PureTech Affiliate Karuna Therapeutics Announces KarXT Met Primary Endpoint in Phase 2 Clinical Trial of Acute Psychosis in Patients with Schizophrenia

November 19, 2019

KarXT Demonstrated Statistically Significant and Clinically Meaningful Improvement in Total PANSS Score at All Time Points Over Five Weeks and was Well-Tolerated Compared to Placebo

Improvement in Total PANSS Score at Five Weeks was 11.6 Points Compared to Placebo (p<0.0001).

No Evidence of Somnolence, Extrapyramidal Side Effects or Weight Gain Relative to Placebo

Data Support Advancing KarXT to Phase 3 and Continued Development in Other CNS Disorders

Karuna Management to Host Conference Call and Webcast Today at 8:30 a.m. EST / 1:30 p.m. GMT

PureTech Health plc (LSE: PRTC) ("PureTech"), a clinical stage biotechnology company dedicated to discovering, developing and commercialising highly differentiated medicines for devastating diseases, is pleased to note that Karuna Therapeutics, Inc. (Karuna), an affiliate of PureTech, today announced results from its Phase 2 clinical trial of KarXT for the treatment of acute psychosis in patients with schizophrenia. In the clinical trial, KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) score compared to placebo (p<0.0001) and also demonstrated good overall tolerability. A statistically significant reduction in the secondary endpoints of PANSS-Positive and PANSS-Negative scores were also observed (p<0.001).

The magnitude of the improvement with KarXT compares favorably to meta-analyses of published clinicals trials of currently approved antipsychotic medicines which reported an average difference of nine to ten points in PANSS score versus placebo. Historically, changes as small as five points have supported the approval of current antipsychotics.

KarXT was well tolerated in the Phase 2 trial, with similar discontinuation rates between KarXT (20%) and placebo (21%). The number of discontinuations due to treatment emergent adverse events (AEs) were equal in the KarXT and placebo arms (N=2 in each group).

Daphne Zohar, founder and chief executive officer of PureTech said: "These impressive results are another important validation of PureTech's innovation engine that has generated highly differentiated platforms to address serious diseases, leading to 24 product candidates, including 14 clinical stage and one recently FDA cleared product. It is very exciting to see Karuna reach this important milestone with its lead candidate KarXT that originated at PureTech. KarXT is now being advanced by one of the leading CNS drug development teams and has the potential to be the first novel therapeutic approach in decades to treat psychosis in patients with schizophrenia and Alzheimer's disease."

Conference Call and Webcast Information

Karuna will hold a webcast and conference call this morning at 8:30 a.m. EST / 1:30 p.m. GMT to provide results from its Phase 2 clinical trial of KarXT for the treatment of acute psychosis in patients with schizophrenia. The dial-in numbers are 1-855-548-1216 for domestic callers and 1-409-216-6318 for international callers. The conference ID number for the live call will be 9498519. A live webcast of the conference call will also be available on the investor relations page of the Karuna Therapeutics corporate website at www.karunatx.com. After the live webcast, the event will remain archived on the Karuna Therapeutics website for three months.

The full text of the announcement from Karuna Therapeutics is as follows:

Karuna Therapeutics Announces KarXT Met Primary Endpoint in Phase 2 Clinical Trial of Acute Psychosis in Patients with Schizophrenia

KarXT Demonstrated Statistically Significant and Clinically Meaningful Improvement in Total PANSS Score at All Time Points Over Five Weeks and was Well-Tolerated Compared to Placebo

Improvement in Total PANSS Score at Five Weeks was 11.6 Points Compared to Placebo (p<0.0001)

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Data Support Advancing KarXT to Phase 3 and Continued Development in Other CNS Disorders

Conference Call and Webcast to Take Place Today at 8:30 a.m. EST

BOSTON—Nov. 18, 2019—Karuna Therapeutics, Inc. (Nasdaq: KRTX), a clinical-stage biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with disabling and potentially fatal neuropsychiatric disorders and pain, today announced results from its Phase 2 clinical trial of KarXT for the treatment of acute psychosis in patients with schizophrenia. In the clinical trial, KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) score compared to placebo (p<0.0001) and also demonstrated good overall tolerability. A statistically significant reduction in the secondary endpoints of PANSS-Positive and PANSS-Negative scores were also observed (p<0.001).

