Vertex Advances VX-147 Into Pivotal Clinical Development for People With APOL1-Mediated Kidney Disease

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– Single pivotal trial to initiate later this month targets the broad patient population with two APOL1 *mutations and proteinuric kidney disease –*

– Pathway for accelerated approval using an interim analysis at Week 48 of eGFR slope, supported by reduction in proteinuria –

– Final analysis evaluating eGFR slope at approximately two years serves as basis for U.S. approval –

BOSTON--(BUSINESS WIRE)--Mar. 22, 2022-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that the company has advanced VX-147 into pivotal development for people living with proteinuric kidney disease mediated by two mutations in the *APOL1* gene (AMKD), which affects approximately 100,000 people in the U.S. and Europe. VX-147 is the first investigational therapy aimed at treating the underlying cause of AMKD. The pivotal study will open for enrollment later this month.

The company will evaluate the safety and efficacy of VX-147 in a single pivotal clinical trial designed to assess the impact of VX-147, on top of standard of care, on kidney function and proteinuria in people with AMKD. The primary endpoint of this study is reduction in the rate of decline of kidney function as measured by estimated glomerular filtration rate (eGFR) slope versus placebo at approximately two years. The study is also designed to have a pre-planned interim analysis at Week 48 evaluating eGFR slope in VX-147 versus placebo, supported by a percent change from baseline in proteinuria. If positive, the interim analysis may serve as the basis for Vertex to seek accelerated approval of VX-147 in the U.S. for patients with AMKD.

"VX-147 holds the potential to be a first-in-class and best-in-class treatment for patients with AMKD, based upon Phase 2 results demonstrating a 47.6% reduction in proteinuria in APOL1-mediated focal segmental glomerulosclerosis (FSGS)," said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. "We are very pleased to have concluded our discussions with the FDA, enabling us to initiate the pivotal development program evaluating VX-147 in the broad patient population with AMKD and to have a clear path forward for potential accelerated approval in the U.S."

About the VX-147 Pivotal Program
This randomized, double-blind, placebo-controlled Phase 2/3 adaptive study will first evaluate two doses of VX-147 for 12 weeks to select a dose for Phase 3 and subsequently evaluate the efficacy and safety of the single, selected dose in the Phase 3 portion of the study.

Patients aged 18 to 60 years, with two *APOL1* mutations, urine protein to creatinine ratio (UPCR) ≥0.7 g/g to <10 g/g, eGFR ≥25 to <75 mL/min/1.73m^2 and on stable doses of standard of care medications are eligible to enroll. Approximately 66 patients are planned to be enrolled in the Phase 2 dose-ranging portion of the study, and approximately 400 additional patients are planned to be enrolled in the Phase 3 portion of the study.

The primary efficacy endpoint for the final analysis is eGFR slope in patients receiving the VX-147 selected dose compared to placebo. The secondary efficacy endpoint is time to composite clinical outcome, which will also be assessed at the final analysis and is defined as a sustained decline of ≥30% from baseline in eGFR, the onset of end-stage kidney disease (i.e., maintenance dialysis for ≥28 days, kidney transplantation or a sustained eGFR of <15 mL/min/1.73 m^2) or death. The final study analysis will occur when subjects have at least two years of eGFR data and when approximately 187 composite clinical outcomes have occurred.

The study is also designed to have a pre-planned interim analysis at Week 48 evaluating eGFR slope, supported by a percent change from baseline in proteinuria in the VX-147 arm versus placebo. If positive, the interim analysis may serve as the basis for Vertex to seek accelerated approval of VX-147 in the U.S. for patients with AMKD.

About APOL1-Mediated Kidney Disease
APOL1-mediated kidney disease is a form of chronic kidney disease caused by mutations in the *APOL1* gene. Approximately 100,000 people in the U.S. and Europe have two *APOL1* genetic mutations and proteinuric kidney disease. People who inherit two mutations in the *APOL1* gene have a course of disease that is far more aggressive than in the absence of *APOL1* genetic mutations. Inherited *APOL1* genetic mutations cause kidney disease through a toxic gain of function, which leads to podocyte injury. This injury disrupts filtration, resulting in proteinuria and rapidly progressive kidney disease. Progressive kidney disease can result in dialysis, kidney transplant or death.

About Vertex
Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF,Vertex has a robust pipeline of investigational small molecule, cell and genetic therapies in other serious diseases where it has deep insight into causal human biology, including sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, pain, type 1 diabetes, alpha-1 antitrypsin deficiency and Duchenne muscular dystrophy.

Founded in 1989 in Cambridge, Mass., Vertex's global headquarters is now located in Boston's Innovation District and its international headquarters is in London. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including 12 consecutive years on Science magazine's Top Employers list and one of the 2021 Seramount (formerly Working Mother Media) 100 Best Companies. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on Facebook, Twitter, LinkedIn, YouTube and Instagram.

Special Note Regarding Forward-Looking Statements
This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements by Dr. Carmen Bozic in this press release, and statements regarding the advancement of VX-147 into a single pivotal clinical study, the potential benefits of VX-147, and our plans, expectations, and anticipated timelines for these clinical trials, including enrollment, study designs and any interim analysis, and for submission for regulatory approval in the U.S. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from a limited number of patients may not be indicative of final clinical trial results, that the trial may not be completed in the expected timeframe, or at all, that data from the company's development programs may not support registration or further development of its compounds due to safety, efficacy, or other reasons, and other risks listed under the heading “Risk Factors” in Vertex's most recent annual report filed with the Securities and Exchange Commission (SEC) and available through the company's website at www.vrtx.com and on the SEC’s website at www.sec.gov. You should not place undue reliance on these statements, or the scientific data presented. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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Vertex Pharmaceuticals Incorporated
Investors:
Michael Partridge, +1 617-341-6108
or
Miroslava Minkova, +1 617-341-6135
or
Manisha Pai, +1 617-961-1899

Media:
mediainfo@vrtx.com
or
U.S.: +1 617-341-6992
or
Heather Nichols: +1 617-839-3607
or
International: +44 20 3204 5275

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