Creating transformative gene-based medicines for serious diseases

Corporate Overview | August 2020
Forward-Looking Statements

The presentation and other related materials may contain a number of “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding CRISPR Therapeutics’ expectations about any or all of the following: (i) the safety, efficacy and clinical progress of our various clinical programs; (ii) the status of clinical trials (including, without limitation, the timing of filing of clinical trial applications and INDs, any approvals thereof and the timing of commencement of clinical trials), development timelines and discussions with regulatory authorities related to product candidates under development by CRISPR Therapeutics and its collaborators; (iii) the number of patients that will be evaluated, the anticipated date by which enrollment will be completed and the data that will be generated by ongoing and planned clinical trials, and the ability to use that data for the design and initiation of further clinical trials; (iv) the intellectual property coverage and positions of CRISPR Therapeutics, its licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property; (v) the sufficiency of CRISPR Therapeutics’ cash resources; and (vi) 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: the potential for initial and preliminary data from any clinical trial not to be indicative of final trial results; the risk that the initial data from a limited number of patients (as is the case with CTX001 at this time) may not be indicative of results from the full planned study population; the outcomes for each of CRISPR Therapeutics’ planned clinical trials and studies may not be favorable; that one or more of CRISPR Therapeutics’ internal or external product candidate programs will not proceed as planned for technical, scientific or commercial reasons; that future competitive or other market factors may adversely affect the commercial potential for CRISPR Therapeutics’ product candidates; uncertainties inherent in the initiation and completion of preclinical studies for CRISPR Therapeutics’ product candidates; availability and timing of results from preclinical studies; whether results from a preclinical trial will be predictive of future results of the future trials; uncertainties about regulatory approvals to conduct trials or to market products; 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 presentation, other than to the extent required by law.
CRISPR Therapeutics Highlights

Leading gene editing company focused on translating revolutionary CRISPR/Cas9 technology into transformative therapies

- Advancing CRISPR in the clinic with CTX001™ in β-thalassemia and sickle cell disease
- Next-generation immuno-oncology platform underlying wholly-owned, potentially best-in-class gene-edited allogeneic cell therapies CTX110™, CTX120™ and CTX130™
- Enabling regenerative medicine 2.0 with CRISPR/Cas9-edited allogeneic stem cells
- Advancing in vivo applications based on in-licensed technologies, platform improvement and strategic partnerships
The CRISPR/Cas9 Revolution

A **SPECIFIC, EFFICIENT** and **VERSATILE** tool for editing genes

- **Disrupt**
- **Delete**
- **Correct or Insert**

“If scientists can dream of a genetic manipulation, **CRISPR can now make it happen**”
# Our Pipeline

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>RESEARCH</th>
<th>IND-ENABLING</th>
<th>CLINICAL</th>
<th>MARKETED</th>
<th>STATUS</th>
<th>PARTNER</th>
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<td><strong>Hemoglobinopathies</strong></td>
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Additional undisclosed, early stage programs subject to collaboration or license agreements with Vertex and Bayer
Hemoglobinopathies – Devastating Blood Diseases

**Sickle Cell Disease (SCD) and β-Thalassemia**

Blood disorders caused by mutations in the β-globin gene

- Sickled
- Normal Cell
- Thalassemic

Significant worldwide burden

**ANNUAL BIRTHS**

- **300K** SCD
- **60K** β-thalassemia

High morbidity and mortality

- Anemia
- Pain
- Early death

Heavy burden of patient care

- Frequent transfusions and hospitalizations

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Our Approach – Upregulating Fetal Hemoglobin

Symptoms in SCD and β-Thalassemia Decrease as HbF Level Increases

- Naturally occurring genetic variants cause a condition known as hereditary persistence of fetal hemoglobin (HPFH), which leads to reduced or no symptoms in patients with SCD and β-thalassemia.