KarXT was well tolerated in the Phase 2 trial, with similar discontinuation rates between KarXT (20%) and placebo (21%). The number of

discontinuations due to treatment emergent adverse events (AEs) were equal in the KarXT and placebo arms (N=2 in each group).

KarXT is an oral coformulation of xanomeline (a novel muscarinic receptor agonist) and trospium (a muscarinic receptor antagonist) designed to treat psychosis and related symptoms through preferential stimulation of muscarinic receptors in the central nervous system (CNS). This combination has the potential to be a new option for treating the difficult symptoms of debilitating CNS disorders, such as schizophrenia, without subjecting patients to the problematic side effects associated with current antipsychotic standard of care therapies.

“The results of the Phase 2 trial are impressive and encouraging because they indicate that KarXT, if approved, could represent a game-changing therapeutic advance in the treatment of patients with schizophrenia,” said Jeffrey Lieberman, M.D., professor and chairman of the Department of Psychiatry, Columbia University, College of Physicians and Surgeons and a member of Karuna’s scientific advisory board. “The effectiveness of antipsychotics has been limited by the frequent and serious side effects of first- and second-generation drugs which are difficult for many patients to tolerate, are potentially harmful, and lead to high rates of discontinuation and relapse. In addition to its novel mechanism of action, KarXT could be a new therapeutic option that has the potential to offer robust efficacy devoid of weight gain, metabolic effects and extrapyramidal side effects.”

In the clinical trial, patients demonstrated a clinically meaningful and statistically significant 11.6 point mean reduction over placebo in total PANSS score, the trial’s primary efficacy endpoint. The magnitude of the improvement with KarXT compares favorably to meta-analyses of published clinicals trials of currently approved antipsychotic medicines which reported an average difference of nine to ten points in PANSS score versus placebo. Historically, changes as small as five points have supported the approval of current antipsychotics.

Overall, KarXT was well tolerated in the clinical trial, with similar discontinuation rates of patients on KarXT, 20%, and placebo, 21%. The number of discontinuations due to treatment emergent AEs were equal in the KarXT and placebo arms (N=2 in each group). The overall AE rate of patients on KarXT was 54% vs. 43% on placebo, with the most common AEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. The tolerability of KarXT was also reflected in the trial’s high rate of dose escalation. In the trial, 91% of KarXT treated patients escalated to the increased dose which was similar to the escalation rate with placebo. Occurrences of somnolence, weight gain, and extrapyramidal symptoms were also similar to placebo. One serious adverse event (SAE) was experienced in the drug treatment arm, in which the patient discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.

“The schizophrenia treatment landscape has remained rather stagnant for decades with therapeutic options relying on discoveries dating back to the 1950s,” said Steve Paul, M.D., chief executive officer, president, and chairman of Karuna. “KarXT and its novel muscarinic receptor mechanism of action represent the potential to become a true advancement in how schizophrenia is treated, allowing patients relief from their debilitating psychotic symptoms without experiencing some of the very troubling side effects associated with current treatments.”

Muscarinic acetylcholine receptors emerged in the 1990s as a promising alternative target to dopamine-receptor based treatments for treating psychosis, but adverse side effects limited their development as a therapeutic option. It is believed that these side effects were the result of the stimulation of muscarinic receptors in peripheral tissues. Karuna addressed this issue by combining xanomeline, a novel muscarinic receptor agonist that preferentially stimulates M1 and M4 muscarinic receptors, with trospium, an approved muscarinic receptor antagonist that does not measurably cross the blood-brain barrier, confining its effects to peripheral tissues. The resulting therapeutic, known as KarXT, was designed to activate muscarinic receptors in the CNS while avoiding the side effects associated with activating muscarinic receptors in peripheral tissues.

