FDA Accepts Biologics License Applications for exagamglogene autotemcel (exa-cel) for Severe Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia

June 8, 2023

- First CRISPR gene-editing filings to be accepted for review by FDA -

- FDA grants Priority Review for severe sickle cell disease (SCD) and Standard Review for transfusion-dependent beta thalassemia (TDT) –

- PDUFA target action date of December 8, 2023, for SCD and March 30, 2024, for TDT –

BOSTON & ZUG, Switzerland--(BUSINESS WIRE)--Jun. 8, 2023-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) and CRISPR Therapeutics (Nasdaq: CRSP) today announced that the U.S. Food and Drug Administration (FDA) has accepted the Biologics License Applications (BLAs) for the investigational treatment exagamglogene autotemcel (exa-cel) for severe sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT). The FDA has granted Priority Review for SCD and Standard Review for TDT and assigned Prescription Drug User Fee Act (PDUFA) target action dates of December 8, 2023, and March 30, 2024, respectively. Updated data from the pivotal trials supporting the regulatory submissions will be presented at the Annual European Hematology Association Congress on June 11, 2023.

“We are very pleased with the acceptance of the submissions and the Priority Review designation for SCD by the FDA, as well as the progress of the exa-cel filings in the EU and U.K.,” said Reshma Kewalramani, M.D., Chief Executive Officer and President of Vertex. “Exa-cel holds the promise to be the first CRISPR gene-editing therapy to be approved, and we continue to work with urgency to bring this treatment with transformative potential to patients who are waiting.”

“We are glad to see that the unmet need and urgency for innovative therapies in SCD was recognized by the FDA with Priority Review,” said Samarth Kulkarni, Ph.D., Chief Executive Officer of CRISPR Therapeutics. “This is an exciting milestone for the CRISPR platform, and we look forward to continuing the close collaboration with our partners at Vertex to bring this medicine to patients in need.”

In the U.S., exa-cel has been granted Regenerative Medicine Advanced Therapy (RMAT), Fast Track, Orphan Drug, and Rare Pediatric Disease designations from the FDA for both TDT and SCD.

In Europe, the Marketing Authorization Applications (MAAs) for exa-cel were submitted in December 2022 and validated by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) in January 2023. In the EU, exa-cel has been granted Orphan Drug Designation from the European Commission, as well as Priority Medicines (PRIME) designation from the EMA, for both SCD and TDT. In the U.K., exa-cel has also been granted an Innovation Passport under the Innovative Licensing and Access Pathway (ILAP) from the MHRA.

About exagamglogene autotemcel (exa-cel)

Exa-cel is an investigational, autologous, *ex vivo* CRISPR/Cas9 gene-edited therapy that is being evaluated for patients with SCD or TDT, 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 reduce or eliminate painful and debilitating VOCs for patients with SCD and alleviate transfusion requirements for patients with TDT. Earlier results from these ongoing trials were published in *The New England Journal of Medicine* in January of 2021 and presented at the American Society of Hematology Annual Congress in 2022.

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

The ongoing long-term, open-label trial, CLIMB-131, is designed to evaluate the safety and efficacy of exa-cel in patients who received exa-cel in CLIMB-111, CLIMB-121, CLIMB-141, CLIMB-151 or CLIMB-161. 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 with the plan to extend to ages 2 to less than 5 years at a later date. Each trial will enroll approximately 15 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 CLIMB-161

The ongoing Phase 3b trial, CLIMB-161, is to support expansion of our manufacturing footprint after initial potential approval and launch. This trial will enroll approximately 12 patients with either TDT or with SCD, characterized by recurrent VOCs, ages 12 to 35 years. Patients will be followed for approximately one year 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 and -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 clinical pipeline of investigational small molecule, mRNA, cell and genetic therapies (including gene editing) in other serious diseases where it has deep insight into causal human biology, including sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, acute and neuropathic pain, type 1 diabetes and alpha-1 antitrypsin deficiency.

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 13 consecutive years on Science magazine's Top Employers list and one of Fortune's 100 Best Companies to Work For. 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, statements made by Reshma Kewalramani, M.D., and Samarth Kulkarni, Ph.D., in this press release, our plans and expectations to present updated clinical data for exa-cel at the Annual European Hematology Association Congress, the status of our clinical trials of our product candidates under development by us and our collaborators, including activities at the clinical trial sites, the gene-editing process, 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 regulatory authorities may not approve, or approve on a timely basis, the exa-cel BLAs, 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.

(CRSP-GEN)

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 in Boston, Massachusetts and San Francisco, California, and business offices in 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, including statements made by statements made by Reshma Kewalramani, M.D., and Samarth Kulkarni, Ph.D., 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 plans to present updated clinical data at the European Hematology Association Congress; (ii) timelines for and expectations regarding a regulatory agency decision (iii) the benefits of its collaboration with Vertex; and (iv) 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: data from a limited number of patients may not to be indicative of final or future clinical 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; 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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