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Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no interpretative value on our existing or future results.

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Disclosures

Dr. Swaminathan P. Iyer

- Professor, Lead of the T Cell Lymphoma Program, Department of Lymphoma/Myeloma, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center
- Dr. Iyer receives research support from CRISPR Therapeutics, Merck & Co., Seagen, Rhizen, Acrotech Biopharma, Legend Biotech, Innate Pharma, AstraZeneca, Dren Bio, Yingli, and Secura Bio; participates in scientific advisory boards for Seagen, Yingli Pharma, and Secura Bio; and participates in BioCure Rx’s and Targeted Oncology’s speaker bureaus as a speaker

Dr. Sumanta Pal

- Professor in the Department of Medical Oncology & Therapeutics Research and the Co-Director of the Kidney Cancer Program at City of Hope
- Dr. Pal does not have relevant research disclosures
Leading gene editing company  |  Broad pipeline  |  Best-in-class platform and capabilities

Broad pipeline of *ex vivo* and *in vivo* programs across four franchises: hemoglobinopathies, immuno-oncology, regenerative medicine, and *in vivo* approaches

In position for first BLA/MAA filing for a CRISPR-edited product with exagamglogene autotemcel (exa-cel), formerly known as CTX001™, in β-thalassemia and sickle cell disease

Proof-of-concept for allogeneic CAR-T achieved with CTX110 and CTX130, with >100 patients dosed with CRISPR-edited CAR-T cells across 4 trials

Proven track record of execution with best in-class-class capabilities and state-of-the-art internal GMP manufacturing facility

Preeminent CRISPR technology platform focused on the innovation that matters for transformative medicines
Transforming Medicine Across Four Core Franchises

**Hemoglobinopathies**
Potential BLA/MAA filing for exa-cel in Q4 2022

**Immuno-oncology**
Smart-edited allogeneic immune cells for cancer

**Regenerative Medicine**
Edited, stem cell-derived beta cells for diabetes

**In vivo**
>10 programs using both AAV and LNP approaches

**Platform** (next-generation editing and delivery)
Presenters on Today’s Call

**CRISPR Therapeutics**

- **Samarth Kulkarni, PhD**  
  Chief Executive Officer

- **PK Morrow, MD**  
  Chief Medical Officer

- **Jon Terrett, PhD**  
  Head of Research

- **Ali Rezania, PhD**  
  Head of Regenerative Medicine

**Principal Investigators**

- **Sumanta Pal, MD**  
  Principal Investigator, COBALT-RCC  
  City of Hope

- **Swami Iyer, MD**  
  Principal Investigator, COBALT-LYM  
  University of Texas MD Anderson Cancer Center
<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Samarth Kulkarni, PhD, CEO</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobinopathies</strong></td>
<td>PK Morrow, MD, CMO</td>
<td></td>
</tr>
<tr>
<td><strong>Immuno-oncology</strong></td>
<td>PK Morrow, MD, CMO</td>
<td>Swami Iyer, MD, MD Anderson Cancer Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sumanta Pal, MD, City of Hope</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jon Terrett, PhD, Head of Research</td>
</tr>
<tr>
<td><strong>Q&amp;A</strong></td>
<td></td>
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<tr>
<td><strong>Break (5 minutes)</strong></td>
<td></td>
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<tr>
<td><strong>Regenerative medicine</strong></td>
<td>Ali Rezania, PhD, Head of Regenerative Medicine</td>
<td></td>
</tr>
<tr>
<td><strong>In vivo</strong></td>
<td>Jon Terrett, PhD, Head of Research</td>
<td></td>
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<tr>
<td><strong>Conclusion</strong></td>
<td>Samarth Kulkarni, PhD, CEO</td>
<td></td>
</tr>
<tr>
<td><strong>Q&amp;A</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hemoglobinopathies Strategy
PK Morrow, MD, Chief Medical Officer
Exa-cel has a Functionally Curative Profile in SCD & TDT

β-thalassemia

- 42/44 patients with transfusion-dependent thalassemia (TDT) stopped RBC transfusions (duration from 0.8 to 36.2 months)
  - 2 patients had not yet stopped transfusions, but have 75% and 89% reductions in transfusion volume

- 31/31 patients with sickle cell disease (SCD) were VOC-free (duration from 2.0 to 32.3 months)

RBC, red blood cell; VOC, vaso-occlusive crisis. Each row represents an individual patient.

