UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 12, 2020

CRISPR THERAPEUTICS AG
(Exact name of Registrant as Specified in Its Charter)

Switzerland	**001-37923**	**Not Applicable**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**
Baarerstrasse 14 **6300 Zug, Switzerland** **(Address of Principal Executive Offices)**		**Not Applicable** **(Zip Code)**

Registrant's Telephone Number, Including Area Code: +41 (0)41 561 32 77

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instructions A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Shares, nominal value CHF 0.03	CRSP	The NASDAQ Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On June 12, 2020, CRISPR Therapeutics AG (the "Company") and its partner Vertex Pharmaceuticals Incorporated (together with its affiliates, "Vertex") issued a press release announcing new clinical data at the 25th European Hematology Association (EHA) Congress from two ongoing Phase 1/2 open-label clinical trials of CTX001™, an investigational CRISPR/Cas9 gene-editing therapy, in transfusion-dependent beta thalassemia, or TDT, and severe sickle cell disease, or SCD. A copy of the press release is attached hereto as Exhibit 99.1.

The information in this Item 7.01 of Form 8-K, including the accompanying Exhibit 99.1, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act"), or otherwise subject to the liability of such section, nor shall such information be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, regardless of the general incorporation language of such filing, except as shall be expressly set forth by specific reference in such filing.

Item 8.01. Other Events.

On June 12, 2020, new clinical data from two ongoing Phase 1/2 open-label clinical trials of CTX001 in TDT (CLIMB THAL-111) and severe SCD (CLIMB SCD-121) were presented during an oral presentation at the EHA virtual congress by Dr. Selim Corbacioglu, Professor of Pediatrics and the Chair of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Regensburg University Hospital, Regensburg, Germany. A copy of the slides used during the oral presentation is attached hereto as Exhibit 99.2 and is incorporated herein by reference.

In addition, on June 12, 2020, the Company and Vertex announced that CLIMB THAL-111 has dosed a total of five patients to date, with all patients having successfully engrafted, and CLIMB SCD-121 has dosed a total of two patients to date, with all patients having successfully engrafted. Both trials are now open for broader concurrent dosing after successful dosing and engraftment of the first two patients in each trial. Additionally, CLIMB THAL-111 has been expanded to allow enrollment of β0/β0 patients and is in the process of being expanded to allow enrollment of pediatric patients ages 12 years or older.

In March 2020, clinical trial sites in the United States and Europe temporarily paused their elective hematopoietic stem cell transplant programs due to the COVID-19 pandemic, and as a result, the Company and Vertex temporarily paused conditioning and dosing in the CLIMB THAL-111 and CLIMB SCD-121 clinical trials. Enrollment, mobilization and drug product manufacturing in each trial remains ongoing. The Company and Vertex are now in the process of re-initiating dosing with CTX001 at certain clinical trial sites.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits:

Exhibit No.	Description
99.1	Press release issued by CRISPR Therapeutics AG and Vertex Pharmaceuticals Incorporated, dated June 12, 2020
99.2	Presentation slides, dated June 12, 2020
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

CRISPR THERAPEUTICS AG

Date: June 12, 2020

By: /s/ Samarth Kulkarni
Samarth Kulkarni, Ph.D.
Chief Executive Officer

CRISPR Therapeutics and Vertex Announce New Clinical Data for Investigational Gene-Editing Therapy CTX001™ in Severe Hemoglobinopathies at the 25th Annual European Hematology Association (EHA) Congress

-Beta thalassemia: Two patients are transfusion independent at 5 and 15 months after CTX001 infusion; data demonstrate clinical proof-of-concept for CTX001 in transfusion-dependent beta thalassemia-

-Sickle cell disease: Patient is free of vaso-occlusive crises at 9 months after CTX001 infusion-

-Five patients with beta thalassemia and two patients with sickle cell disease have been treated to date with CTX001 and all have successfully engrafted-

ZUG, Switzerland and CAMBRIDGE and BOSTON, Mass., June 12, 2020 – CRISPR Therapeutics (Nasdaq: CRSP) and Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced new clinical data for CTX001, an investigational CRISPR/Cas9 gene-editing therapy, from the CLIMB-111 and CLIMB-121 Phase 1/2 trials in transfusion-dependent beta thalassemia (TDT) and severe sickle cell disease (SCD), and highlighted recent progress in the CTX001 development program. These data were presented during an oral presentation at the European Hematology Association (EHA) virtual congress by Dr. Selim Corbacioglu, Professor of Pediatrics and the Chair of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Regensburg University Hospital, Regensburg, Germany.

CLIMB-111 Trial in Transfusion-Dependent Beta Thalassemia Updated Results
Data presented today at EHA demonstrate clinical proof-of-concept for CTX001 in TDT. Data include longer-duration follow-up data for the first patient with TDT treated with CTX001 and new data for the second TDT patient treated. CRISPR Therapeutics and Vertex announced initial data for the first TDT patient in November of 2019.

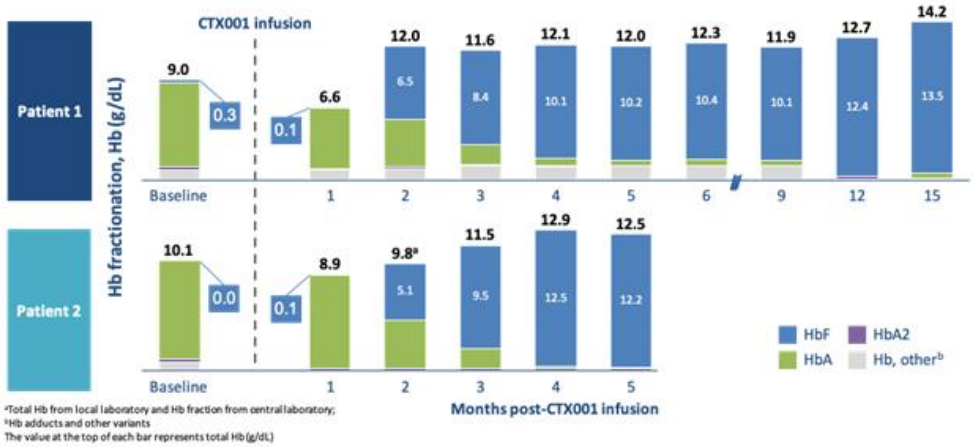
Patient 1 with TDT has the β0/IVS-I-110 genotype, which is associated with a severe phenotype similar to β0/β0, and had a transfusion requirement of 34 units of packed red blood cells per year (annualized rate during the two years prior to consenting for the trial) before enrolling in the clinical trial. As previously reported, the patient achieved neutrophil engraftment 33 days after CTX001 infusion and platelet engraftment 37 days after infusion. After CTX001 infusion, two serious adverse events (SAEs) occurred, neither of which the principal investigator (PI) considered related to CTX001: pneumonia in the presence of neutropenia, and veno-occlusive liver disease attributed to busulfan conditioning; both subsequently resolved. New data presented today show that at 15 months after CTX001 infusion, the patient was transfusion independent and had total hemoglobin levels of 14.2 g/dL, fetal hemoglobin of 13.5 g/dL, and F-cells (erythrocytes

expressing fetal hemoglobin) of 100.0%. Bone marrow allelic editing was 78.1% at 6 months and 76.1% at one year.

