Vertex and CRISPR Therapeutics Present New Data on More Patients With Longer Follow-Up Treated With exagamglogene autotemcel (exa-cel) at the 2022 European Hematology Association (EHA) Congress

June 11, 2022

– Data from 75 patients with transfusion-dependent beta thalassemia or severe sickle cell disease with follow-up of up to 37.2 months continue to demonstrate that exa-cel has the potential to be a one-time functional cure –

– Safety profile generally consistent with myeloablative conditioning and autologous stem cell transplant –

BOSTON & ZUG, Switzerland & CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 11, 2022-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) and CRISPR Therapeutics (Nasdaq: CRSP) announce presentation of new data on exa-cel, formerly known as CTX001™, from CLIMB-111, CLIMB-121 and CLIMB-131 highlighting the potentially transformative profile of this investigational therapy for people with transfusion-dependent beta thalassemia (TDT) or severe sickle cell disease (SCD) and provided additional program updates.

New Data for exa-cel from CLIMB Clinical Studies
The data presented at the European Hematology Association (EHA) Congress are from 75 patients (44 with TDT and 31 with SCD) with follow-up ranging from 1.2 to 37.2 months after exa-cel dosing.

Of the 44 patients with TDT, 26 had beta-zero/beta-zero or other beta-zero-like severe genotypes. Forty-two of 44 patients with TDT were transfusion-free with follow-up ranging from 1.2 to 37.2 months after exa-cel infusion. Two patients who were not yet transfusion-free had 75% and 89% reductions in transfusion volume. TDT patients had substantial mean increases in fetal hemoglobin (HbF) and corresponding increases in mean total hemoglobin (Hb) with mean total Hb levels increasing to >11 g/dL by Month 3 and maintained thereafter.

All 31 patients with severe SCD characterized by recurrent vaso-occlusive crises (VOCs) (mean of 3.9 VOCs per year over the prior two years) were free of VOCs after exa-cel infusion through duration of follow-up, with follow-up ranging from 2.0 to 32.3 months. SCD patients had mean HbF (as a proportion of total Hb) of approximately 40% by Month 4 and maintained thereafter.

The safety was generally consistent with myeloablative conditioning with busulfan and autologous stem cell transplant. All patients engrafted neutrophils and platelets after exa-cel infusion. Among the 44 patients with TDT, two patients had serious adverse events (SAEs) considered related to exa-cel. As previously reported, one patient had three SAEs considered related to exa-cel, hemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome and headache, and one SAE of idiopathic pneumonia syndrome that was considered related to both exa-cel and busulfan. All four SAEs occurred in the context of HLH and have resolved. One patient had SAEs of delayed neutrophil engraftment and thrombocytopenia, both of which were considered related to exa-cel and busulfan, and both SAEs have resolved. Among the 31 patients with SCD, there were no SAEs considered related to exa-cel.

Additional details were presented during the EHA media briefing and can be found in the published abstract and presentation.

Late-breaking abstract #LB2367 entitled “Efficacy and Safety of a Single Dose of CTX001 For Transfusion-Dependent Beta-Thalassemia and Severe Sickle Cell Disease,” will be an oral presentation on Sunday, June 12 at 09:45-11:15 CEST.

“These robust data from 75 patients, of which 33 have one year or more of follow-up after exa-cel infusion, further demonstrate the potential of this investigational therapy as a one-time functional cure for patients with transfusion-dependent beta thalassemia or severe sickle cell disease,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex.

“By reactivating a naturally occurring developmental process, exa-cel restores fetal hemoglobin production and thereby can ameliorate the course of these diseases,” said Haydar Frangoul, M.D., Medical Director of Pediatric Hematology and Oncology at Sarah Cannon Research Institute, HCA Healthcare’s The Children’s Hospital at TriStar Centennial Medical Center. “The remarkable results based on this approach give me great optimism and confidence in the potential of this treatment for patients.”

“I have seen first-hand the impact that this investigational therapy has had on patients in these clinical trials and continue to be impressed by the totality of the data,” said Franco Locatelli, M.D., Ph.D., Professor of Pediatrics at the Sapienza University of Rome, Director of the Department of Pediatric Hematology and Oncology at Bambino Gesù Children’s Hospital. “Given the urgency for highly effective and curative therapies for patients with hemoglobinopathies, I am excited to be part of the team

working towards the goal of addressing this unmet need."

Exa-cel Study Updates
Following ongoing discussions with regulators, the clinical trial protocols for CLIMB-111 and CLIMB-121 were amended to incorporate feedback on the primary endpoints for regulatory submission. Specifically, the primary endpoint in CLIMB-111 for TDT has been amended from proportion of subjects achieving transfusion reduction after exa-cel infusion to proportion of subjects maintaining weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months after exa-cel infusion.