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Exa-cel has a Large Addressable Market

Opportunity to broaden market via innovation in conditioning and delivery

**β-thalassemia**

- Exa-cel addressable market with standard of care conditioning: 7,000
- Exa-cel potential market with targeted conditioning: 16,000
- Potential market with in vivo delivery: 100,000+

**Sickle Cell Disease**

- Exa-cel addressable market with standard of care conditioning: 25,000
- Exa-cel potential market with targeted conditioning: 150,000
- Potential market with in vivo delivery: 350,000+
Advancing an Internal Program in Targeted Conditioning

Attributes of an optimal targeted conditioning agent

- High on-target potency
- Low off-target & systemic toxicity
- Established manufacturing
- Rapid clearance from circulation

Differentiated cKit ADC approach

- Best-in-class cKit mAb
- Well-validated toxin with HSC activity
- Extensive ADC development expertise within CRISPR Therapeutics
Our cKit-ADC has High Potency with Limited Toxicity in NHPs

**cKit-ADC eliminates Kasumi-1 AML xenograft tumor in mice**

![Graph showing tumor volume over days for different treatments.]

- **No treatment**
- **cKit-ADC**
  - 10 mg/kg (IV Days 1, 8, 15)

**Single 13 mg/kg dose of cKit-ADC depletes functional HSCs in non-human primates**

![Graph showing CFU counts in bone marrow aspirate.]

- **Pre-Dose**
- **Day 7**

**No clinically significant toxicities observed** across all doses evaluated thus far, up to 30 mg/kg in NHPs and mice.
Progressing Multiple Approaches to \textit{In Vivo} HSC Editing

AAV

LNP

Targeted LNP

AAV: Adeno-associated virus; LNP: Lipid nanoparticle
POC Established for *In Vivo* Editing of HSCs with AAV

~60% editing of CD34+/CD90+ HSC population in humanized mice

Dual AAV vectors to deliver Cas9 and gRNA

Additionally, preservation of editing in secondary engraftment studies confirms editing of true long-term HSCs
# Hemoglobinopathies 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>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exa-cel: β-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fully enrolled</td>
<td></td>
<td>Collaboration</td>
</tr>
<tr>
<td>Exa-cel: Sickle cell disease (SCD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fully enrolled</td>
<td>VERTEX</td>
<td>Wholly-owned¹</td>
</tr>
<tr>
<td>Next-generation conditioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vivo editing of HSCs</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

1 Collaboration with Vertex for applications in β-thalassemia and SCD
Immuno-Oncology Strategy
PK Morrow, MD, Chief Medical Officer
Jon Terrett, PhD, Head of Research
Significant Progress in the CTX110 Program

RMAT kickoff discussion held to align on key clinical and CMC questions

15+ patients dosed in consolidation cohorts

Up to 30% of eligible patients unable to be infused with autologous CAR-T

Path Forward for BCMA-Directed CAR-T

- Completed CTX120 dose escalation up to Dose Level (DL) 4; 1 subject treated at DL5
- No dose limiting toxicities (DLT) observed, including no CRS above Grade 2 and no ICANS or GvHD, of any grade
- Dose dependent responses seen, but aiming to improve efficacy given competitive context
- Pivot to next-generation allogeneic CAR-T program for multiple myeloma (CTX121)
- Further data disclosure in a future scientific publication
CTX130 – New Biology, Advanced Engineering

**CTX130 Construct**

- Anti-CD70 CAR
- TCR disruption
- MHC I disruption
- CD70 disruption

- **B2M locus**
- **TRAC locus**
- **CD70 locus**

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CD70 – Novel Target with Expression in Multiple Cancers

Member of TNF ligand family involved in T cell activation via cognate receptor CD27