- Our gene editing strategy aims to mimic these variants in symptomatic patients, an approach supported by well-understood genetics.
Pioneering CRISPR Trials

**Design**
Phase 1/2, international, multi-center, open-label, single arm studies to assess the safety and efficacy of CTX001 in patients with β-thalassemia and SCD, respectively

**Target enrollment**
- 45 patients between 18 - 35 years of age with transfusion dependent thalassemia (TDT), including β0/β0 genotypes
- 45 patients between 18 - 35 years of age with severe SCD and a history of ≥2 vaso-occlusive crises/year over the previous two years

**Primary endpoint**
- Proportion of patients achieving sustained transfusion reduction 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

**Potential to expand into registrational trials**, as well as into additional age cohorts, if supported by safety and efficacy
### TDT Patient Baseline and Treatment Characteristics

#### Patient baseline

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>$\beta_0 / \beta^+$ (IVS-I-110)</td>
<td>$\beta_0 / \beta^+$ (IVS-II-745)</td>
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<td>Age at consent, years</td>
<td>19</td>
<td>26</td>
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<td>Gender</td>
<td>Female</td>
<td>Male</td>
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<td>Pre-study pRBC transfusions(^1)</td>
<td>34, 16.5</td>
<td>61, 15</td>
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<td>Units/year</td>
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<tr>
<td></td>
<td>Transfusion episodes/year</td>
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#### Treatment characteristics

<table>
<thead>
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<th>Patient 1</th>
<th>Patient 2</th>
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<td>Cell dose, CD34+ cells/kg</td>
<td>$17.0\times10^6$</td>
<td>$12.3\times10^6$</td>
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<td>Neutrophil engraftment(^2), Study day</td>
<td>33</td>
<td>36</td>
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<tr>
<td>Platelet engraftment(^3), Study day</td>
<td>37</td>
<td>34</td>
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Data disclosed June 12, 2020

\(^1\) Annualized number during the 2 years before consenting to study participation

\(^2\) Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days

\(^3\) 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

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**Overall safety consistent with myeloablative conditioning and autologous transplant**

- Each patient experienced 2 SAEs, none considered related to CTX001 by study investigators, all resolved:
  - Patient 1: Veno-occlusive liver disease attributed to busulfan conditioning and pneumonia in the presence of neutropenia
  - Patient 2: Pneumonia and upper respiratory tract infection
TDT Patient 1: High Levels of HbF and Total Hb Achieved Rapidly and Sustained at 15 Months

**Hemoglobin fractionation, Hb (g/dL)**

<table>
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<th>Months post CTX001 infusion</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
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<td>HbF</td>
<td>10.1</td>
<td>3.9</td>
<td>59.4</td>
<td>83.4</td>
<td>95.4</td>
<td>97.4</td>
<td>99.7</td>
<td>99.8</td>
<td>99.9</td>
<td>100</td>
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<tr>
<td>HbA</td>
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</table>

Peripheral F-cells, %

- Baseline: 100%
- 12 months: 78.1%
- 15 months: 76.1%

Allelic editing in the bone marrow, %

- Baseline: 76.1%
- 12 months: 99.9%
- 15 months: 100%

Data disclosed June 12, 2020

1. Hb adducts and other variants
2. Circulating RBCs expressing fetal hemoglobin
TDT Patient 2: High Levels of HbF and Total Hb Achieved Rapidly and Sustained at 5 Months

Hemoglobin fractionation, Hb (g/dL)

<table>
<thead>
<tr>
<th>Months post CTX001 infusion</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Peripheral F-cells (%)</td>
<td>6.3</td>
<td>5.4</td>
<td>55.8</td>
<td>83.2</td>
<td>97.3</td>
<td>99.4</td>
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</tbody>
</table>

Data disclosed June 12, 2020

1 Total hemoglobin from local lab and hemoglobin fraction from central lab
2 Hb adducts and other variants
3 Circulating RBCs expressing fetal hemoglobin
Both TDT Patients Have Stopped pRBC Transfusions

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.

Patient 1
- 34 units/year pre-study RBC transfusions
- 14.2 months post-CTX001 infusion
- Total Hb at last visit: 14.2 g/dL

Patient 2
- 61 units/year pre-study RBC transfusions
- 3.5 months post-CTX001 infusion
- Total Hb at last visit: 12.5 g/dL

Data disclosed June 12, 2020

1 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>βS/βS</td>
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<tr>
<td>Age at consent, years</td>
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<tr>
<td>Gender</td>
<td>Female</td>
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<tr>
<td>Pre-study VOCs, VOCs/year</td>
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</table>

#### Treatment characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell dose, CD34+ cells/kg</td>
<td>$3.3 \times 10^6$</td>
</tr>
<tr>
<td>Neutrophil engraftment, Study day</td>
<td>30</td>
</tr>
<tr>
<td>Platelet engraftment, Study day</td>
<td>30</td>
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</tbody>
</table>

Overall safety consistent with myeloablative conditioning and autologous transplant