Patient 2 with TDT has the β0/IVS-II-745 genotype and had a transfusion requirement of 61 units of packed red blood cells per year (annualized rate during the two years prior to consenting for the trial) before enrolling in the clinical trial. The patient achieved neutrophil engraftment 36 days after CTX001 infusion and platelet engraftment 34 days after infusion. After CTX001 infusion, two SAEs occurred, neither of which the PI considered related to CTX001: pneumonia and an upper respiratory tract infection; both subsequently resolved. At 5 months after CTX001 infusion, the patient was transfusion independent and had total hemoglobin levels of 12.5 g/dL, fetal hemoglobin of 12.2 g/dL, and F-cells (erythrocytes expressing fetal hemoglobin) of 99.4%.

Hemoglobin data over time are presented for Patient 1 and Patient 2 below.

Figure 1: Total hemoglobin and hemoglobin fractionation data over time for TDT Patients 1 and 2

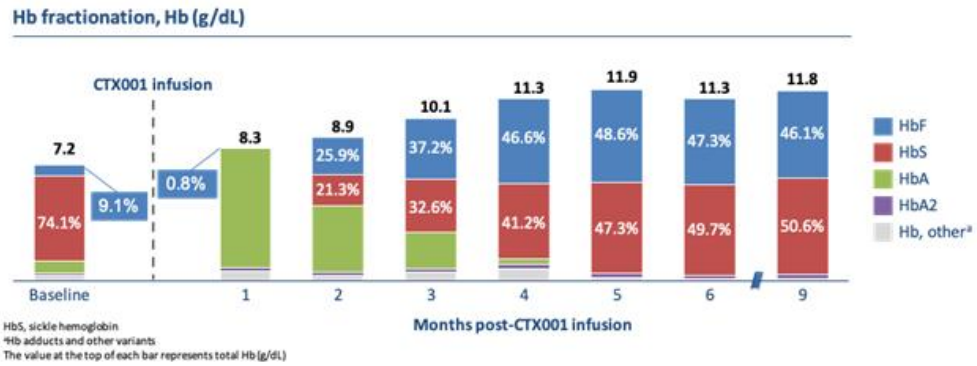


CLIMB-121 Trial in Severe Sickle Cell Disease Updated Results
Data presented today at EHA reflect longer-duration follow-up data for the first patient with SCD treated with CTX001. CRISPR Therapeutics and Vertex announced initial data for this first SCD patient in November of 2019.

Patient 1 with SCD experienced seven vaso-occlusive crises (VOCs) and five packed red blood cell transfusions per year (annualized rate during the two years prior to consenting for the trial) before enrolling in the clinical trial. As previously reported, the patient achieved neutrophil and platelet engraftment 30 days after CTX001 infusion. After CTX001 infusion, three SAEs occurred, none of which the PI considered related to

CTX001: sepsis in the presence of neutropenia, cholelithiasis and abdominal pain; all subsequently resolved. New data presented today show that at 9 months after CTX001 infusion, the patient was free of VOCs, was transfusion independent and had total hemoglobin levels of 11.8 g/dL, 46.1% fetal hemoglobin, and F-cells (erythrocytes expressing fetal hemoglobin) of 99.7%. Bone marrow allelic editing was 81.4% at 6 months. Figure 2 presents the hemoglobin data over time for this patient.

Figure 2: Total hemoglobin and hemoglobin fractionation data over time for SCD Patient 1



“With these new data, we are beginning to see early evidence of the potential durability of benefit from treatment with CTX001, as well as consistency of the therapeutic effect across patients,” said Samarth Kulkarni, Ph.D., Chief Executive Officer of CRISPR Therapeutics. “These highly encouraging early data represent one more step toward delivering on the promise and potential of CRISPR/Cas9 therapies as a new class of potentially transformative medicines to treat serious diseases.”

“The data announced today are remarkable, including the demonstration of clinical proof-of-concept in TDT,” said Reshma Kewalramani, M.D., Chief Executive Officer and President of Vertex. “While these are still early days, these data mark another important milestone for this program and for the field of gene editing. The results presented at this medical conference add to results previously shared demonstrating that CRISPR/Cas9 gene editing has the potential to be a curative therapy for severe genetic diseases like sickle cell and beta thalassemia.”

“In my 25 years of caring for children and young adults facing both sickle cell disease and beta thalassemia, I have seen how these diseases can adversely affect patients’ lives in very significant ways,” said Dr. Haydar Frangoul, Medical Director of Pediatric Hematology and Oncology at Sarah Cannon Research Institute, HCA Healthcare’s TriStar Centennial Medical Center and senior author of the abstract presented at the EHA

virtual congress. “I am encouraged by the preliminary results, which demonstrate, in essence, a functional cure for patients with beta thalassemia and sickle cell disease.”

Recent Progress in the Phase 1/2 Clinical Trials
CLIMB-111 for TDT has dosed a total of 5 patients, and all patients have successfully engrafted. The trial is also now open for concurrent dosing after successful dosing and engraftment of the first two patients. Additionally, CLIMB-111 has been expanded to allow enrollment of β0/β0 patients and is in the process of being expanded to allow enrollment of pediatric patients ages 12 years or older.

CLIMB-121 for SCD has dosed a total of 2 patients and both patients have successfully engrafted. The trial is also now open for concurrent dosing after successful dosing and engraftment of these first two patients.

The initial safety profile in these trials appears to be consistent with myeloablative busulfan conditioning and an autologous hematopoietic stem cell transplant.

In March 2020, clinical trial sites in the U.S. and Europe temporarily paused their elective hematopoietic stem cell transplant programs due to the COVID-19 pandemic, and as a result, CRISPR and Vertex temporarily paused conditioning and dosing in these trials. Enrollment, mobilization and drug product manufacturing in each trial remains ongoing. The companies are now in the process of re-initiating dosing with CTX001 at certain clinical trial sites. The CLIMB-111 and CLIMB-121 clinical trials are ongoing, and patients will be followed for 2 years following CTX001 infusion. The companies expect to provide additional data in the second half of 2020.

About CTX001
CTX001 is an investigational *ex vivo* CRISPR gene-edited therapy that is being evaluated for patients suffering from TDT or severe SCD in which a patient’s hematopoietic stem cells are engineered to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells. HbF is a form of the oxygen-carrying hemoglobin that is naturally present at birth, which then switches to the adult form of hemoglobin. The elevation of HbF by CTX001 has the potential to alleviate transfusion requirements for TDT patients and reduce painful and debilitating sickle crises for SCD patients.

Based on progress in this program to date, CTX001 has been granted Regenerative Medicine Advanced Therapy (RMAT) from the U.S. FDA, Orphan Drug Designation from both the FDA and the European Medicines Agency (EMA), and Fast Track Designation from the FDA for both SCD and TDT.