High expression in multiple hematological malignancies, e.g., T cell lymphoma (TCL), DLBCL, and AML

Significant expression in solid tumors, including clear cell renal cell carcinoma (ccRCC), glioblastoma, pancreatic, lung, ovarian, head and neck, and esophageal cancers

Minimal expression on healthy tissues – viability established in clinical studies with ADCs

AML, acute myeloid leukemia; DLBCL, diffuse large B cell lymphoma

### T Cell Lymphoma Represents a Large Unmet Need and Significant Opportunity

<table>
<thead>
<tr>
<th>Indication</th>
<th>Annual U.S. + EU5 Incidence of Patients with CD70 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL - NOS</td>
<td>1800 - 2200</td>
</tr>
<tr>
<td>ALCL</td>
<td>1000 - 1150</td>
</tr>
<tr>
<td>AITL</td>
<td>950 - 1050</td>
</tr>
<tr>
<td>ATLL</td>
<td>300 - 400</td>
</tr>
<tr>
<td>Advanced MF / SS</td>
<td>1500 - 2300</td>
</tr>
</tbody>
</table>

Total annual U.S. + EU5 addressable market is 5000 – 7000 patients per year

PTCL-NOS: Peripheral T Cell Lymphoma – Not Otherwise Specified; ALCL: Anaplastic Large Cell Lymphoma; AITL: Angioimmunoblastic T cell Lymphoma; ATLL: Adult T cell Leukemia/Lymphoma; MF / SS: Mycosis Fungoides / Sezary Syndrome

Sources: SEER database 2021; KOL analysis; Office of National Statistics 2021; Eurostat 2021
### COBALT-LYM Patient Demographics and Pharmacokinetics

#### Patient characteristics, All Dose Levels n = 18

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>65 (39 – 78)</td>
</tr>
<tr>
<td>ECOG PS at screening, n (%)</td>
<td>0: 8 (44); 1: 10 (56)</td>
</tr>
<tr>
<td>Prior lines of therapy, median n (range)</td>
<td>4 (1 – 8)</td>
</tr>
<tr>
<td>TCL subtype, n (%)</td>
<td>PTCL: 8 (44); AITL: 3 (17); ALCL: 1 (6); ATLL: 3 (17); PTCL - NOS: 1 (6); CTCL (MF, SS, tMF): 10 (56)</td>
</tr>
<tr>
<td>Skin involvement, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Blood involvement, n (%)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>CD70 expression level, median % (range)</td>
<td>90 (20 – 100)</td>
</tr>
<tr>
<td>Second CTX130 infusion received, n (%)</td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

#### Pharmacokinetics, All Dose Levels n = 18

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak expansion concentration ($C_{max}$)*†, geometric mean copies/µg (range)</td>
<td>80.9 (&lt;4.9 – 61,349.8)</td>
</tr>
<tr>
<td>Time to peak expansion ($T_{max}$)†, median days (range)</td>
<td>8.5 (5 – 14)</td>
</tr>
</tbody>
</table>

* For summary statistics of $C_{max}$, values below the limit of detection (LOD) were imputed as half the LOD and values below the limit of quantification (LOQ) were imputed as (LOQ+LOD)/2.
† From Screening to D28 post infusion. † Includes first infusions only.

---

**Data cutoff date:** 26 April 2022

**Presented at the European Hematology Association Annual Meeting. 11 June 2022**
### Adverse Events of Interest, N (%)

<table>
<thead>
<tr>
<th></th>
<th>DL1 3x10⁷ N=4</th>
<th>DL2 1x10⁸ N=4</th>
<th>DL3 3x10⁸ N=5</th>
<th>DL4 9x10⁸ N=5</th>
<th>DL≥3 N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 1-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr ≥3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>1 (25)</td>
<td>-</td>
<td>4 (80)</td>
<td>-</td>
<td>8 (80)</td>
</tr>
<tr>
<td>ICANS</td>
<td>-</td>
<td>-</td>
<td>3 (60)</td>
<td>-</td>
<td>3 (30)</td>
</tr>
<tr>
<td>GvHD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infections</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>2 (40)</td>
<td>3 (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

