Creating transformative gene-based medicines for serious diseases

Corporate Overview | Q4 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 approval of a CRISPR-based gene-editing therapy** with CASGEVY™ (exa-cel), now approved in the U.S. for certain eligible patients with sickle cell disease.

- **Next-generation allogeneic CAR T programs, CTX112 and CTX131,** advancing in the clinic with potency edits to improve tumor killing capacity and resistance to suppression.

- **Proven track record of execution** with best in-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**

First approval of a CRISPR-based gene-editing therapy in the world\(^1\)

**Immuno-oncology**

Next-generation edited allogeneic immune cells for cancer

**Regenerative Medicine**

Edited, stem cell-derived beta cells for diabetes

**In vivo**

>10 programs using both LNP and AAV approaches

**Platform** (next-generation editing and delivery)

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(1) CASGEVY approved by the U.S. FDA for certain eligible patients with SCD and granted conditional marketing authorization from the UK MHRA and Bahrain NHRA for certain eligible patients with SCD or TDT in Q4 2023
Our Pipeline

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(1) Currently approved in some countries for certain eligible patients with SCD or TDT; (2) Collaboration with Vertex for applications in SCD and β-thalassemia; (3) Initiation of additional trial in systemic lupus erythematosus planned for 1H 2024; (4) CRISPR retains commercial rights; (5) Partnered with Vertex on several additional disease areas, including DMD, DM1, and CF
Potential Functional Cure with CASGEVY (exa-cel)

**CASGEVY (exagamglogene autotemcel [exa-cel]) approved by the U.S. FDA** for the treatment of SCD in eligible patients 12 years and older with recurrent vaso-occlusive crises, and **granted conditional marketing authorization from the UK MHRA and Bahrain NHRA** for certain eligible patients with SCD or TDT in Q4 2023.

**U.S. FDA PDUFA target action date of March 30, 2024, for TDT (Standard Review);** MAA for SCD and TDT filed and validated in the EU.

**CASGEVY could address >30K patients** in the U.S. and EU with severe SCD and TDT if approved, with the **opportunity to expand the market even further** with targeted conditioning and **in vivo editing**.

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Exa-cel: Groundbreaking Data Across >95 Patients

**TDT: Transfusion independence achieved out to 45 months**

Exa-cel treatment resulted in early and sustained increases in Hb and HbF leading to **transfusion independence (TI12)** in 91.4% of patients with TDT, elimination of VOCs (VF12) and inpatient hospitalization for VOCs (HF12) in 96.7% and 100% of patients with SCD, respectively.

* Participant evaluable for the primary endpoint; † participant achieved TI12 (TDT) or VF12 (SCD); § participant did not achieve TI12; # participant did not achieve VF12; ‡ Death from respiratory failure due to COVID-19 infection

Hb, hemoglobin; HbF, fetal hemoglobin; HF12, proportion of participants free from inpatient hospitalization for severe VOCs for ≥12 months; RBC, red blood cell; TI12, proportion of patients transfusion independent for 12 consecutive months while maintaining weighted average Hb ≥9 g/dL; VF12, proportion of participants free of severe VOCs for ≥12 months; VOC, vaso-occlusive crisis

Presented at the American Society of Hematology Annual Meeting. 11 Dec 2023

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**SCD: VOC-free and no in-patient hospitalizations for VOCs achieved out to 45.5 months**
Exa-cel has a Large Addressable Market

Opportunity to broaden market via innovation in conditioning and delivery

**β-thalassemia**
- 100,000+
- 16,000
- 7,000

**Sickle Cell Disease**
- 350,000+
- 150,000
- 25,000

Exa-cel addressable market with standard of care conditioning
Exa-cel potential market with targeted conditioning
Potential market with *in vivo* delivery

Represents estimated number of addressable patients in U.S. and EU
Allogenic platform allows immediate “off-the-shelf” dosing, alleviating the complex supply barriers associated with approved autologous cell therapies.

CTX112 and CTX131 advancing in the clinic: Next-generation CAR T candidates with potency edits to improve tumor killing capacity and resistance to suppression, manufactured at internal GMP facility.

Proof of concept that allogeneic CAR T cells can produce durable complete remissions following a standard lymphodepletion regimen demonstrated by first-generation programs.