CTX001 is being developed under a co-development and co-commercialization agreement between CRISPR Therapeutics and Vertex. CTX001 is the most advanced gene-editing approach in development for TDT and SCD.

About CLIMB-111
The ongoing Phase 1/2 open-label trial, CLIMB-Thal-111, is designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with TDT. The trial will enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in a long-term follow-up trial.

About CLIMB-121
The ongoing Phase 1/2 open-label trial, CLIMB-SCD-121, is designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with severe SCD. The trial will enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in 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, CTX001, will then be infused back into the patient as part of a stem cell transplant, a process which involves, among other things, a patient being treated with myeloablative busulfan conditioning. Patients undergoing stem cell transplants may also encounter side effects (ranging from mild to severe) that are unrelated to the administration of CTX001. 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 CTX001 on multiple measures of disease and for safety.

About the CRISPR-Vertex Collaboration
CRISPR Therapeutics and Vertex 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. CTX001 represents the first treatment to emerge from the joint research program. CRISPR Therapeutics and Vertex will jointly develop and commercialize CTX001 and equally share all research and development costs and profits worldwide.

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.

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 Dr. Kulkarni, Dr. Kewalramani and Dr. Frangoul in this press release, as well as statements regarding CRISPR Therapeutics’ expectations about any or all of the following: (i) the status of clinical trials (including, without limitation, the expected timing of data releases and activities at clinical trial sites) related to product candidates under development by CRISPR Therapeutics and its collaborators, including expectations regarding the data that is being presented at the European Hematology Association’s virtual congress; (ii) the expected benefits of CRISPR Therapeutics’ collaborations; 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, forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. 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: potential impacts due to the coronavirus pandemic, such as the timing and progress of clinical trials; 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 CTX001 at this time) not to be indicative of final trial results; the potential that CTX001 clinical trial results may not be favorable; that future competitive or other market factors may adversely affect the commercial potential for CTX001; uncertainties regarding the intellectual property protection for CRISPR Therapeutics’ technology and intellectual property belonging to third parties, and the outcome of proceedings (such as an interference, an opposition or a similar proceeding) involving all or any portion of such intellectual property; and those risks and uncertainties described under the heading "Risk Factors" in CRISPR Therapeutics’ most recent annual report on Form 10-K, 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. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. 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.

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 medicines in other serious diseases where it has deep insight into causal human biology, including pain, alpha-1 antitrypsin deficiency and APOL1-mediated kidney diseases. In addition, Vertex has a rapidly expanding pipeline of genetic and cell therapies for diseases such as sickle cell disease, beta thalassemia, Duchenne muscular dystrophy and type 1 diabetes mellitus.

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, UK. 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 10 consecutive years on Science magazine's Top Employers list and top five on the 2019 Best Employers for Diversity list by Forbes. 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.

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, including, without limitation, statements made by Dr. Kulkarni, Dr. Kewalramani and Dr. Frangoul in this press release, and statements regarding our plans and expectations for our clinical trials and clinical trial sites, and our expectations regarding future data announcements. 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 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 Risk Factors in Vertex's annual report and subsequent quarterly reports filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

(VRTX-GEN)

CRISPR Therapeutics Investor Contact:
Susan Kim, +1 617-307-7503
susan.kim@crisprtx.com

CRISPR Therapeutics Media Contact:
Rachel Eides
WCG on behalf of CRISPR
+1 617-337-4167
reides@wcgworld.com

Vertex Pharmaceuticals Incorporated
Investors:
Michael Partridge, +1 617-341-6108
or
Zach Barber, +1 617-341-6470
or
Brenda Eustace, +1 617-341-6187

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

Exhibit 99.2


EUROPEAN
HEMATOLOGY
ASSOCIATION
EHA25
VIRTUAL
25th Congress of the European Hematology Association
VIRTUAL EDITION

Initial Safety and Efficacy Results with a Single Dose of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells in Transfusion-Dependent β-Thalassemia and Sickle Cell Disease

Selim Corbacioglu[1], Maria Domenica Cappellini[2], John Chapin[3], Nicole Chu-Osier[4], Christine Marie Fernandez[3], Juergen Foell[1], Josu de la Fuente[5], Stephan Grupp[6], Tony W. Ho[3], Antonis Kattamis[7], Julie Lekstrom-Himes[4], Franco Locatelli[8], Yimeng Lu[4], Mariane de Montalembert[9], Damiano Rondelli[10], Ainsley Ross[3], Niraj Shanbhag[4], Sujit Sheth[11], Sandeep Soni[12], Martin H. Steinberg[13], Donna A. Wall[14], Haydar Frangoul[15]

[1]Paediatric Haemotology, Oncology and Stem Cell Transplantation, Regensburg University Hospital, Clinic and Polyclinic for Paediatric and Adolescent Medicine, Regensburg, Germany; [2]Department of Clinical Sciences and Community, University of Milan, IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Milan, Italy; [3]CRISPR Therapeutics, Cambridge, United States; [4]Vertex Pharmaceuticals Incorporated, Boston, United States; [5]Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom; [6]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States; [7]Division of Pediatric Hematology-Oncology, First Dept of Pediatrics, University of Athens, Athens, Greece; [8]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; [9]Hôpital Universitaire Necker-Enfants Malades, Paris, France; [10]University of Illinois at Chicago, Chicago, United States; [11]Division of Pediatric Hematology / Oncology, Weill Cornell Medicine, New York, United States; [12]Lucile Packard Children's Hospital, Palo Alto, United States; [13]Boston University, Boston, United States; [14]Blood and Marrow Transplant/Cellular Therapy, Division of Haematology / Oncology, The Hospital for Sick Children and the University of Toronto, Toronto, Canada; [15]The Children's Hospital at TriStar Centennial Medical Center / Sarah Cannon Center for Blood Cancers, Nashville, United States

June 12, 2020
Session topic: 25. Gene therapy, cellular immunotherapy and vaccination - Clinical