- 3 SAEs occurred, none considered related to CTX001 by study investigator, all resolved:
  - Sepsis in the presence of neutropenia
  - Cholelithiasis
  - Abdominal pain

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Data disclosed June 12, 2020

1 Patient had received hydroxyurea treatment from 2016 to November 22, 2018 (Study Day -222)
2 Annualized rate during the 2 years before consenting to study participation
3 Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL for 3 consecutive days with platelet count ≥50,000/µL without a platelet transfusion for 7 consecutive days
4 Defined as the first of 3 consecutive measurements on 3 separate days
### Hemoglobin fractionation, Hb (g/dL) and % of total Hb

<table>
<thead>
<tr>
<th>Months post CTX001 infusion</th>
<th>Hb adducts and other variants</th>
<th>Circulating RBCs expressing fetal hemoglobin</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>7.2</td>
<td>94.1%</td>
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<td>1</td>
<td>8.3</td>
<td>9.1%</td>
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<td>2</td>
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<td>21.3%</td>
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<td>49.7%</td>
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<tr>
<td>9</td>
<td>11.8</td>
<td>50.6%</td>
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**Data disclosed June 12, 2020**

1. Hb adducts and other variants
2. Circulating RBCs expressing fetal hemoglobin
No pRBC transfusions have occurred since Study Day 19

Data disclosed June 12, 2020
1  Exchange transfusions per study protocol occurred during the on-study / pre-CTX001 period (not included here)
CRISPR Enables the Next Generation of I/O Cell Therapy

**ALLOGENEIC CAR-T**

- Off-the-shelf
- More potent starting material
- More consistent product
- Broader access
- Flexible dosing (e.g., re-dosing)

**SOLID TUMOR EFFICACY**

- Avoid exhaustion
- Modulate suppressive TMEs
- Target tumors with greater selectivity
- Sense and respond via genetic circuits
- Recruit endogenous immunity
Allogeneic CAR-T Therapy Has Transformative Potential

Before Patient Diagnosis

Autologous: patient derived

After Patient Diagnosis

WEEK 1
Apheresis

WEEK 2
Manufacture

WEEK 3
Single Treatment

DAY 1: DIAGNOSIS

T Cells
Manufacture
100+ Doses

Treated

Allogeneic CAR-T allows for immediate treatment without risk of manufacturing failure, saving patients valuable time in which their disease could progress.
CRISPR-Edited Allogeneic T Cell Design

Initial Allogeneic CAR-T Candidate – CTX110

- Improve persistence in the allo setting with β2M knock-out to eliminate MHC I expression
- Prevent GvHD via TCR disruption
- Improve safety and potency by precise insertion of CAR construct into TRAC locus

Multiplex editing in one step
CRISPR Editing Allows for a More Consistent Product

Precise and Efficient Editing to Produce CTX110

- Consistently high editing across 5 different donors
- >50% of cells have all three desired edits

Greater Consistency than Viral Approaches

54-66% CAR$^+$ range with CRISPR vs. 6-45% for lentiviral CAR-T$^1$

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1 Maude, et al. NEJM 2014
Initial Allogeneic CAR-T Trials for CTX110 and CTX120

CRSP-ONC-001 and CRSP-ONC-002: Single-arm trials to assess the safety and efficacy of CTX110 and CTX120, respectively

Patients and Sites
- CTX110 – Subjects with relapsed or refractory (r/r) B-cell malignancies, starting with adult patients with r/r non-Hodgkin lymphoma
- CTX120 – Subjects with r/r multiple myeloma
- Conducted at sites with CAR-T or cell therapy experience

Trial Design and Dosing
- Dose escalation followed by dose expansion cohort
- Allogeneic CAR-T enables simplified trial design with short screening timeframe, no apheresis, no bridging chemo, and on-site availability of CAR-T cell product
- Lymphodepleting chemotherapy regimen administered before CAR-T infusion
CTX110/CTX120 – Novel Approach Against Validated Targets

**CTX110 – Anti-CD19 Allogeneic CAR-T**

Prolonged survival in disseminated Nalm6 B-ALL xenograft tumor model

- **No treatment**
  - n=6 mice
- **CTX110**
  - 4x10^6 cells/mouse
  - n=6 mice

**Survival (%)**

- **No treatment**
  - p=0.0004
  - Log-rank (Mantel-Cox test)

