Creating transformative gene-based medicines for serious diseases

Corporate Overview | Q3 2023
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CRISPR Therapeutics Highlights

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

Historic first BLA and MAA filings for a CRISPR-edited product with exagamglogene autotemcel (exa-cel), formerly known as CTX001, in transfusion-dependent β-thalassemia and severe 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

Several catalysts upcoming across each franchise
Transforming Medicine Across Four Core Franchises

**Hemoglobinopathies**
BLAs accepted and MAA validated for exa-cel

**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)
## Our Pipeline

<table>
<thead>
<tr>
<th>Program</th>
<th>Research</th>
<th>IND-enabling</th>
<th>Clinical</th>
<th>Marketed</th>
<th>Partner</th>
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(1) Collaboration with Vertex for applications in β-thalassemia and SCD; (2) CRISPR retains commercial rights; (3) Partnered with Vertex on several additional disease areas, including DMD, DM1, and CF
Potential Functional Cure with Exa-Cel

Historic first BLA and MAA filings for a CRISPR-based medicine – BLAs accepted for severe SCD (Priority Review) and transfusion-dependent β-thalassemia (TDT) (Standard Review); PDUFA target action date of December 8, 2023, for SCD and March 30, 2024, for TDT; MAA filed and validated in the EU and UK

Exa-cel could address >30K patients in the U.S. and EU with severe SCD and TDT if approved

Opportunity to expand the market even further with targeted conditioning and in vivo editing

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<tr>
<th>Program</th>
<th>Research</th>
<th>IND-enabling</th>
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(1) Collaboration with Vertex for applications in β-thalassemia and SCD
Participants who achieved Ti12 had durable transfusion independence with normal mean Hb. The 3 who did not achieve Ti12 had substantial benefit: 1 stopped transfusions 14.5 months post-infusion; 2 had significant reductions in transfusion volume (80% and 96%)

42 of 44 (95.5%) participants with >3.5 months of follow-up stopped RBC transfusions (duration 2.9-40.7 months)

Participants who achieved VF12 had a duration of VOC-free of 13.1-36.5 months. All remained VOC-free through follow-up, except 1 who had a VOC in the setting of a parvovirus infection 22.8 months after exa-cel infusion, fully recovered, and has been VOC-free since

1 participant with multiple complex comorbidities, including a history of chronic pain, did not achieve VF12 but achieved HF12
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+
Robust Early and Late Stage I/O Pipeline

- **Allogenic platform allows immediate “off-the-shelf” dosing**, alleviating the complex supply barriers associated with approved autologous cell therapies

- **Potentially registrational trial underway for CTX110**

- **Positive data in T cell lymphomas and the first signs of meaningful activity in solid tumors with CTX130**

- **Next-generation candidates in the clinic with potency edits** to improve tumor killing capacity and resistance to suppression

- **State-of-the-art internal GMP manufacturing facility**

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(1) CRISPR retains commercial rights
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
Multiplex CRISPR gene editing in one step designed to:

- **Improve persistence in the allo setting** via β2M knock-out to eliminate MHC I expression
- **Avoid need** for more toxic lymphodepletion regimens
- **Prevent GvHD** via TCR disruption
- **Improve consistency and safety** by precise insertion of CAR construct into TRAC locus without using lentivirus or retrovirus

CTX112, CTX130, and CTX131 utilize the *same CRISPR-edited allogeneic T cell design, but with additional editing* (including CD70 knock-out and use an anti-CD70 CAR in the case of CTX130 and CTX131)
Unlocking the Market with CTX110

Only ~23% of 3L+ R/R DLBCL patients receive autologous CAR-T

Opportunity to address larger share of patients with off-the-shelf administration and positively differentiated safety profile

~8,500 3L+ R/R DLBCL patients in U.S.