Disclosures

- This study was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics AG
- JC is a shareholder of CRISPR Therapeutics and was an employee of CRISPR Therapeutics at the time this research was conducted. NC-O, JL-H, YL, and NS are employees of Vertex Pharmaceuticals Incorporated and hold stock and / or stock options in that company. CMF, TWH, and AR are employees of CRISPR Therapeutics and hold stock and / or stock options in that company. SG receives study support from Novartis, Kite, and Servier, consults for Novartis, Roche, GSK, Cure Genetics, Humanigen, CBMG, and Janssen / J&J, participates in study steering committees or scientific advisory boards for Jazz, Adaptimmune, TCR2, Eureka, Cellectis, Juno, and Vertex, and has a patent (Toxicity management for anti-tumor activity of CARs, WO2014011984A1) that is managed according to the University of Pennsylvania patent policy. AK has participated in advisory boards for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, Novartis, Vifor, Ionis, and BMS / Celgene, has participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, has received research support from Novartis, and has received speaker fees from BMS / Celgene. MM has participated in advisory boards for Addmedica, Bluebird Bio, and Novartis. MHS has participated in advisory boards for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, Fulcrum Therapeutics, DSMB, and Imara. S. Sheth has served as a consultant for Acceleron, Agios, Bluebird Bio, Celgene, and Novartis, has received research support from Agios, Celgene, Dispersol, LaJolla, Novartis, and Terumo, and has participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics. S. Soni and HF have participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics. SC, MDC, JF, J de la F, FL, DR, and DAW have no conflicts to disclose
- Medical writing support was provided by Katie L. Beski, PhD of Complete HealthVizion, Inc., Chicago, IL, USA, funded by Vertex Pharmaceuticals Incorporated. Development and review coordination was provided by Leah Eardley, PhD of Vertex Pharmaceuticals Incorporated, who holds stock and / or stock options in that company

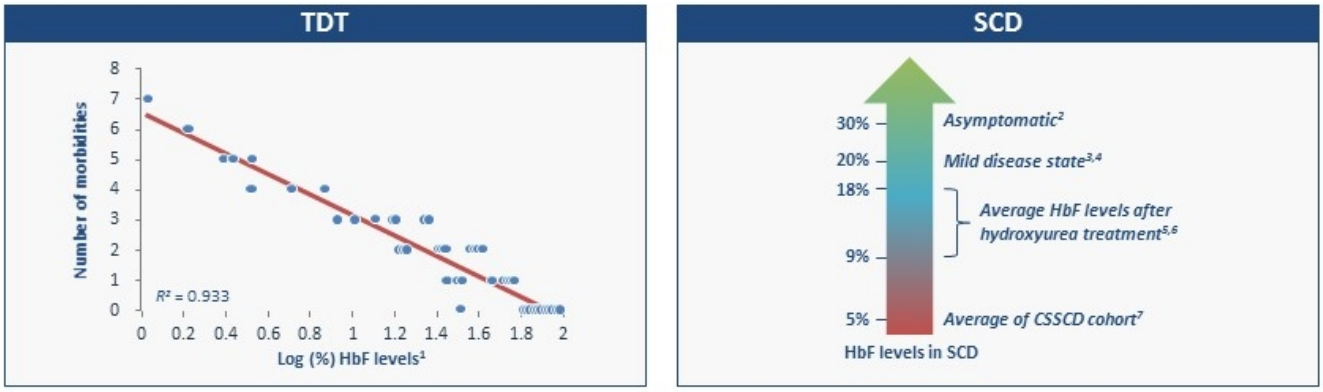
Transfusion-Dependent β-Thalassemia (TDT) and Sickle Cell Disease (SCD) Cause Significant Morbidity and Mortality

	TDT	SCD
Blood disorders caused by mutations in the β-globin gene[1,2]	Loss-of-function mutations reduce the level of β-globin, lowering total Hb	Single-point mutation causes hemoglobin to polymerize, leading to sickling of RBCs
Significant worldwide burden[1,2]	**60,000** ANNUAL BIRTHS[a]	**300,000** ANNUAL BIRTHS
Significant morbidity and mortality, and heavy burden of patient care[1-4]	Severe anaemia, frequent transfusions, complications related to iron overload	Pain, anaemia, frequent hospitalizations, end-organ damage, early death

Hb, hemoglobin; RBC, red blood cell
[a]Symptomatic individuals (not all are transfusion-dependent)

1. Kato et al. *Nat Rev Dis Primers*. 2018;4:18010; 2. Galanello, Origo. *Orphanet J Rare Dis*. 2010;5:11; 3. Taher et al. *Lancet*. 2018;391:155-167; 4. Ware et al. *Lancet*. 2017;390:311-323

Elevated Fetal Hemoglobin (HbF) is Associated With Decreased Disease Severity

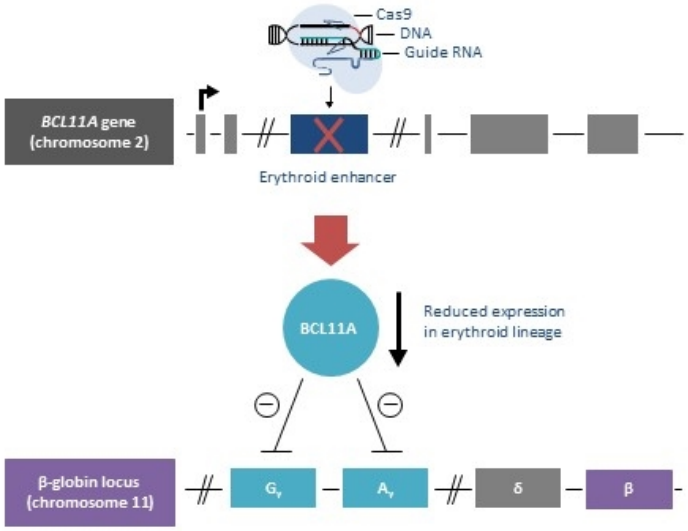


Rare patients with β-thalassemia or SCD continue to express HbF into adulthood, a condition known as hereditary persistence of HbF, and these patients experience **reduced or no symptoms**[8-10]

CSSCD, Cooperative Study of Sickle Cell Disease

1. Musallam et al. *Blood*. 2012;119:364-367; 2. Ngo et al. *Brit J Haematol*. 2012;156:259-264; 3. Akinsheye et al. *Blood*. 2011;118:19-27; 4. Alsultan et al. *Am J Hematol*. 2012;87:824-826; 5. Nevitt et al. *Cochrane Database Syst Rev*. 2017;4:CD002202; 6. Fitzhugh et al. *PLoS One*. 2015;10:e0141706; 7. Sebastiani P et al. *Am J Hematol*. 2008;83:189-195; 8. Murray et al. *Br J Haematol*. 1988;69:89-92; 9. Conley et al. *Blood*. 1963;21:261-281; 10. Bank. *Blood*. 2006;107:435-443