**CTX110 dosed**

**CTX120 – Anti-BCMA Allogeneic CAR-T**

Subcutaneous RPMI-8226 multiple myeloma model completely eliminated

- **No treatment**
  - n=5 mice
- **CTX120**
  - 2.5x10^6 cells/mouse
  - n=5 mice

**Tumor volume (mm^3)**

- **No treatment**
- **CTX120 dosed**

Strong anti-tumor activity observed with healthy donor-derived CAR-T cells – potential for better outcomes than autologous CAR-T given poor health of patient T cells
CTX130 – Anti-CD70 Program as a Bridge to Solid Tumors

Subcutaneous A498 Renal Cell Carcinoma Model Completely Eliminated

- No treatment
  - n=5 mice
- CTX130
  - 1x10^7 cells/mouse
  - n=5 mice

CTX130
- Anti-CD70 allogeneic CAR-T
- Additional editing beyond TCR and β2M knock-outs
- For both heme and solid tumors

Strong rationale for targeting CD70 for solid tumors
- Initial focus on clear cell renal cell carcinoma – immune-infiltrated disease and >80% CD70-positive
- Minimal CD70 expression on healthy tissues

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1 Adam, et al. Br J Cancer 2006
Rapid Generation of Novel Candidates Using CRISPR

**Multiplex Editing**

Single-shot sextuple knock-out plus CAR insertion performed at high efficiency

**Speed of Discovery**

6 WEEKS
Concept to CAR-T cell

6 MONTHS
Concept to *in vivo* preclinical POC

Septuple-edited CAR-T cells show **no viability decrease**, **no cytokine-independent growth** and **robust target-specific cytotoxicity**
CRISPR Enables Regenerative Medicine 2.0

CRISPR/Cas9 Technology Opens Broader Applications for Regenerative Medicine

CRISPR/Cas9 Technology:
- Allow immune evasion
- Improve cell function
- Direct cell fate

Stem Cell Technology

Therapeutic Targets, e.g., diabetes

Exemplified by our collaboration with ViaCyte:
- Aim to develop beta-cell replacement product to treat diabetes that does not require immunosuppression
- Applies immune-evasive gene-editing expertise from our allo CAR-T programs to stem cells
Unlocking In Vivo Applications of CRISPR/Cas9

**AAV Vectors for Neuromuscular Indications**
- Adeno-associated virus (AAV) to deliver Cas9 and gRNA to muscle, the nervous system and other tissues
- Collaboration with StrideBio to improve tissue specificity and reduce immunogenicity
- Programs include DMD and DM1 in collaboration with Vertex, as well as other early research programs

**LNPs for Liver Indications**
- Lipid nanoparticles (LNPs) containing mRNA encoding Cas9 and gRNA for delivery to the liver
- Lipid technology from MIT and mRNA technology from CureVac
- Programs include GSD Ia and other early research programs

Enabling collaborations
- StrideBio
- MIT
- CureVac
- ProBioGen

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Optimizing the CRISPR/Cas9 Platform

**Nuclease Engineering**
Enhance CRISPR/Cas9 system through protein engineering

**Guide RNA Optimization**
Identify optimal guide RNA formats and sequences for therapeutic editing

**Advanced Editing**
Improve efficiency of gene correction and multiplexing

**Synthetic Biology**
Engineer improved cellular therapeutics
**Strong U.S. and Global Foundational IP Position**

**United States**

Charpentier / UC Berkeley / U. Vienna granted patents of broad scope; multiple applications progressing

- 30 Patents of broad scope granted, including the patent involved in the first interference
- 1 Patent applications of broad scope allowed
- >30 Additional patent applications moving forward in parallel with both broad and narrow claims
- 2\(^{nd}\) Interference declared June 2019 to determine who was first to invent CRISPR/Cas9 gene editing in eukaryotic cells

**Europe and Global**

Charpentier / UC Berkeley / U. Vienna granted foundational patents, including use in eukaryotes

- 3 Patents of broad scope granted in the EU
- 23 Patents of broad scope granted in the UK, Germany, Japan, China, Singapore, Hong Kong, Ukraine, Israel, Australia, New Zealand, Mexico, South Africa and elsewhere
- ~80 Jurisdictions worldwide in which applications with both broad and narrow claims are advancing

As of April 2020
Building a Great Company

EXPERIENCED Management Team

END-TO-END CAPABILITIES With >300 Employees

COLLABORATIVE & ENTREPRENEURIAL Culture