“We are extremely pleased with these results, as the 11.6-point PANSS score separation from placebo far exceeded the five-point minimum improvement that has historically supported approval of current antipsychotics,” said Stephen Brannan, M.D., chief medical officer of Karuna. “With this information, and following our anticipated end-of-Phase 2 meeting with the FDA in the second quarter of 2020, we will work to initiate a Phase 3 clinical trial of KarXT in patients with schizophrenia by the end of 2020. We also plan to further analyze these results to better understand the potential of KarXT in patients with schizophrenia experiencing negative and cognitive symptoms, and to explore other CNS disorders that could benefit from this approach, such as psychosis in Alzheimer’s disease as well as the management of pain.”

About the Trial

The Phase 2, randomized, double-blind, placebo-controlled, inpatient trial enrolled 182 adult patients, age 18 to 60, who had been diagnosed with DSM-5 schizophrenia and were experiencing acute psychosis. Patients were washed-out of antipsychotic medicines and randomized 1:1 to receive either KarXT or placebo for five weeks. The primary outcome measure of the trial was the change from baseline on the total PANSS score on KarXT vs. placebo treatment at week five.

KarXT was dosed as xanomeline 50 mg/trospium 20 mg twice a day for two days and then increased to xanomeline 100 mg/trospium 20 mg starting on day three. Beginning on day eight, if KarXT was well tolerated, an option was given to escalate the dose of KarXT to xanomeline 125 mg/trospium 30 mg twice a day. If a patient escalated to the highest dose, the dose could be decreased back to xanomeline 100 mg/trospium 20 mg twice per day, based on tolerability, if needed. No dose changes were allowed during the last two weeks of the trial.

About Schizophrenia

Schizophrenia is a chronic, disabling disorder typically diagnosed in late teenage years or early adulthood. Characterized by recurring episodes of psychosis requiring long-term treatment with antipsychotic drugs in most patients, it affects more than 21 million people worldwide and 2.7 million Americans (0.5% - 1.0% of U.S. population).

At least one-third of patients with schizophrenia fail to respond to current treatments, with 74% of patients discontinuing within 18 months of initiation. People with schizophrenia have a 10- to 15-year reduction in life expectancy and struggle to maintain meaningful interpersonal relationships. The World Health Organization ranks psychosis as the third-most disabling medical condition in the world.

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About Karuna

Karuna is a clinical-stage biopharmaceutical company committed to developing and delivering first-in-class therapies with the potential to transform the lives of people with CNS disorders – which remain among the most disabling and potentially fatal disorders worldwide. Galvanized by the understanding that today's neuropsychiatric and pain management patients deserve better, Karuna's mission is to harness the untapped potential of the brain's complex biology in pursuit of novel therapeutic pathways that will advance the standard of care. For more information, please visit karunatx.com.

About PureTech Health

PureTech is a clinical stage biotechnology company dedicated to discovering, developing and commercialising highly differentiated medicines for devastating diseases, including intractable cancers, lymphatic and gastrointestinal diseases, central nervous system disorders, and inflammatory and immunological diseases, among others. The Company has created a broad and deep pipeline through the expertise of its experienced research and development team and its extensive network of scientists, clinicians and industry leaders. This pipeline, which is being advanced both internally and through PureTech's affiliates, is comprised of 24 product candidates and one product that has been cleared by the US Food and Drug Administration (FDA). All of the underlying programmes and platforms that resulted in this pipeline of product candidates were initially identified or discovered and then advanced by the PureTech team through key validation points based on the Company's unique insights into the biology of the brain, immune, and gut, or BIG, systems and the interface between those systems, referred to as the BIG Axis.

For more information, visit www.puretechhealth.com or connect with us on Twitter @puretechh.

Forward Looking Statement

This press release contains statements that are or may be forward-looking statements, including statements that relate to the company's future prospects, developments, and strategies. The forward-looking statements are based on current expectations and are subject to known and unknown risks and uncertainties that could cause actual results, performance and achievements to differ materially from current expectations, including, but not limited to, those risks and uncertainties described in the risk factors included in the regulatory filings for PureTech Health plc. These forward-looking statements are based on assumptions regarding the present and future business strategies of the company and the environment in which it will operate in the future. Each forward-looking statement speaks only as at the date of this press release. Except as required by law and regulatory requirements, neither the company nor any other party intends to update or revise these forward-looking statements, whether as a result of new information, future events or otherwise.