Disruption of *BCL11A* Expression Increases HbF Levels



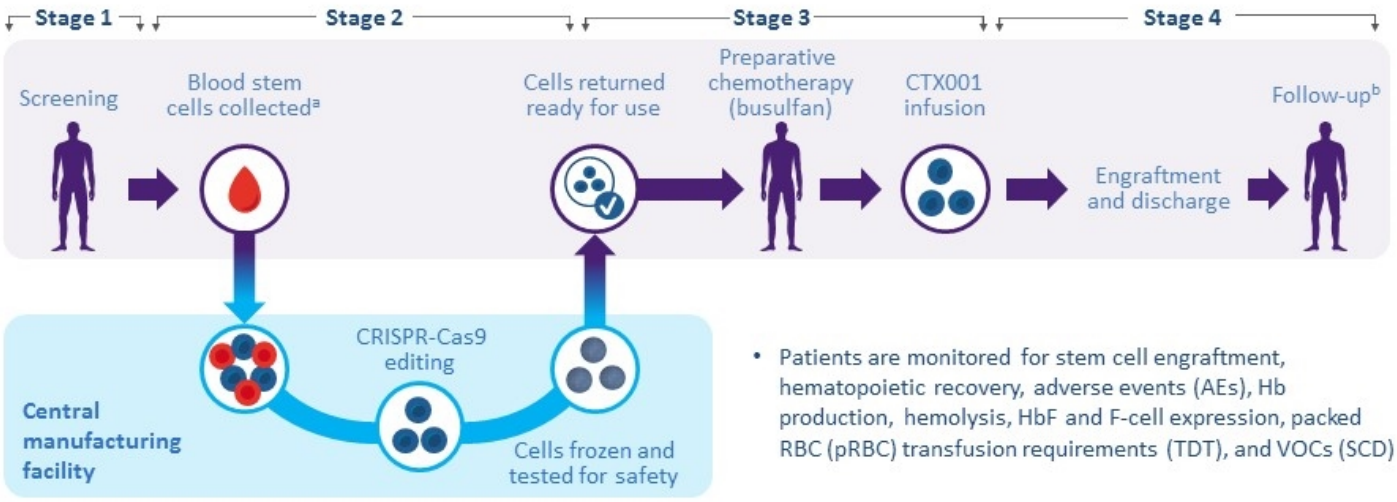
- BCL11A suppresses expression of the γ-globin subunit of HbF
- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF
- CTX001: CD34+ cells gene edited with CRISPR-Cas9, resulting in reduction of erythroid-specific expression of BCL11A
- *In vivo,* infusion of CTX001 leads to an increase in HbF levels in erythroid cells
- Here we report preliminary results of the first-in-human therapeutic trial of CRISPR-Cas9 editing in TDT and SCD

Modified from Canver, Orkin. *Blood.* 2016;127:2536-2545

Phase 1 / 2 Studies in Patients with TDT and SCD

	CLIMB THAL-111	CLIMB SCD-121
Design	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03655678)	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03745287)
Target enrollment	45 patients aged between 18 and 35 years with TDT, including β0 / β0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the previous 2 years	45 patients aged between 18 and 35 years with severe SCD and a history of ≥2 vaso-occlusive crises (VOCs)/year over the previous 2 years
Primary endpoint	Proportion of patients achieving sustained transfusion reduction of 50% for at least 6 months starting 3 months after CTX001 infusion	Proportion of patients with HbF ≥20% sustained for at least 3 months starting 6 months after CTX001 infusion

CTX001 Infusion Process



- Patients are monitored for stem cell engraftment, hematopoietic recovery, adverse events (AEs), Hb production, hemolysis, HbF and F-cell expression, packed RBC (pRBC) transfusion requirements (TDT), and VOCs (SCD)

[a]Patients enrolled in CLIMB THAL-111 received a combination of plerixafor and filgrastim for mobilization, while patients enrolled in CLIMB SCD-121 received plerixafor only;
[b]Patients will be followed for 24 months after CTX001 infusion with physical exams, laboratory and imaging assessments, and AE evaluations. All patients who receive CTX001 will be followed for 15 years in a long-term follow-up study (NCT04208529) after completion or withdrawal from CLIMB THAL-111 or CLIMB SCD-121

TDT Patient Baseline and Treatment Characteristics

Patient baseline	Patient 1	Patient 2
Genotype	**β0 / β+ (IVS-I-110)**	**β0 / β+ (IVS-II-745)**
Age at consent, *years*	**19**	**26**
Gender	**Female**	**Male**
Pre-study pRBC transfusions[a]		
Units/year	**34**	**61**
Transfusion episodes/year	**16.5**	**15**
Treatment characteristics		
Cell dose, *CD34+ cells/kg*	**17.0×10^6**	**12.3×10^6**
Neutrophil engraftment[b]**,** *Study day*	**33**	**36**
Platelet engraftment[c]**,** *Study day*	**37**	**34**

Phenotype associated with genotype of Patient 1 (IVS-I-110) is severe and similar to that of β0/β0

[a]Annualized number during the 2 years before consenting to study participation; [b]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/μL on 3 consecutive days; [c]Defined as the first day of 3 consecutive measurements of platelet count ≥20,000/μL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days

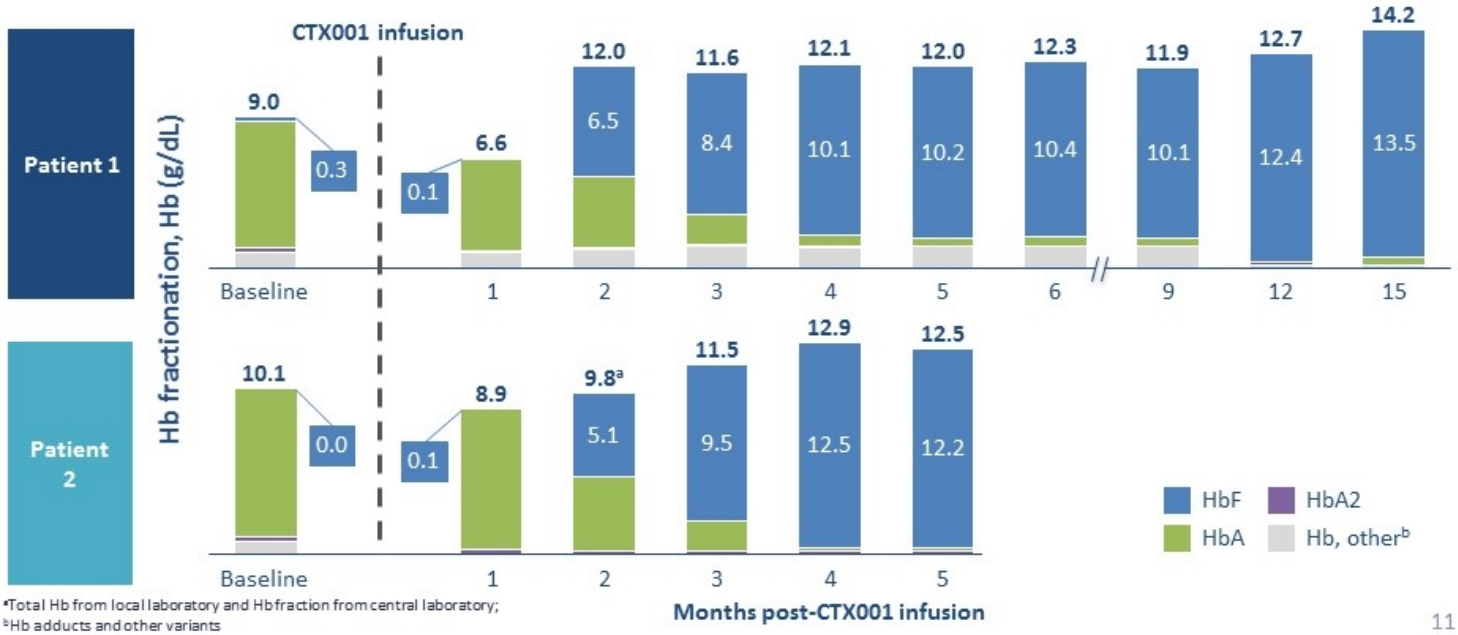
TDT: Adverse Events

	Patient 1	Patient 2
Screening to CTX001 infusion		
AEs	12	8
Serious AEs	0	0
Post-CTX001 infusion		
AEs	32	34
Serious AEs	2[a]	2[b]
Weeks of follow-up	66.6	24.7
AE relationship[c]		
Related to filgrastim only	4[d]	2
Related to plerixafor and filgrastim	0	2
Related to busulfan only	8[e]	15[f]
Related to CTX001 only	0	1[g]
Related to busulfan and CTX001	0	3[h]
Not related to any study drug	32	19