All events listed in table are treatment-emergent adverse events. CRS, cytokine release syndrome; DLT, dose-limiting toxicity; EBV, Epstein-Barr virus; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; LDC, lymphodepleting chemotherapy; SAE, serious adverse events; TLS, tumor lysis syndrome

- Acceptable safety profile across all DLs: no DLTs or instances of TLS with LDC or CTX130
- Treatment-emergent (TE) SAEs occurred in 10/18 (56%) patients and included Gr ≥3 infections (n=4, 22%), Gr 1-2 tumor hemorrhage, Gr ≥3 syncope, Gr ≥3 presyncope, Gr ≥3 HLH, Gr ≥3 drug eruption, and Gr 1-2 ligament sprain (n=1 each, 6%). With exception of one Gr 3 infection, all other TE SAEs were not found to be related to CTX130
- There was a sudden death in 1 patient with William’s syndrome in the context of a lung infection, deemed unrelated to CTX130
- Three cancers were diagnosed in patients with CTCL post treatment: 1 patient had EBV-associated lymphoma which resolved and a squamous cell carcinoma, 1 patient had invasive ductal breast carcinoma which was resected and cured. These were deemed unrelated to CTX130
70% ORR and 30% CR Rate at DL3 and Above

### Best overall response, n (%)

<table>
<thead>
<tr>
<th>Cell dose (CAR+ T cells)</th>
<th>DL1 3x10^7 N=4</th>
<th>DL2 1x10^8 N=4</th>
<th>DL3 3x10^8 N=5</th>
<th>DL4 9x10^8 N=5</th>
<th>DL≥3 N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td>2 (50)</td>
<td>0</td>
<td>3 (60)</td>
<td>4 (80)</td>
<td>7 (70)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>1 (25)</td>
<td>0</td>
<td>2 (40)*</td>
<td>1 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>1 (25)</td>
<td>0</td>
<td>1 (20)</td>
<td>3 (60)</td>
<td>4 (40)</td>
</tr>
<tr>
<td><strong>Disease Control Rate (DCR = CR + PR + SD)</strong></td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>5 (100)</td>
<td>4 (80)</td>
<td>9 (90)</td>
</tr>
</tbody>
</table>

### Disease Control Rate (DCR = CR + PR + SD)

<table>
<thead>
<tr>
<th></th>
<th>PTCL</th>
<th>CTCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL≥3 N=5</td>
<td>Total N=8</td>
</tr>
<tr>
<td>ORR</td>
<td>4 (80)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (40)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (40)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>DCR</td>
<td>4 (80)</td>
<td>5 (63)</td>
</tr>
</tbody>
</table>

*1 patient in DL3 who initially achieved a PR was re-infused at DL4 following a change to SD and achieved a CR at DL4.

CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; DCR, disease control rate; DL, dose level; ORR, overall response rate; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022
CTCL Responses Observed Across All Compartments

*Day 7 assessment; †Initially unconfirmed CR, later confirmed to be PR by mSWAT and biopsy.
CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; SD, stable disease

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022
Clinically Meaningful Responses with CTX130

AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T cell leukemia/lymphoma; CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; SD, stable disease

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022
Opportunity to Change the Paradigm in T Cell Lymphomas

Opportunity for CTX130 in TCL

- Significant unmet need with limited treatment options in both PTCL & CTCL
- CTX130 has demonstrated high ORR with multi-compartment response and a tolerable safety profile
- Re-dosing can deepen responses and further improve durability
- Given high unmet need, potential path to accelerated approval