The primary endpoint in CLIMB-121 for SCD has been updated from proportion of subjects with HbF ≥20% after exa-cel infusion, to proportion of subjects who have not experienced any severe VOCs for at least 12 consecutive months after exa-cel infusion.

Both clinical trials are now in Phase 3 and are fully enrolled. All patients will have the opportunity to join CLIMB-131, a long-term follow-up study, after completing participation in the initial studies.

Additional Pediatric Studies
In line with the company's strategy of developing therapies for patients of all ages, two additional Phase 3 studies of exa-cel have begun. Earlier this year, the Independent Data Monitoring Committee (DMC) met to review the data in adults and adolescents and endorsed expanding into younger pediatric patients. CLIMB-141 and CLIMB-151 are Phase 3 open-label trials designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 2 to 11 years with TDT or SCD, respectively. The trials are now open for enrollment and currently enrolling patients ages 5 to 11 years and will plan to extend to patients 2 to less than 5 years of age at a later date. Each trial will enroll approximately 12 patients. Patients will be followed for approximately two years after infusion. Each patient will be asked to participate in CLIMB-131, a long-term follow-up trial.

Vertex also presented three additional abstracts on the burden of disease in sickle cell disease and beta thalassemia at the EHA Congress.

1. Abstract #P1704 entitled "Projected Lifetime Economic Burden of Severe Sickle Cell Disease in the United States," presented via poster on Friday, June 10 at 16:30-17:45 CEST.
2. Abstract #P1703 entitled "Economic Burden of Transfusion-Dependent Beta-Thalassemia in the United States," presented via poster on Friday, June 10 at 16:30-17:45 CEST.
3. Abstract #P1482 entitled "Patients With Severe Sickle Cell Disease on Standard-of-Care Treatment Are Very Unlikely to Become VOC-Free for One Year: A Cohort Study of Medicaid Enrollees," presented via poster on Friday, June 10 at 16:30-17:45 CEST.

About exagamglogene autotemcel (exa-cel)
Exa-cel, formerly known as CTX001, is an investigational, autologous, *ex vivo* CRISPR/Cas9 gene-edited therapy that is being evaluated for patients with TDT or SCD characterized by recurrent VOCs, in which a patient's own hematopoietic stem cells are edited to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells. HbF is the form of the oxygen-carrying hemoglobin that is naturally present during fetal development, which then switches to the adult form of hemoglobin after birth. The elevation of HbF by exa-cel has the potential to alleviate transfusion requirements for patients with TDT and reduce painful and debilitating sickle crises for patients with SCD. Earlier results from these ongoing trials were published in *The New England Journal of Medicine* in January of 2021.

Based on progress in this program to date, exa-cel has been granted Regenerative Medicine Advanced Therapy (RMAT), Fast Track, Orphan Drug, and Rare Pediatric Disease designations from the U.S. Food and Drug Administration (FDA) for both TDT and SCD. Exa-cel has also been granted Orphan Drug Designation from the European Commission, as well as Priority Medicines (PRIME) designation from the European Medicines Agency (EMA), for both TDT and SCD.

Among gene-editing approaches being evaluated for TDT and SCD, exa-cel is the furthest advanced in clinical development.

About CLIMB-111 and CLIMB-121
The ongoing Phase 1/2/3 open-label trials, CLIMB-111 and CLIMB-121, are designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 12 to 35 years with TDT or with SCD, characterized by recurrent VOCs, respectively. The trials are now closed for enrollment. Patients will be followed for approximately two years after exa-cel infusion. Each patient will be asked to participate in CLIMB-131, a long-term follow-up trial.

About CLIMB-131
This is a long-term, open-label trial to evaluate the safety and efficacy of exa-cel in patients who received exa-cel in CLIMB-111, CLIMB-121, CLIMB-141 or CLIMB-151. The trial is designed to follow participants for up to 15 years after exa-cel infusion.

About CLIMB-141 and CLIMB-151
The ongoing Phase 3 open-label trials, CLIMB-141 and CLIMB-151, are designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 2 to 11 years with TDT or with SCD, characterized by recurrent VOCs, respectively. The trials are now open for enrollment and currently enrolling patients ages 5 to 11 years of age and will plan to extend to patients 2 to less than 5 years of age at a later date. Each trial will enroll approximately 12 patients. Patients will be followed for approximately two years after infusion. Each patient will be asked to participate in CLIMB-131, a long-term follow-up trial.

About the Gene-Editing Process in These Trials
Patients who enroll in these trials will have their own hematopoietic stem and progenitor cells collected from peripheral blood. The patient's cells will be edited using the CRISPR/Cas9 technology. The edited cells, exa -cel, will then be infused back into the patient as part of an autologous hematopoietic stem cell transplant (HSCT), a process which involves a patient being treated with myeloablative busulfan conditioning. Patients undergoing HSCT may also encounter side effects (ranging from mild to severe) that are unrelated to the administration of exa-cel. Patients will initially be monitored to determine when the edited cells begin to produce mature blood cells, a process known as engraftment. After engraftment, patients will continue to be monitored to track the impact of exa-cel on multiple measures of disease and for safety.