AEs were generally consistent with myeloablation and autologous stem cell transplant

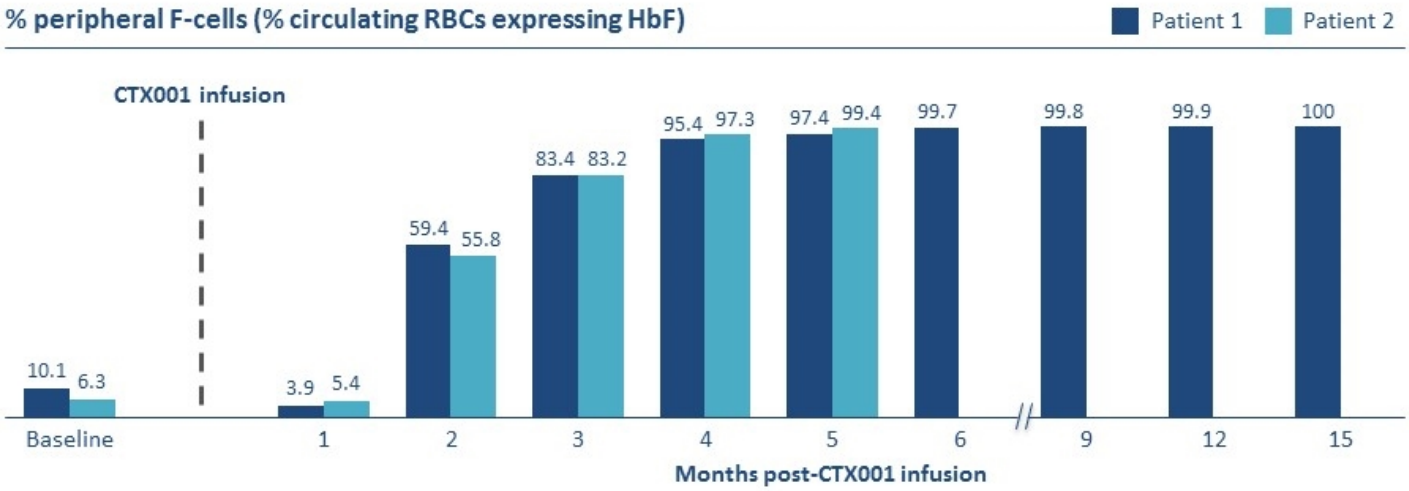
[a]Venoocclusive liver disease (related to busulfan only) and pneumonia (not considered related to CTX001 or other study drug), both resolved; [b]Pneumonia and upper respiratory tract infection, both not considered related to CTX001 or other study drug, both resolved; [c]Includes both related and possibly related AEs. Only those AEs which occurred ≥2 times are described in the footnote for all AE listings except for "Related to CTX001" AEs where all are listed; [d]Bone pain (×2); [e]Stomatitis (×3); [f]Vomiting (×2), stomatitis (×2); [g]Anaemia; [h]Pyrexia (×2), petechiae

TDT: Clinically Meaningful HbF and Total Hb are Achieved Early and Maintained

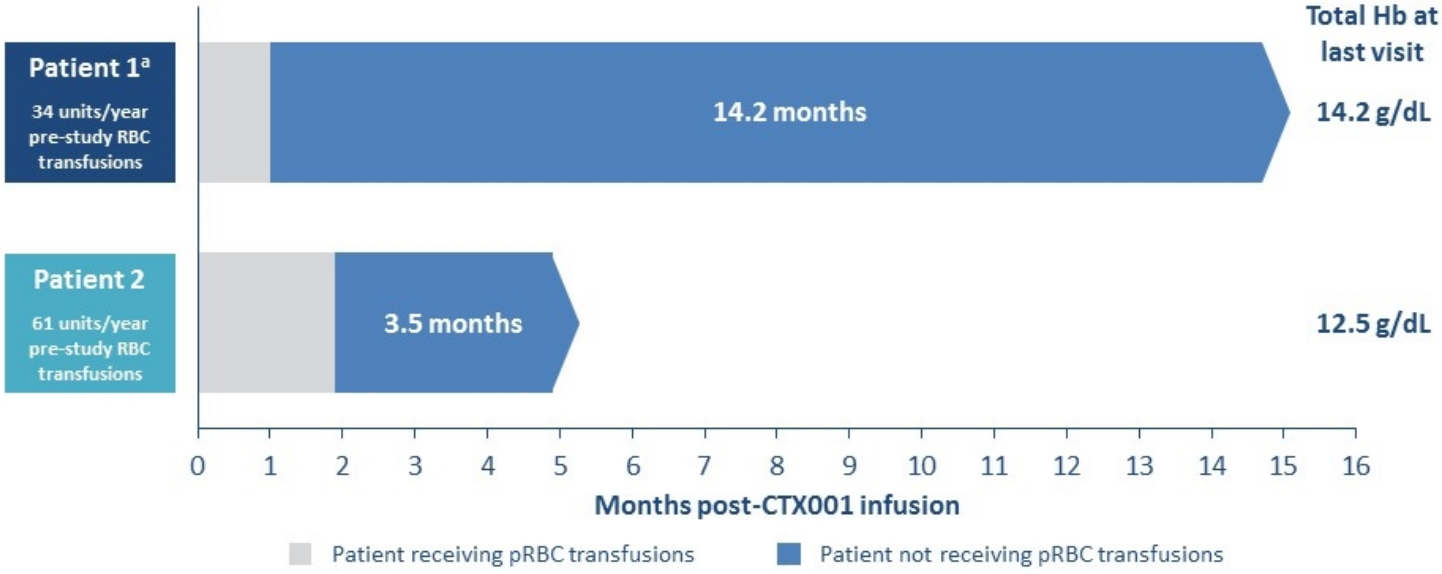


[a]Total Hb from local laboratory and Hb fraction from central laboratory;
[b]Hb adducts and other variants

TDT: Pancellular Expression of HbF is Maintained



Both TDT Patients Have Stopped pRBC Transfusions



[a]In the 15 months after CTX001 infusion, phlebotomy for iron reduction occurred on Study Days 98, 147, 170, and 191. Iron chelation therapy received from Study Day 205 to Study Day 316