44% referred for CAR-T

23% receive CAR-T

Factors affecting eligibility
- ECOG performance status
- Patient comorbidities
- Response to bridging/prior therapy

Reasons for not receiving autologous CAR-T
- Condition deterioration
- Side effect management
- Unexpected manufacturing delays
- Patient refusal/discomfort with AE profile
- Treating physician deeming patient ineligible

~15% of patients apheresed cannot wait the time required for manufacturing

Sources: SEER 2021; Globocan; Sehn & Salles. NEJM. 2021;384(9):842-858; NCCN Guidelines; secondary research
CARBON: Part A Trial Design

**Key eligibility criteria**
- Age ≥18 years
- Relapsed/refractory non-Hodgkin lymphoma, as evidenced by 2+ lines of prior therapy
- ECOG performance status 0 or 1
- Adequate renal, liver, cardiac, and pulmonary organ function
- No prior allogeneic SCT or treatment with CAR-T therapy

**Primary endpoints**
- Incidence of adverse events, defined as DLTs
- ORR

**Key secondary endpoints**
- CR rate, DoR, and OS

For Part B: patients received CTX110 at DL4 following standard LD, as well as a consolidation dose of CTX110 at the same dose level 4-8 weeks after the initial dose for patients that demonstrate clinical benefit.
CARBON only enrolled patients with aggressive LBCL:

- **High burden of disease** with significant baseline tumor volume
- Both relapsed and refractory patients, including primary refractory patients that had no prior response to any anti-cancer therapy
- **History of rapidly progressive disease**, including patients who had progressed through 2+ lines of therapy and received CTX110 within 9 months of their first lymphoma treatment

<table>
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<th>N (%) (unless otherwise noted)</th>
<th>All Dose Levels N=32</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
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<td>Female</td>
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<td>13 (41)</td>
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<td>1</td>
<td>19 (59)</td>
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<td>Refractory disease</td>
<td>17 (53)</td>
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<td>Prior anticancer therapies</td>
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<td>Median prior therapies, n (range)</td>
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<td>≥3 prior therapies</td>
<td>15 (47)</td>
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<td>Prior stem cell transplant</td>
<td>11 (34)</td>
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<td>NHL subtype, n (%)</td>
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<td>DLBCL, NOS</td>
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<td>High-grade LBCL</td>
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<td>Baseline SPD &gt;50 cm²</td>
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<td>Baseline LDH &gt; ULN</td>
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*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3
†1 patient in DL1 had Richter’s transformation of CLL, 1 patient in DL3 had both Grade 3b follicular lymphoma and germinal center B-cell like-DLBCL, and 1 patient at DL4 had Grade 3b follicular lymphoma
CARBON: CTX110 Showed Encouraging Efficacy in Part A

- 3 patients have achieved and maintained a CR for more than 24 months†
- 6-month CR rate of 19% with single infusions of CTX110 (5/27)
- Unlike autologous CAR-T, almost all enrolled patients received treatment with CTX110: just 2/34 enrolled patients not treated due to intercurrent infections (COVID-19 and pneumonia)

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<th>Best response per 2014 Lugano criteria¹</th>
<th>≥1 infusion at DL≥3* N=27</th>
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<tr>
<td>Overall response rate (ORR) N (%)</td>
<td>18 (67%)</td>
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<tr>
<td>Complete response (CR) rate N (%)</td>
<td>11 (41%)</td>
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*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3; †2 patients as of the data cutoff and 3 patients as of ASH 2022

Data cutoff date: 6 October 2022
*PET CT identified a single new small FDG avid node located in the left upper arm. The lesion was completely excised. The patient remained clinically well and required no subsequent anti cancer therapy including no steroids, no radiotherapy and no chemotherapy;  **On the Month 9 scan, the PET CT identified unspecific localized small FDG uptake in the right upper arm. The patient did not have subsequent surgery nor anticancer therapy, and the lesion spontaneously resolved

Data cutoff date: 6 October 2022
CARBON: CTX110 Well Tolerated in Part A

Positively differentiated safety profile with CTX110:

- No DLTs, no GvHD or infusion reactions of any grade, and no Grade ≥3 CRS observed