CTX130 has higher response rates than existing therapies

<table>
<thead>
<tr>
<th></th>
<th>CTX130 DL ≥ 3 N = 5</th>
<th>Vorinostat N = 74</th>
<th>Mogamulizumab N = 186</th>
<th>Romidepsin N = 96</th>
<th>Brentuximab vedotin (CD30+) N = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (ORR), N (%)</td>
<td>3 (60%)</td>
<td>22 (30%)</td>
<td>52 (28%)</td>
<td>33 (34%)</td>
<td>31 (65%)^2</td>
</tr>
<tr>
<td>Complete response (CR), N (%)</td>
<td>1 (20%)</td>
<td>1 (1%)</td>
<td>5 (3%)</td>
<td>6 (6%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CTX130 DL ≥ 3 N = 5</th>
<th>Pralatrexate N = 109</th>
<th>Belinostat N = 120</th>
<th>Brentuximab vedotin (CD30+ ALCL only) N = 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (ORR), N (%)</td>
<td>4 (80%)</td>
<td>32 (29%)</td>
<td>31 (26%)</td>
<td>50 (86%)</td>
</tr>
<tr>
<td>Complete response (CR), N (%)</td>
<td>2 (40%)</td>
<td>12 (11%)</td>
<td>13 (11%)</td>
<td>33 (57%)</td>
</tr>
</tbody>
</table>

RCC has Large Unmet Need and Significant Addressable Population

Renal Cell Carcinoma (RCC)

- Significant worldwide burden
- High morbidity and mortality
- Poor response rates to current therapies
- High potential opportunity

50K US
45K EU5

Annual incidence
18%
40%
80%

5-year survival for stage IV
Primary refractory
CD70 expression in RCC

Patient Baseline Characteristics and Safety in COBALT-RCC

Patient characteristics

<table>
<thead>
<tr>
<th>All Dose Levels, N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Stage IV at screening, n (%)</td>
</tr>
<tr>
<td>Prior treatments, median n (range)</td>
</tr>
<tr>
<td>CD70 expression level, median % (range)</td>
</tr>
</tbody>
</table>

Adverse Events of Interest, N (%)

<table>
<thead>
<tr>
<th>All Dose Levels, N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable safety profile across all dose levels to date, including no DLTs</td>
</tr>
<tr>
<td>No instances of tumor lysis syndrome, infusion reactions, HLH, ICANS, GvHD or secondary malignancies occurred</td>
</tr>
<tr>
<td>7 (50%) patients had Gr 1-2 CRS; no Gr ≥ 3 CRS events</td>
</tr>
<tr>
<td>3 patients with SAEs related to CTX130; all were CRS events</td>
</tr>
<tr>
<td>3 patients with SAEs of infections, all found to be unrelated to CTX130, including a pneumonia with Gr 5 dyspnea resulting in death</td>
</tr>
</tbody>
</table>

CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; SAE, serious adverse events

Data cutoff: May 2022
Evidence of Activity for CTX130 in RCC – a First for Allogeneic Cell Therapy in Solid Tumors

<table>
<thead>
<tr>
<th>Cell dose (CAR+ T cells)</th>
<th>DL1 3x10^7 N=3</th>
<th>DL2 1x10^8 N=3</th>
<th>DL3 3x10^8 N=4</th>
<th>DL4 9x10^8 N=4</th>
<th>Total N=14</th>
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<tr>
<td>Overall response rate</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Stable disease</td>
<td>2 (67)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>4 (100)</td>
<td>10 (71)</td>
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<tr>
<td>Disease Control Rate (DCR = CR + PR + SD)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>4 (100)</td>
<td>11 (79)</td>
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</table>

- One patient with complete response has maintained their CR through their most recent visit at M18
- Typical PK seen with peak time to expansion at a median of D10 and peak concentration of ~3500 copies/µg
- Encouraging results underscore the potential of further increasing potency
Subject Overview

Patient profile
- 64-year-old male with clear cell RCC diagnosed in 2017
- 1 prior line of therapy with cabozantinib and atezolizumab
- Relapsed after PR with lesions in the lung and pleura
- CD70+ expression: 100% at baseline

Efficacy
- PR at D42 after a single infusion of 3x10^7 CAR+ T cells
- CR at M3 and remains in CR at M18

Safety
- Only Gr 1-2 adverse events
- No AEs considered related to CTX130
Executing on Our Immuno-oncology Strategy

Validate

- Our allogeneic platform with proven targets
  - Proof of concept with CTX110, showing durable complete remissions with allogeneic CAR-T

Expand

- From hematologic cancers into solid tumors
  - Promising data with CTX130 in TCL
  - 1st activity in solid tumors with allogeneic CAR-T

