longer time to remission.

About Karuna Therapeutics

Karuna Therapeutics is a clinical-stage biopharmaceutical company driven to create 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 expectations about the timing of our ongoing and planned clinical trials and regulatory filings, 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, risks relating to business interruptions resulting from the coronavirus (COVID-19) pandemic, and other risks set forth under the heading "Risk Factors" of our Annual Report on Form 10-K for the year ended December 31, 2021. 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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Investor Contact:

Alexis Smith
518-338-8990
asmith@karunatx.com

Media Contact:

Falon Moran

media@karunatx.com

Source: Karuna Therapeutics, Inc.