### Robust Immuno-Oncology Pipeline

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<td>Anti-GPC3 CAR T</td>
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</table>

(1) Initiation of additional trial in systemic lupus erythematosus planned for 1H 2024; (2) CRISPR retains commercial rights.
Our Gene-Edited Allogeneic CAR T Franchise

**First-generation**

- **Consolidation dosing**
  - Improved 6-month complete response rate

- **Single-dose**
  - PoC that allogeneic CAR T cells can produce durable remissions following a standard LD regimen

**Next-generation with novel potency edits**

- **CTX112 and CTX131**
  - Preliminary clinical data suggest next-gen may improve upon the clinical profile of first-gen
    - Significantly higher CAR T cell expansion and functional persistence
    - Increased manufacturing robustness; manufactured at internal GMP facility
    - Opportunity to expedite development based on clinical and regulatory learnings from CTX110 and CTX130

**Further indications/targets**

- Advancing next-gen candidates in new areas, e.g., CTX112 in autoimmune disease, GPC3-targeted autologous CAR T with Roswell Park, and others in the pipeline
CTX112 and CTX131 Incorporate Novel Potency Edits

Next-generation CRISPR gene-edited allogeneic CAR T chassis:

- **MHC I KO**: Improve persistence in the allogeneic setting and avoid need for more toxic lymphodepletion
- **TGFBR2 KO**: Reduce tumor microenvironment inhibition of multiple CAR T cell functions
- **TCR KO**: Prevent GvHD
- **Regnase-1 KO**: Increase functional persistence, cytokine secretion and sensitivity, and effector function
- **CAR KI**: Site-specific insertion into TRAC locus without using lentivirus

**CTX112 and CTX131 utilize the same CRISPR-edited allogeneic T cell design**, but CTX112 incorporates a CD19-targeted CAR while CTX131 incorporates a CD70-targeted CAR and knock-out of CD70.
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

CAR-T Cell

CRISPR KO of TGFBR2

CRISPR KO of Regnase-1

No TGFBR2

TGFBR1

Increase in mRNAs that Regnase-1 targets

No Regnase-1

Ribosome

Stem Loop

Tumor microenvironment

Figure created using BioRender
Potency edits in CTX112 lead to extended survival in Nalm6-Luc mice

- CTX112: TGFBR2 KO + Regnase-1 KO
- Regnase-1 KO
- TGFBR2 KO
- CTX110
- Untreated

N=15 mice per treated group
N=5 mice for untreated group

Presented at the American Association for Cancer Research Annual Meeting, 16 April 2023
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)

- No treatment
- CTX131: CTX130 + Regnase-1 KO + TGFBR2 KO

N=5 mice per group

Single dose CAR-T

ACHN

Caki-1

Days

Days

Days

Tumor Volume (mm³)
# CTX112 and CTX131 Clinical Trials

## Phase 1/2 safety and efficacy study evaluating CTX112

- Relapsed or refractory B-cell malignancies
- Expanding into autoimmune diseases with planned trial initiation in 1H 2024 in systemic lupus erythematosus (SLE)

## Phase 1/2 safety and efficacy study evaluating CTX131

- Relapsed or refractory solid tumors starting with renal cell carcinoma (RCC)
- Expanding into hematological malignancies

## Indications

- **LD regimen**
  - Standard lymphodepletion regimen of cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) for 3 days

**Allogeneic CAR T enables simplified trial design** with short screening timeframe, no apheresis, no bridging chemotherapy, and on-site availability of CAR T cell product.
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 Enables Regenerative Medicine 2.0

- 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>Approved</th>
<th>Status</th>
<th>Partner</th>
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<td>VCTX212: Type I/II diabetes mellitus</td>
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Multi-staged Product Strategy

**Perforated Device Approach**
- Entered clinic Nov 2021
- Safety and immune evasion
- Informs 211 trial design
- Progenitor cells (stage 4)
- Retrievable, enabling broader initial patient population

**Deviceless approach**
- Unencapsulated, stage 6 cell aggregates containing additional edits beyond 211
- Research stage program
- Immature β-cells (stage 6)
- Portal vein injection

**210**
- Progenitor cells (stage 4)
- Retrievable
- Safety and immune evasion
- Informs 211 trial design

**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
- Immature β-cells (stage 6)
- Portal vein injection
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**

- Control (no STZ)
- STZ

Treated rats maintain glucose sensitivity

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

STZ: Streptozotocin (β-cell toxin)
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

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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

Single intravenous dose of LNP formulated with Cas9 mRNA and gRNA

70+% editing in whole liver typically equates to 90+% hepatocyte editing and reduction in serum protein levels
Our Initial *In Vivo* Programs Could Transform the Treatment Paradigm for ASCVD