SCD Patient Baseline and Treatment Characteristics

Patient baseline[a]

Genotype	**βS / βS**
Age at consent, *years*	**33**
Gender	**Female**
Pre-study VOCs, *VOCs/year*[b]	**7**

Treatment characteristics

Cell dose, *CD34+ cells/kg*	**3.3×10^6**
Neutrophil engraftment[c]**,** *Study day*	**30**
Platelet engraftment[d]**,** *Study day*	**30**

[a]Patient had received hydroxyurea treatment from 2016 to November 22, 2018 (Study Day −222); [b]Annualized rate during the 2 years before consenting to study participation; [c]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/μL for 3 consecutive days; [d]Defined as the first of 3 consecutive measurements on 3 separate days with platelet count ≥50,000/μL without a platelet transfusion for 7 consecutive days

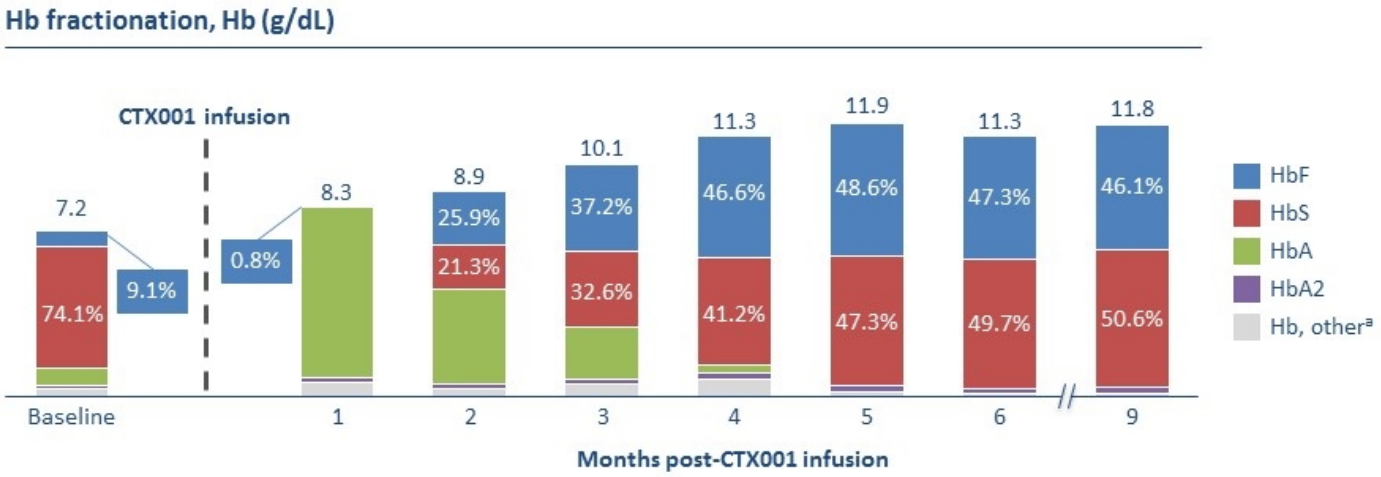
SCD: Adverse Events

	SCD Patient
Screening to CTX001 infusion	
AEs	35
Serious AEs	11
Post-CTX001 infusion	
AEs	91[a]
Serious AEs	3[b]
Weeks of follow-up	45.1
AE relationship[c]	
Related to plerixafor only	6
Related to busulfan only	21[d]
Related to CTX001 only	0
Related to busulfan and CTX001	5[e]
Not related to any study drug	94

AEs were generally consistent with myeloablation and autologous stem cell transplant

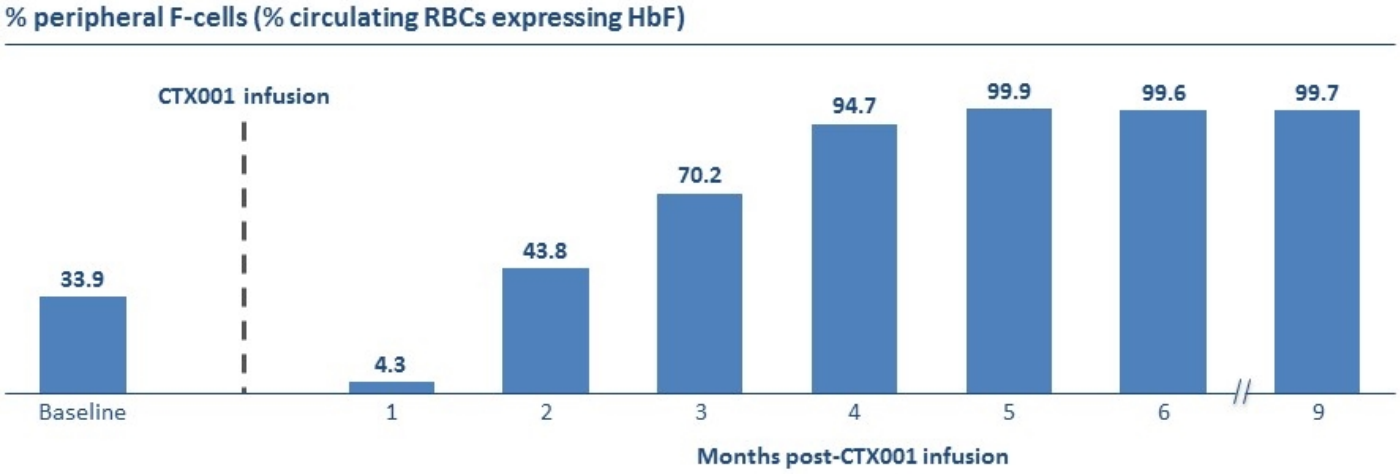
[a]Most common grade ≥3 AEs (occurring ≥2 times) post-CTX001: headache, neck pain, cholelithiasis, oesophagitis, leukopenia, musculoskeletal chest pain, non-cardiac chest pain, stomatitis; [b]Sepsis (related to busulfan), cholelithiasis and abdominal pain (both not related to CTX001 or other study drug), all resolved; [c]Includes related and possibly related AEs. Only those AEs which occurred ≥2 times are described in the footnote except for "Related to CTX001" AEs where all are listed; [d]Oesophagitis (×3), leukopenia (×2), vulvovaginal inflammation (×2), stomatitis (×2); [e]Lymphopenia (×5), attributed to the CD34+ hematopoietic stem cell enrichment of the CTX001 product