Unlock

- The full potential of I/O cell therapy with next-gen edits and targets
  - 2nd-generation programs with novel potency edits
  - Novel targets, including via collaborations with top cancer centers
Autologous and allogeneic CAR-T trial data suggest initial depth of response, rather than CAR-T persistence, matters most for durability

**CTX110**
Durable complete responses after a single dose

**Yescarta**
Patients have durable responses even though CAR-T cells are undetectable by 3 months

**Early MRD negativity**
Correlated with durable responses

**Carvykti**
mDOR of 21.8 months even though 79% of patients have undetectable CAR-T cells by 6 months

Optimal Potency Edits Identified Via Systematic Screening

High-throughput CRISPR screening identified synergistic potency edits

**Regnase-1 KO:** removes intrinsic “brake” on T cell function

**TGFBR2 KO:** removes key extrinsic “brake” on T cell anti-tumor activity

Only Regnase-1 + TGFBR2 KO CAR-T cells can eliminate a difficult tumor re-challenge model.
CTX131 eliminates three different xenograft tumor models in succession without exhaustion

Tumor 1: NCI-H1975 (Lung)
Tumor 2: Rechallenge 1 with ACHN (RCC)
Tumor 3: Rechallenge 2 with Caki-1 (RCC)

n=5 mice per group

CTX131 Shows Enhanced Potency
We expect to advance two next-generation constructs to IND by end of 2022: CTX131 and CTX112 targeting CD70 and CD19, respectively.

Superior performance of CTX131 over CTX130 in an RCC (Caki-2) xenograft model

- CTX130: 0.1M cell dose cannot regress tumors
- CTX131: 0.1M cell dose clears tumors
- CTX130: 1M cell dose clears tumors

2nd-Gen Edits Enhance Potency ~10x Over 1st-Gen
Developing Base Editors for CAR-T Programs with 7+ Edits

Large-scale screen to identify proprietary base editor to enable 7+ edits for 3rd-generation CAR-T

Promising new APOBEC1 candidates for cytosine base editors identified from natural world screening

High base editing rates achieved to generate multiplexed CAR-T cells

- Control (Rat)
- Mammal 1
- Mammal 2
- Mammal 3
- Mammal 4
- Mammal 5
- Mammal 6
- Mammal 7
- Mammal 8
- Mammal 9
- Mammal 10
- Yeast
- Reptile

Editing (%) (flow cytometry)

- CAR KI
- Gene 1 KO
- Gene 2 KO
- Gene 3 KO
Building on Our Success in Advancing Novel Targets

CD70, our first novel CAR-T target for lymphomas and solid tumors, validated through our COBALT trials.

We have prioritized additional novel targets with the potential to address a variety of cancers, pairing them with our next-generation edits.

We’re accelerating clinical validation of these targets with autologous and allogeneic platforms through collaborations with leading cancer centers.
Collaborations with Top Cancer Centers on New Targets

**Clinical trial to begin in next 12 months**

- First-in-human trial for autologous CAR-T therapy targeting CD83

  **CD83:** Expressed on certain cancers and activated T cells – potential in AML and other oncology and autoimmune indications

- Additional research in collaboration with the Masonic Cancer Center, University of Minnesota

**IND-enabling studies to begin this year**

- Initial trial for gene-edited, autologous CAR-T therapy targeting GPC3

  **GPC3:** Solid tumor target for hepatocellular carcinoma (HCC) with limited expression in healthy tissues – potency edits have potential to enhance CAR-T activity against solid tumors

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Cancer centers conduct viral vector manufacturing, cell manufacturing, and Phase I trial

CRISPR retains commercial rights
# Robust Early and Late Stage I/O Pipeline

<table>
<thead>
<tr>
<th>Program</th>
<th>Generation</th>
<th>Research</th>
<th>IND-enabling</th>
<th>Clinical</th>
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</table>

1 CRISPR retains commercial rights

Allogeneic

Autologous
Questions
Regenerative Medicine Strategy
Ali Rezania, PhD, Head of Regenerative Medicine
Combining Breakthroughs in Gene Editing and Stem Cells