<table>
<thead>
<tr>
<th>The chronic care model</th>
<th>A new treatment paradigm</th>
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<tbody>
<tr>
<td>Daily medications</td>
<td>One-time CRISPR-based therapies with the potential to:</td>
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<tr>
<td>Weekly injections</td>
<td>Recapitulate the proven benefit of targets like ANGPTL3, as validated by natural human genetics and other therapeutic modalities</td>
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<tr>
<td>Multiple infusions annually</td>
<td>Improve long-term cardiovascular outcomes by durably lowering atherogenic lipoproteins for a patient’s lifetime</td>
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<tr>
<td>Surgical interventions</td>
<td>Minimize or eliminate the need for additional treatments</td>
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</tbody>
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**Heavy burden for patients and the healthcare system**

14M people with very high CV risk in U.S. and Europe, including ~4M with genetic dyslipidemias

45% not adherent to lipid-lowering therapy despite prior major CV events

82% not at LDL-C target goal

ASCVD: atherosclerotic cardiovascular disease; (1) Gu et al. 2022; (2) Ray et al. 2021; (3) Hu et al. 2020; (4) Dron et al. 2018; (5) Guglielmi et al. 2017
CTX310: A One-Time Dose to Stop Expression of ANGPTL3

Transient expression of Cas9 and sgRNA in hepatocytes to reduce ANGPTL3 expression permanently

Intravenous delivery targeting the liver

CRISPR/Cas9-based editing of ANGPTL3

Reduced atherogenic lipoprotein concentrations

CTX310 consists of Cas9 mRNA and guide RNA (sgRNA) targeting ANGPTL3 encapsulated in lipid nanoparticles (LNPs)

Clinical trial of CTX310 initiated
A Single Dose of CTX310 Resulted in Durable Reduction in ANGPTL3 and Triglycerides in Non-Human Primates

- Sustained reduction in plasma ANGPTL3 at 1 year
- Sustained reduction in TG at 1 year
- ~70% editing of ANGPTL3 at 1 year

Single dose of CTX310 (2 mg/kg) administered to NHPs (N=8) on Day 1; dose levels reflect mg total RNA; study ongoing

Presented at the American Heart Association Scientific Sessions. 11 Nov 2023
Lp(a): An Independent Risk Factor for ASCVD

- Lipoprotein(a): an LDL-like lipoprotein synthesized and secreted by hepatocytes that contains apo(a) bound to ApoB

- The LPA gene encodes apo(a) and determines plasma Lp(a) levels

- Epidemiologic studies, Mendelian randomization, and GWAS have shown that elevated Lp(a) levels increase ASCVD risk, whereas those with low Lp(a) levels (~12.5 nmol/L) have better cardiometabolic outcomes, e.g., 29% reduced risk of coronary heart disease, 37% reduced risk of aortic valve stenosis\(^1,2,3,6,7,8\)

- >20% of the global population have elevated circulating Lp(a) concentrations above ~125 nmol/L\(^4,5\)

\(*A\ one\-time, CRISPR\-based \ therapy \ could \ recapitulate\ the \ protective \ effect \ of \ naturally \ low \ Lp(a) \ levels*

---

Independent association with long-term MACE\(^8\)

![Graph showing cumulative incidence](image)

Adjusted HR for 91st-100th percentile: 1.34, [95% CI 1.16-1.54], \(p<0.001\)

- 1st-50th percentile (0-41 nmol/L)
- 51st-70th percentile (42-111 nmol/L)
- 71st-90th percentile (112-215 nmol/L)
- 91st-100th percentile (>216 nmol/L)

Association of Lp(a) with MACE among individuals with a history of ASCVD, adjusted for age, sex, self-reported race and ethnicity, hypertension, chronic kidney disease status, non-Lp(a) hyperlipidemia, diabetes, insulin use (in diabetic individuals), and smoking status; \(N=10,181\)

---

A Single Dose of CTX320 Resulted in Durable Lp(a) Reduction in Non-Human Primates

- 70% editing of LPA at 1 year
- 95% reduction in plasma Lp(a) sustained at 1 year

Single dose of CTX320 (2 mg/kg) administered to NHPs (N=4) on Day 1; study ongoing

Presented at the American Heart Association Scientific Sessions. 11 Nov 2023
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
Strong U.S. and Global Foundational IP Position

**United States**

- **CVC granted patents of broad scope; multiple applications progressing**
  - Patents of broad scope granted: 55
  - Additional patent applications moving forward in parallel with both broad and narrow claims: 16
  - 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**
  - 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.: 46
  - Jurisdictions worldwide in which CVC has patent protection: ~80
  - 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

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As of Q3 2023
EXPERIENCED management team

BEST-IN-CLASS platform and capabilities

COLLABORATIVE & ENTREPRENEURIAL culture

~$1.75 BILLION cash balance

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

As of Q3 2023