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**PureTech Health plc**

**Karuna Pharmaceuticals and PureTech Health Announce Positive Results from Tolerability Proof-of-Concept Study of KarXT, Being Developed for Schizophrenia and Alzheimer's**

*Trial builds on prior compelling efficacy data in xanomeline and suggests enhanced safety and tolerability with novel KarXT combination approach*

*Initiation of Phase 2 clinical trial planned for 2017*

**BOSTON, Massachusetts**, December 15, 2016 – Karuna Pharmaceuticals, focused on targeting muscarinic receptors for the treatment of central nervous system (CNS) disorders and a subsidiary of PureTech Health (LSE: PRTC), today announced positive results from a tolerability proof-of-concept study of its proprietary product, KarXT. In the study, KarXT (xanomeline plus trospium chloride), which is being developed as a novel antipsychotic for schizophrenia and Alzheimer's disease, was found to be generally well-tolerated and have superior tolerability to xanomeline alone. Based on these positive safety results and previous efficacy data on xanomeline, which is exclusively licensed to Karuna from Eli Lilly, Karuna intends to initiate a Phase 2 clinical trial of KarXT in 2017.

"We are extremely pleased with these results, which provide a clear proof-of-concept that the KarXT approach improves the tolerability of xanomeline and move us closer toward our goal of developing the first truly novel antipsychotic agent in more than sixty years for patients with schizophrenia or Alzheimer's," said Andrew Miller, Ph.D., Karuna's CEO and Vice President at PureTech Health. "Given the strong efficacy data shown in previous clinical trials with xanomeline, our goal was to demonstrate the improved tolerability of KarXT compared to xanomeline. Now we look forward to initiating a Phase 2 trial in 2017 to replicate the efficacy previously observed with xanomeline with this greatly improved product profile."

In the 70 subject, double-blind, placebo-controlled trial, participants received either placebo or trospium chloride during a two-day run-in period before receiving xanomeline plus placebo or xanomeline plus trospium chloride (KarXT) for seven days. Safety and tolerability were analyzed using adverse event incidence rates with a prespecified focus on the cholinergic adverse events that were previously observed with xanomeline alone and hindered development efforts: diarrhea, nausea, vomiting, excessive sweating and excessive salivation. A series of visual analogue scales (VAS) were also piloted to track each cholinergic adverse event.

KarXT was shown to reduce the incidence of prespecified cholinergic adverse events by a statistically significant and clinically meaningful extent (46%  $p=0.016$ ) compared to xanomeline alone and each individual cholinergic adverse event was reported at a lower rate in the KarXT treatment arm. No severe or serious adverse events were reported. VAS scores (maximum weekly composite VAS) were reduced by 42% in the KarXT treatment arm, but this measure was not statistically significant ( $p=0.31$ ). The low VAS score in the xanomeline-only arm (3.82 out of 100, reduced to 2.29 in the KarXT arm) indicates that the VAS score was not a sufficiently sensitive metric, likely due to the episodic nature of the cholinergic adverse events.

The placebo-only group during the two-day run-in period also served to indicate the baseline cholinergic adverse reporting rate in the study population, which was 32%. This rate is similar to the cholinergic adverse event rate of the KarXT treatment arm during the active phase of the study (34% vs 32%, respectively), indicating an excellent tolerability profile in the KarXT treatment arm.

“For many years, researchers have been excited about the therapeutic application of muscarinic agonists. The impressive tolerability data reported in this study, together with the previous compelling efficacy data generated with xanomeline, highlight the great potential of this novel approach to targeting muscarinic receptors and unlocking the development of a first-in-class medicine,” said Alan Breier, M.D., Professor of Psychiatry at Indiana University, Karuna Chief Clinical Advisor, and former Chief Medical Officer at Eli Lilly. “Patients with Alzheimer’s and schizophrenia are in dire need of new treatments, and KarXT may offer a potentially transformative new path towards treating these serious and debilitating diseases.”