SCD: Clinically Meaningful HbF is Achieved Early and Maintained

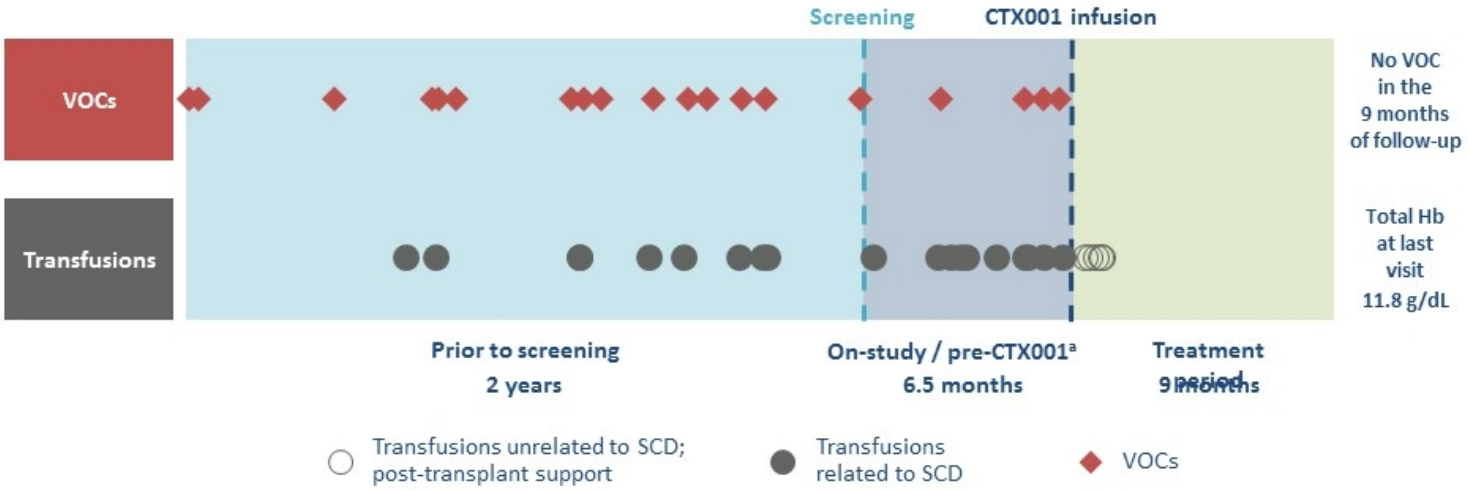


HbS, sickle hemoglobin
[a]Hb adducts and other variants

SCD: Pancellular HbF Expression is Maintained



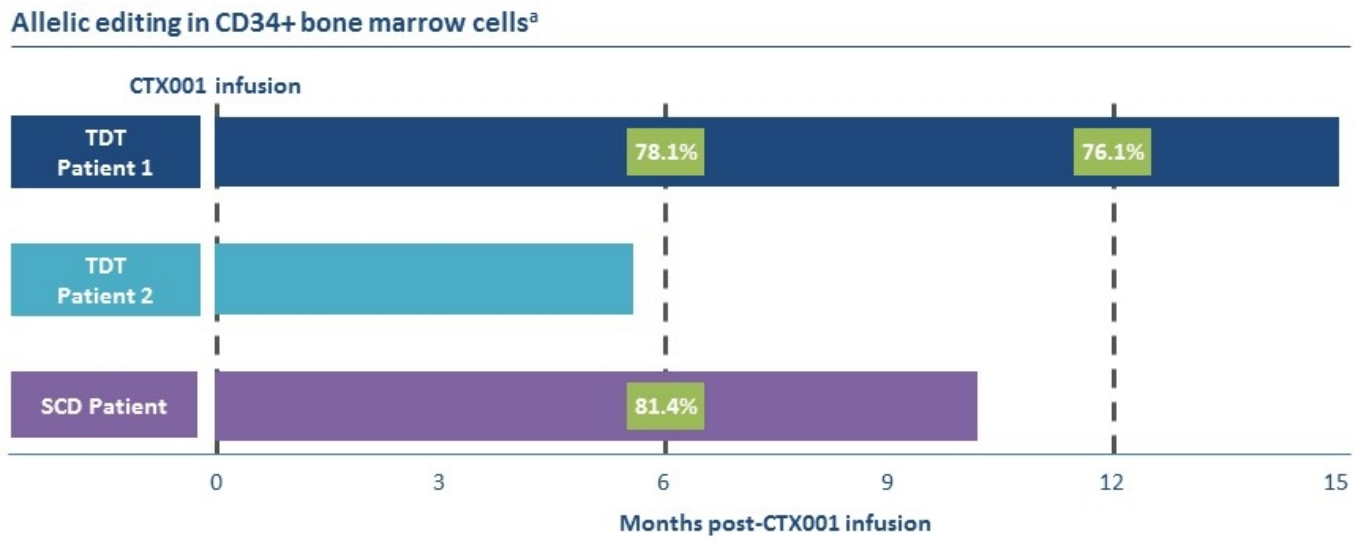
SCD: No VOCs Post-CTX001 Infusion



No pRBC transfusions have occurred since Study Day 19

[a]Exchange transfusions per study protocol occurred during the on-study / pre-CTX001 period (not included here)

Durable *BCL11A* Editing Observed in Bone Marrow CD34+ Cells



[a]Allelic editing in CD34+ bone marrow cells assessed every 6 months

Conclusions

- These studies are the first demonstration of the clinical impact of CRISPR-Cas9-based gene editing for hemoglobinopathies and establish proof of concept for TDT
- Overall safety is consistent with myeloablative conditioning and autologous transplant
- Clinically meaningful HbF and total Hb levels, as well as pancellular expression of HbF in red blood cells, are observed early and maintained in TDT and SCD
- First 2 TDT patients have been free of pRBC transfusions for >14 and >3 months respectively; first SCD patient has had no VOCs in >9 months
- Sustained engraftment of edited hematopoietic stem cells is supportive of long-term clinical efficacy
- Enrollment and manufacturing of CTX001 for TDT and SCD are ongoing with further dosing planned in 2020

CTX001 has been granted Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA, Orphan Drug Designation from both the FDA and the EMA, and Fast Track Designation from the FDA

Thank You to Study Participants and Their Families

CLIMB THAL-111 and CLIMB SCD-121 sites

Both

- Lucille Packard Children's Hospital of Stanford University, Palo Alto
- Columbia University Medical Center, New York
- The Children's Hospital at TriStar Centennial Medical Center / Sarah Cannon Center for Blood Cancers, Nashville
- The Hospital for Sick Children, Toronto
- Regensburg University Hospital, Clinic and Polyclinic for Paediatric and Adolescent Medicine, Paediatric Haemotology, Oncology and Stem Cell Transplantation
- Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica Ospedale Pediatrico Bambino Gesù – IRCCS, Rome

SCD-121

- University of Illinois at Chicago Hospitals and Health Systems
- Children's Hospital of Philadelphia
- St. Jude Children's Research Hospital, Memphis
- Methodist Children's Hospital / Texas Transplant Institute, San Antonio
- Hôpital Universitaire des Enfants Reine Fabiola, Brussels

THAL-111

- BC Children's Hospital, Vancouver
- University Hospital Tübingen
- Imperial College Healthcare, London

Thank you to study participants and their families, as well as **sites, investigators, nurses, and the entire CTX001 team** from CRISPR Therapeutics and Vertex Pharmaceuticals