About the Vertex-CRISPR Collaboration
Vertex and CRISPR Therapeutics entered into a strategic research collaboration in 2015 focused on the use of CRISPR/Cas9 to discover and develop potential new treatments aimed at the underlying genetic causes of human disease. Exa-cel represents the first potential treatment to emerge from the joint research program. Under an amended collaboration agreement, Vertex now leads global development, manufacturing and commercialization of exa-cel and splits program costs and profits worldwide 60/40 with CRISPR Therapeutics.

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.

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Vertex 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, (i) statements by Dr. Carmen Bozic, Dr. Haydar Frangoul, and Dr. Franco Locatelli in this press release, (ii) our plans and expectations to present clinical data from the ongoing exa-cel clinical trials during the EHA Congress, (iii) the progress of the ongoing exa-cel clinical trials, including expectations regarding the abstracts that will be made available on the virtual platform including anticipated projections and estimates related to the various economic impacts of SCD and TDT, (iv) the potential benefits, efficacy, and safety of exa-cel, including the potentially transformative nature of the therapy and the potential of the treatment for patients, (v) our plans and expectations for our clinical trials and pipeline products, and (vi) the status of our clinical trials of our product candidates under development by us and our collaborators, including activities at the clinical trial sites, patient enrollment, and expectations regarding clinical trial follow-up. 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 data from the company's development programs, including its programs with its collaborators, may not support registration or further development of its compounds due to safety and/or efficacy, or other reasons, that internal or external factors could delay, divert, or change our plans and objectives with respect to our research and development programs, that future competitive or other market factors may adversely affect the commercial potential for exa-cel, and other risks listed under the heading "Risk Factors" in Vertex's most recent annual report and subsequent quarterly reports 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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About CRISPR Therapeutics
CRISPR Therapeutics is a leading gene editing company focused on developing transformative gene-based medicines for serious diseases using its proprietary CRISPR/Cas9 platform. CRISPR/Cas9 is a revolutionary gene editing technology that allows for precise, directed changes to genomic DNA. CRISPR Therapeutics has established a portfolio of therapeutic programs across a broad range of disease areas including hemoglobinopathies, oncology, regenerative medicine and rare diseases. To accelerate and expand its efforts, CRISPR Therapeutics has established strategic collaborations with leading companies including Bayer, Vertex Pharmaceuticals and ViaCyte, Inc. CRISPR Therapeutics AG is headquartered in Zug, Switzerland, with its wholly-owned U.S. subsidiary, CRISPR Therapeutics, Inc., and R&D operations based in Cambridge, Massachusetts, and business offices in San Francisco, California and London, United Kingdom. For more information, please visit www.crisprtx.com.

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CRISPR Therapeutics Forward-Looking Statement

This press release may contain a number of "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, as well as statements made by Dr. Carmen Bozic, Dr. Haydar Frangoul, and Dr. Franco Locatelli in this press release, as well as statements regarding CRISPR Therapeutics' expectations about any or all of the following: i) the safety, efficacy and clinical progress of the ongoing exa-cel clinical trials, including expectations regarding the abstracts that will be made available on the virtual platform and our plans and expectations to present and the clinical data that are being presented during the EHA Congress, as well as the potentially transformative nature of exa-cel and the potential of the treatment for patients; and (ii) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects" and similar expressions are intended to identify forward-looking statements. You are cautioned that forward-looking statements are inherently uncertain. Although CRISPR Therapeutics believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, existing and prospective investors are cautioned that forward-looking statements are inherently uncertain, are neither promises nor guarantees and not to place undue reliance on such statements, which speak only as of the date they are made. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: the potential for initial and preliminary data from any clinical trial and initial data from a limited number of patients (as is the case with exa-cel at this time) not to be indicative of final or future trial results; the potential that the exa-cel clinical trial results may not be favorable or may not support registration or further development; that future competitive or other market factors may adversely affect the commercial potential for exa-cel; CRISPR Therapeutics may not realize the potential benefits of its collaboration with Vertex; potential impacts due to the coronavirus pandemic, such as to the timing and progress of clinical trials; uncertainties regarding the intellectual property protection for CRISPR Therapeutics' technology and intellectual property belonging to third parties; and those risks and uncertainties described under the heading "Risk Factors" in CRISPR Therapeutics' most recent annual report on Form 10-K, quarterly report on Form 10-Q, and in any other subsequent filings made by CRISPR Therapeutics with the U.S. Securities and Exchange Commission, which are available on the SEC's website at www.sec.gov. CRISPR Therapeutics disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this press release, other than to the extent required by law.

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