- Grade ≥3 infections occurred in 13% of patients, including 1 patient who died with HHV6 encephalitis, and 1 infection considered possibly related to CTX110

- 7 patients experienced serious AEs attributed to CTX110, which included CRS, ICANS, and febrile neutropenia

- No change in the overall safety profile for patients who received a second infusion of CTX110 (N=13)

Adverse events (AEs) of interest, N (%)

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<td>GvHD</td>
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<td>Infections</td>
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All events listed in table are treatment-emergent adverse events. CRS and ICANS graded per ASTCT criteria; other adverse events graded per CTCAE
(1) Cytokine Release Syndrome; (2) Immune Effector Cell-associated Neurotoxicity Syndrome; (3) All infections (bacterial, fungal, and viral) included

Data cutoff date: 6 October 2022
CTX110: Potentially Best-in-Class Allogeneic Cell Therapy

CARBON Part A demonstrates the potential of CTX110

- Initial response rates in line with approved autologous CAR-T therapies: ORR of 67% and CR rate of 41% at DL≥3 in a heavily pre-treated patient population with R/R LBCL

- Potential for long-term durable complete remissions: 3 patients in ongoing CR beyond 2 years

- Positively differentiated safety profile that may support broadening patient access into outpatient and community settings

- RMAT designation granted by the FDA in November 2021

Emerging data from Part B supports advancement to potentially registrational trial

- Encouraging efficacy profile with several patients in ongoing CR beyond 6 months

- Clear evidence of the benefits of consolidation dosing, with deepening of CRs and conversions of stable disease and partial response to ongoing CRs after the second dose

- Safety profile consistent with Part A, confirming the tolerability of the consolidation regimen

- Peak expansion and overall pharmacokinetics comparable between the initial and consolidation doses

Following discussions with regulatory agencies, single-arm, potentially registrational trial of CTX110 initiated with consolidation dosing at DL4 and standard LD
CTX130: 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

Annual U.S. + EU5 incidence of patients with CD70 expression by indication subtype

<table>
<thead>
<tr>
<th>Indication</th>
<th>PTCL - NOS</th>
<th>ALCL</th>
<th>AITL</th>
<th>ATLL</th>
<th>Advanced MF / SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1800 - 2200</td>
<td>1000 - 1150</td>
<td>950 - 1050</td>
<td>300 - 400</td>
<td>1500 - 2300</td>
</tr>
</tbody>
</table>

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

PTCL: Peripheral T Cell Lymphoma; CTCL: Cutaneous T Cell Lymphoma; 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 2021; KOL analysis; Office of National Statistics 2021; Eurostat 2021
**Phase 1 study (NCT04502446) evaluating the safety and efficacy of CTX130 in relapsed or refractory T or B cell malignancies**

**Patient characteristics, All Dose Levels N=18**

<table>
<thead>
<tr>
<th>Parameter</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></td>
</tr>
<tr>
<td>0</td>
<td>8 (44)</td>
</tr>
<tr>
<td>1</td>
<td>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></td>
</tr>
<tr>
<td>PTCL</td>
<td>8 (44)</td>
</tr>
<tr>
<td>AITL</td>
<td>3 (17)</td>
</tr>
<tr>
<td>ALCL</td>
<td>1 (6)</td>
</tr>
<tr>
<td>ATLL</td>
<td>3 (17)</td>
</tr>
<tr>
<td>PTCL - NOS</td>
<td>1 (6)</td>
</tr>
<tr>
<td>CTCL (MF, SS, tMF)</td>
<td>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>

*As assessed by Lugano response criteria for PTCL, International Society for Cutaneous Lymphoma Response Criteria for CTCL. CR, complete response; CTCL, cutaneous T cell lymphoma; LD, lymphodepletion; PD, progressive disease; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease

Data cutoff date: 26 April 2022

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

<table>
<thead>
<tr>
<th></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>Gr 1-2</td>
<td>1 (25)</td>
<td>4 (80)</td>
<td>1 (25)</td>
<td>4 (80)</td>
<td>8 (80)</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>4 (80)</td>
<td>8 (80)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ICANS</td>
<td>-</td>
<td>3 (60)</td>
<td>-</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>2 (40)</td>
<td>1 (20)</td>
<td>1 (20)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

- All events listed in table are treatment-emergent adverse events.
- CRS, CR, cytokine release syndrome; DLT, dose-limiting toxicity; EBV, Epstein-Barr virus; 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 – except for one Gr 3 infection, all other TE SAEs were deemed unrelated 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 – these were deemed unrelated to CTX130

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COBALT-LYM: 70% ORR and 30% CR Rate at DL3 and Above

<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>

*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.
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
COBALT-LYM: CTCL Responses 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
COBALT-LYM: 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
RCC: Large Unmet Need and Significant Addressable Population

Renal Cell Carcinoma (RCC)

- Significant worldwide burden
  - Annual incidence
    - 50K US
    - 45K EU5

- High morbidity and mortality
  - 18% 5-year survival for stage IV

- Poor response rates to current therapies
  - 40% Primary refractory

- High potential opportunity
  - 80% CD70 expression in RCC

COBALT-RCC: Durable Complete Response with CTX130

Case Study

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

Deepening of response over time

Screening
Day 42
Month 18
Advancing Next-generation Allogeneic CAR-T Candidates

Next-generation allogeneic CAR-T chassis with additional potency edits:

- **Regnase-1**: Removes intrinsic “brake” on T cell function
- **Increases functional persistence, cytokine secretion/sensitivity, and effector function on tumors**
- **TGFBR2 KO**: Removes key extrinsic “brake” on T cell anti-tumor activity
- **Reduces tumor microenvironment inhibition of multiple CAR-T cell functions**

CTX112 and CTX131, our next-generation CD19 and CD70 targeting therapies, utilize this chassis
Regnase-1 and TGFBR2 Knock-Outs Work Synergistically

- No TGF-β mediated inhibition
- Increased proliferation
- Broad cytokine secretion
- Increased cytotoxicity
- Repeat response to antigen challenge

Figure created using BioRender
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)

Single dose CAR-T

Tumor Volume (mm$^3$)

No treatment

CTX131: CTX130 + Regnase-1 KO + TGFBR2 KO

n=5 mice per group
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

Cancer centers conduct viral vector manufacturing, cell manufacturing, and Phase I trial
CRISPR retains commercial rights
CRISPR gene editing and pluripotent stem cell technology enable a new class of cell replacement therapies

Developing a beta-cell replacement product that aims to treat diabetes without requiring immunosuppression in partnership with ViaCyte – gene editing key to achieve this goal

Clinical trial initiated for VCTX211, which includes novel edits to promote cell survival – CRISPR platform enables continuous innovation with next-generation products incorporating incremental edits to increase benefit

<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>
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<tbody>
<tr>
<td>VCTX210: Type I diabetes mellitus</td>
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<tr>
<td>VCTX211: Type I diabetes mellitus</td>
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<td>Enrolling</td>
<td>ViaCyte</td>
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<td>VCTX212: Type I/II diabetes mellitus</td>
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</tbody>
</table>
Multi-staged Product Strategy

Perforated Device Approach
- Entered clinic Nov 2021
- Safety and immune evasion
- Informs 211 trial design

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

210
- Progenitor cells (stage 4)
- Retrievable, enabling broader initial patient population

211
- Two additional edits to promote cell survival
- CTA cleared in 2H 2022

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*

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

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

Demonstrates broad immune evasive potential of 211 cells – humanized mouse model contains human DC, B cells, T cells, NK cells, and monocytes
VCTX211 Reverses Hyperglycemia in Diabetic Rat Model

Normalization of blood glucose by 12-16 weeks

Blood glucose (mg/dL)

- Control (no STZ)
- STZ

Weeks after transplant

Insulin Treatment

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

STZ: Streptozotocin (β-cell toxin)

Treated rats maintain glucose sensitivity

Serum C-peptide (pM)