Enables a new class of cell replacement therapies for both rare and common diseases

Pluripotent stem cell technology
CRISPR gene editing
Potential Functional Cure for T1D via Beta Cell Replacement

Cadaveric islet transplant has curative efficacy in T1D

Gene edited stem cells can enable broad applicability

- Off-the-shelf, pluripotent stem cell-derived scalable source of cells
- Multiplex genome editing to avoid need for long-term immunosuppression and improve fitness and functionality

Not scalable due to scarcity of islet tissue

Requires chronic immunosuppression

First in the clinic with a gene-edited cell replacement approach for T1D

Multi-staged Product Strategy

Perforated Device Approach
- Progenitor cells (stage 4)
- Retrievable, enabling broader initial patient population

Deviceless approach
- Immature \( \beta \)-cells (stage 6)
- Portal vein injection

210
- Entered clinic Nov 2021
- Safety and immune evasion
- Informs 211 trial design

211
- Two additional edits to promote cell survival
- CTA filing planned for 2H22

212
- Unencapsulated, stage 6 cell aggregates containing additional edits beyond 211
- Research stage program
VCTX211 – Further Optimized for Cell Fitness

**VCTX211 has 2 gene KOs and 4 insertions to improve functionality**

### Immune evasion

- **MHC-I KO** eliminates T cell mediated rejection
- **PD-L1 KI** reduces immune rejection, particularly from T cells
- **HLA-E KI** further reduces immune rejection, particularly from NK cells

### Cell fitness

- **Thioredoxin interacting protein (TXNIP) KO** protects from oxidative and ER stress
- **A20 (TNFAIP3) KI** induces graft acceptance and protection from cytokine induced apoptosis
- **MANF KI** enhances β cell proliferation and protection against inflammatory stress

Edited Cells Evade Immunity *In Vitro* and *In Vivo*

**Adaptive** – T cells do not respond to 211 cells *in vitro*

![Graph showing T cell proliferation](image)

**Innate** – 211 cells resist NK attack *in vitro*

![Graph showing cells killed](image)

**Adaptive & Innate** – 211 cells survive in humanized mouse model

![Graph showing luminescence](image)

Demonstrates broad immune evasive potential of 211 cells – humanized mouse model contains human DC, B cells, T cells, NK cells, and monocytes
VCTX211 Edits Improve Stimuli-Responsive Insulin Production

- Increased insulin production
- Robust glucose responsiveness
- Preserved insulin sensitivity

Assessed 12 weeks post-transplant
Robust Engraftment of VCTX211 in Nude Rat Model

Presence of cells demonstrates abundance of β-cells and avoidance of innate immune rejection

Device membrane

H&E section of VCTX211 in nude rats at 24 weeks show vascularization

Blood vessels

Cells shows favorable differentiation with a β/α ratio of approximately 2

Insulin/Glucagon

PD-L1

Retention of PD-L1 expression in long-term grafts
VCTX211 Reverses Hyperglycemia in Diabetic Rat Model

Normalization of blood glucose by 12-16 weeks

Insulin Treatment

Control (no STZ) vs. STZ

Blood glucose (mg/dL)

Weeks after transplant

Treated rats maintain glucose sensitivity

Serum C-peptide (pM)

Fasted vs. 90 min post glucose

Rats either treated with STZ ~4 weeks before VCTX211 implantation or untreated (normoglycemic control)

STZ: Streptozotocin (β-cell toxin)
# Regenerative Medicine Pipeline

<table>
<thead>
<tr>
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In Vivo Strategy

Jon Terrett, PhD, Head of Research
Our *In Vivo* Focus is on Disruption and Whole Gene Correction

Whole gene correction & gene disruption are needed to cover 90% of monogenic diseases

Editing approach required to address more than ~1/3 of the patient population with a single therapy for the 100 most prevalent severe monogenic diseases

- **Gene disruption**
  - Examples: TTR, HAE
- **Single nucleotide correction**
  - Example: A1AT
- **≤100 base pair correction**
  - Example: Tyrosinemia type 1
- **Whole gene correction**
  - Examples: Hemophilia