KarXT combines xanomeline, a novel clinical-stage muscarinic acetylcholine receptor agonist, with trospium chloride, a muscarinic antagonist, and is being developed to selectively target muscarinic receptors in the CNS. Exclusively licensed to Karuna, xanomeline has demonstrated robust efficacy in reducing psychosis in both schizophrenia and Alzheimer’s disease in previous studies; however, it has been associated with side effects that have limited its development. The results of the KarXT proof-of-concept study indicate that the addition of trospium chloride results in improved tolerability of xanomeline. Based on these positive safety results and previous efficacy data on xanomeline, Karuna intends to initiate a Phase 2 clinical trial of KarXT in 2017.

This announcement contains inside information for the purposes of Article 7 of Regulation (EU) 596/2014.

### **About Karuna**

Karuna is a clinical-stage drug development company targeting muscarinic receptors for the treatment of central nervous system (CNS) disorders and a subsidiary of PureTech Health. Karuna's lead program, [KarXT](#), is a product candidate consisting of xanomeline, a novel muscarinic acetylcholine receptor agonist that has demonstrated efficacy in placebo-controlled human trials in schizophrenia and Alzheimer’s disease, and trospium chloride, an FDA-approved and well-established muscarinic receptor antagonist that has been shown not to enter the CNS.

Schizophrenia is a severe and chronic mental health disorder that affects more than 21 million people worldwide. The disease is characterized by profound disruptions in thinking, affecting language, perception and the sense of self, and it typically includes psychotic episodes. Antipsychotics are the mainstay therapy for the treatment of schizophrenia; however, significant unmet needs remain due to the limited efficacy and potential serious side effects associated with current antipsychotic medications.

Alzheimer’s disease is a chronic, progressive, neurodegenerative disorder characterized by loss of memory and other important mental functions. The type, severity, sequence and progression of mental changes vary widely, and it represents an enormous burden on victims of the disease and their families. Alzheimer’s is the most common form of dementia in people over the age of 65, and it is estimated to affect more than 5 million Americans. It is the sixth leading cause of death in the United States, and there is currently no cure.

Karuna’s Board of Directors includes Ben Shapiro, M.D., former Executive Vice President of Research for Merck & PureTech Health Non-Executive Director; Edmund Harrigan, M.D., former Senior Vice President

for Worldwide Safety and Regulatory, Head of Worldwide Business Development at Pfizer; and Atul Pande, M.D., Former Senior Vice President, Head of Neuroscience and Senior Advisor, Pharmaceutical R&D at GlaxoSmithKline & PureTech Health Senior Advisor. Karuna's Chief Clinical Advisor is Alan Breier, M.D., the former Chief Medical Officer at Eli Lilly. Karuna has a worldwide exclusive license for xanomeline and has a patent portfolio more broadly covering selective muscarinic targeting enabled by the KarXT approach. For more information, visit [www.karunapharma.com](http://www.karunapharma.com).

PureTech Health plc (PRTC.L) owns 79.6% of Karuna on a diluted basis as of June 30, 2016, plus potential product royalties as a co-inventor of the KarXT platform. The ownership calculation includes issued and outstanding shares as well as options to purchase shares and written commitments to issue shares or options, but excludes unallocated shares authorized to be issued pursuant to equity incentive plans and any convertible debt.

### **About PureTech Health**

**PureTech Health** (PureTech Health plc, PRTC.L) is a cross-disciplinary biopharma company creating 21<sup>st</sup> century medicines that modulate the adaptive human systems. Our therapies target the immune, nervous, and gastro-intestinal systems by addressing the underlying pathophysiology of disease from a systems perspective rather than through a single receptor or pathway. We are advancing more than 20 clinical studies across our pipeline, with multiple human proof-of-concept studies and pivotal or registration studies expected to read out in the next two years. PureTech Health's rich and growing research and development pipeline has been developed in collaboration with some of the world's leading scientific experts, who along with PureTech's experienced team and board analyses more than 650 scientific discoveries per year to identify and advance the opportunities we believe hold the most promise for patients. This process places PureTech Health on the cutting edge of ground-breaking science and technological innovation and leads the Company between and beyond existing disciplines. For more information, visit [www.puretechhealth.com](http://www.puretechhealth.com) or connect with us on [Twitter](#).

### **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.

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