- 12 wk
- 16 wk
- Fasted
- 90 min post glucose
In Vivo Platform Advancing Rapidly

- 90% of the most prevalent severe monogenic diseases only addressable with gene disruption and/or whole gene correction
- Established plug-and-play LNP/mRNA platform for *in vivo* gene disruption, starting in the liver
- Developing a multi-modal whole gene correction platform, starting with AAV+LNP in the liver and advancing to AAV-free, HDR-independent methodologies
- Advancing a broad portfolio across both rare and common diseases leveraging our translational capabilities and balance sheet

<table>
<thead>
<tr>
<th>Program</th>
<th>Research</th>
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<th>Clinical</th>
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<th>Structure</th>
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<tr>
<td>Disruption or deletion</td>
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<td>CTX310: ANGPTL3</td>
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<td>Undisclosed CV programs</td>
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<td>Wholly-owned</td>
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<td>Other gene disruption programs</td>
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<td>Collaboration</td>
</tr>
</tbody>
</table>

Partnered with Vertex on several additional disease areas, including Duchenne muscular dystrophy (DMD), myotonic dystrophy type 1 (DM1), and cystic fibrosis (CF)
Becoming an *In Vivo* Leader – Our Strategy

**Focus on disruption and whole gene correction – needed to address ~90% of the most prevalent severe monogenic diseases**

- Establish a leading platform for *in vivo* gene disruption, starting in the liver
- Advance a broad portfolio of programs across both rare and common diseases, leveraging our translational capabilities, balance sheet, and plug-and-play LNP/mRNA platform
  - Targets/indications include ANGPTL3, Lp(a), PCSK9, HAE, TTR, PH1, and other undisclosed ocular and liver targets
  - Wholly-owned portfolio creates opportunity for internal development or partnership
- Develop leading whole gene correction platform, starting with AAV+LNP in the liver and advancing to AAV-free, HDR-independent methodologies
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
ASCVD Programs: Proven Targets in a Once-and-Done Format

- CTX310 – ANGPTL3
  - Proven benefit based on natural human genetics (like 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
CTX310: Potentially Transformative for Cardiovascular Disease

~90% reduction in serum ANGPTL3 protein in NHPs

>50% reduction in serum triglycerides at one month

N=8 per group

Change from baseline (%) vs Days

- Control
- 0.5 mg/kg
- 1.5 mg/kg
- 3 mg/kg

-56%
-84%
-89%

Change from baseline (%) vs mg/kg

- Control
- 0.5 mg/kg
- 1.5 mg/kg
- 3 mg/kg

-100
-80
-60
-40
-20
0
-100
-80
-60
-40
-20
0
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

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

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
Strong U.S. and Global Foundational IP Position

**United States**

- **CVC granted patents of broad scope; multiple applications progressing**
  - 55 Patents of broad scope granted
  - 16 Additional patent applications moving forward in parallel with both broad and narrow claims
  - PTAB decision in CVC/Broad interference appealed to the CAFC; interferences between CVC/Sigma, CVC/ToolGen, Broad/Sigma and Broad/ToolGen put “on hold” by PTAB

**Europe and Global**

- **CVC granted foundational patents, including use in eukaryotes**
  - 46 Patents of broad scope granted in the EU, Canada, China, Japan, Brazil, Mexico, Singapore, Hong Kong, Ukraine, Israel, UAE, Australia, New Zealand, South Africa, etc.
  - ~80 Jurisdictions worldwide in which CVC has patent protection
  - In August, CVC prevailed against ToolGen’s challenge to CVC’s Japanese patent; challenges pending in China and India

CVC: Charpentier, University of California, and University of Vienna

As of Q3 2023

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Building a Great Company

EXPERIENCED Management Team

END-TO-END CAPABILITIES with ~450 employees

COLLABORATIVE & ENTREPRENEURIAL culture

~$1.8 BILLION cash balance

INTERNAL MANUFACTURING in state-of-the-art GMP facility