---

1. 100 most prevalent severe monogenic diseases addressable by somatic gene editing, excluding systemic diseases
Becoming an *In Vivo* Leader – Our Strategy

- Establish a leading platform for *in vivo* gene disruption, starting in the liver
- Leverage our translational capabilities and balance sheet to advance a broad portfolio of disruption programs across both rare and common diseases
- Establish a leading whole gene correction platform, using AAV LNP and starting in the liver
- Advance whole gene correction to an HDR-independent, AAV-free methodology
Established a Leading mRNA/LNP Platform for Gene Disruption

Dose-dependent liver editing up to 70% in NHPs

70+% editing in whole liver typically equates to 90+% hepatocyte editing and reduction in serum protein levels

Single intravenous dose of LNP formulated with Cas9 mRNA and gRNA
Advancing a Broad Portfolio of Gene Disruption Programs

- Leverage CRISPR’s translational capabilities, balance sheet, and plug-and-play nature of LNP/mRNA
- Advance multiple programs to NHP PoC stage, select programs proceed to clinical development
- Wholly-owned *in vivo* portfolio creates opportunities for partnership as well as internal development

**Cardiovascular**
- ANGPTL3
- Lp(a)
- PCSK9
- Other undisclosed targets

**Other liver targets**
- HAE
- TTR
- PH1
- Other undisclosed targets

**Ocular**
- Undisclosed targets
ASCVD Programs – Proven Benefit in a Once-and-Done Format

- **CTX310 – ANGPTL3**: Proven benefit based on natural human genetics (similar to BCL11A) and antibody / small RNA therapeutics
- **CTX320 – Lp(a)**: Paradigm shift possible with single-dose, potentially lifetime durable editing approach
- **CTX330 – PCSK9**: Development paths starting with severe disease, and expanding to much larger patient populations
- Potential for combination therapy across the 3 targets

ASCVD: Atherosclerotic Cardiovascular Disease

© 2022 CRISPR Therapeutics
CTX310: Potentially Transformative for Cardiovascular Disease

~90% reduction in serum ANGPTL3 protein in NHPs

>50% reduction in serum triglycerides at one month

Progressing CTX310 program to the clinic in 2023

-56%
-84%
-89%
CTX320: Lp(a) is Emerging as an Ideal Target for ASCVD

Coronary artery disease risk increases with increasing Lp(a) level

>90% reduction in serum Lp(a) in NHPs

Unlocking Whole Gene Correction and Insertion

**AAV + LNP**

- Proven technologies allow whole gene correction via repair mechanisms at specific loci
- Potential for improved consistency and durability compared to episomal gene transfer via AAV
- Ability to address majority of monogenic diseases, where mutations span the length of the gene

**Next-generation technologies**

- Dedicated internal group focused on emerging technologies to allow HDR-independent and/or AAV-free whole gene correction/insertion
- Natural systems require further optimization of efficiency and specificity for clinical application
- Research ongoing focused on non-viral DNA delivery and all-RNA systems

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Whole Gene Insertion/Correction: Novel Safe Harbor Loci

**Gene expression can be optimized by targeting different loci**

Different transgenes require different insertion loci to achieve desired therapeutic effect

**Normal levels of FVIII activity can be achieved in NHPs**

LNP for CRISPR machinery + AAV for transgene
<table>
<thead>
<tr>
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Partnered on several disease areas, including Duchenne muscular dystrophy (DMD), myotonic dystrophy type 1 (DM1), and cystic fibrosis (CF)
Advancing the Broadest Gene Editing Platform

**Hemoglobinopathies**
Targeted conditioning & *in vivo* editing to enable the next phase of exa-cel

**Immuno-oncology**
Optimal edits & targets to unlock CAR-T in solid tumors

**Regenerative Medicine**
Multi-gen approach to unleash the combined power of editing & pluripotent stem cells

**In vivo**
Proven translational capabilities plus robust LNP platform for rare & common diseases

**Platform** (enabling whole gene correction)
Questions