Vertex and CRISPR Therapeutics Announce Global exa-cel Regulatory Submissions for Sickle Cell Disease and Beta Thalassemia in 2022

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- Exa-cel will be submitted to the U.S. FDA for rolling review beginning in November, with completion of the U.S. submission package in Q1 2023 -
- EMA and MHRA submissions are on track for Q4 2022 -
- Exa-cel granted Fast Track, Regenerative Medicine Advanced Therapy (RMAT) and Orphan Drug designations in the U.S., and Priority Medicines (PRIME) and Orphan Drug designations in Europe -

BOSTON & ZUG, Switzerland--(BUSINESS WIRE)--Sep. 27, 2022-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) and CRISPR Therapeutics (Nasdaq: CRSP) today announced that Vertex has concluded discussions with the U.S. Food and Drug Administration (FDA), and the FDA granted exagamglogene autotemcel (exa-cel) a rolling review for the potential treatment of sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT). Vertex will submit its biologics licensing application (BLA) for exa-cel for rolling review, beginning in November 2022 and expects to complete the submission by the end of Q1 2023.

Vertex previously completed discussions with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) on the data required to support those marketing applications and is on track to submit by the end of 2022.

“We are pleased to have concluded our exa-cel pre-submission meetings with regulators and are excited that FDA has granted a rolling review,” said Nia Tatsis Ph.D., Executive Vice President, Chief Regulatory and Quality Officer. “We continue to work with urgency to bring forward the first CRISPR therapy for a genetic disease, and one that holds potential to transform the lives of patients with sickle cell disease or beta thalassemia.”

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

Exa-cel is being investigated in multiple ongoing clinical trials as a potential one-time therapy for patients with either SCD or TDT.

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, 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 and updated results were shared at the annual European Hematology Association (EHA) Congress in June 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 SCD, 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 SCD, 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 ages 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 and CRISPR Therapeutics 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 2022 Seramount 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, statements made by Nia Tatsis, Ph.D., in this press release, and statements regarding our plans to submit our BLA for exa-cel to the FDA for rolling review and to submit exa-cel to EMA and MHRA, including expectations related to the timing of the submissions, our plans and expectations regarding the exa-cel clinical trials, including patient enrollment, eligible patient populations, timing, the gene editing process and clinical trial follow-up, and expectations regarding 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. 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 that could delay, divert, or change our plans and objectives with respect to our research and development programs and/or our regulatory submissions, 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 Boston, 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. Nia Tatsis 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 the potentially transformative nature of exa-cel and the potential of the treatment for patients; (ii) anticipated regulatory filings for exa-cel and the timing of such regulatory submissions to the FDA, EMA and MHRA, including plans to submit to the FDA for rolling review; and (iii) 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 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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