Creating transformative gene-based medicines for serious diseases

Corporate Overview | Q1 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 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

Several catalysts across each franchise in 2023

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Transforming Medicine Across Four Core Franchises

Hemoglobinopathies

MAA for exa-cel filed in the EU and UK[1]

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)

(1) In the U.S., rolling BLA submission began in November and remains on track for completion by the end of Q1 2023

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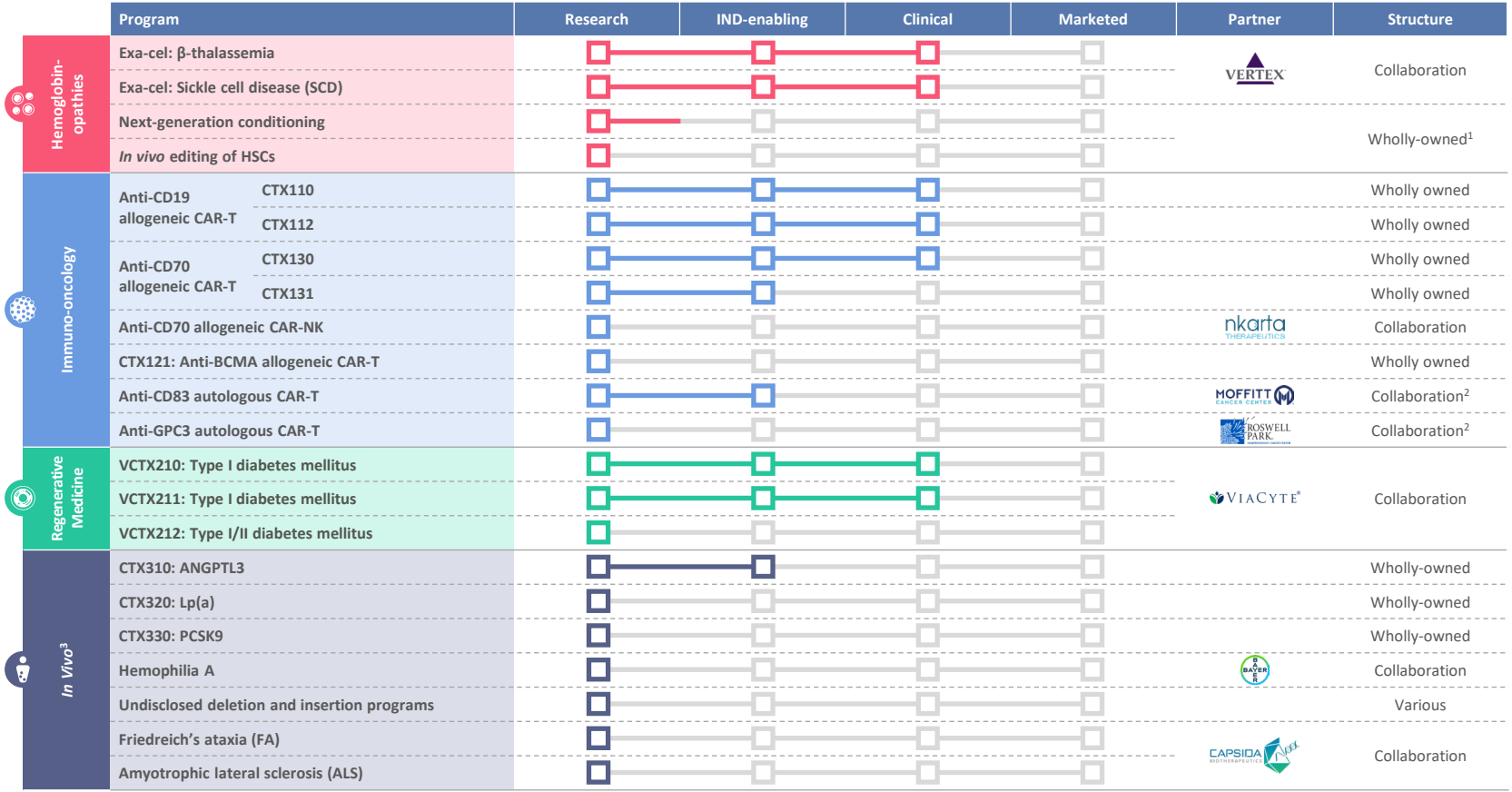
Our Pipeline



(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

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Historic First MAA Filing for a CRISPR-Based Medicine

- **Potential functional cure with exa-cel –** MAA filed in the EU and UK; rolling BLA submission remains on track for completion by the end of Q1 2023
- **Exa-cel could address >30K patients** in the U.S. and EU with severe SCD and β-thalassemia if approved
- **Opportunity to expand the market even further** with targeted conditioning and *in vivo* editing

Program	Research	IND-enabling	Clinical	Marketed	Status	Partner	Structure
Exa-cel: β-thalassemia					MAA filed	VERTEX	Collaboration
Exa-cel: Sickle cell disease (SCD)					MAA filed		
Next-generation conditioning							Wholly-owned[1]
In vivo editing of HSCs							

(1) Collaboration with Vertex for applications in β-thalassemia and SCD

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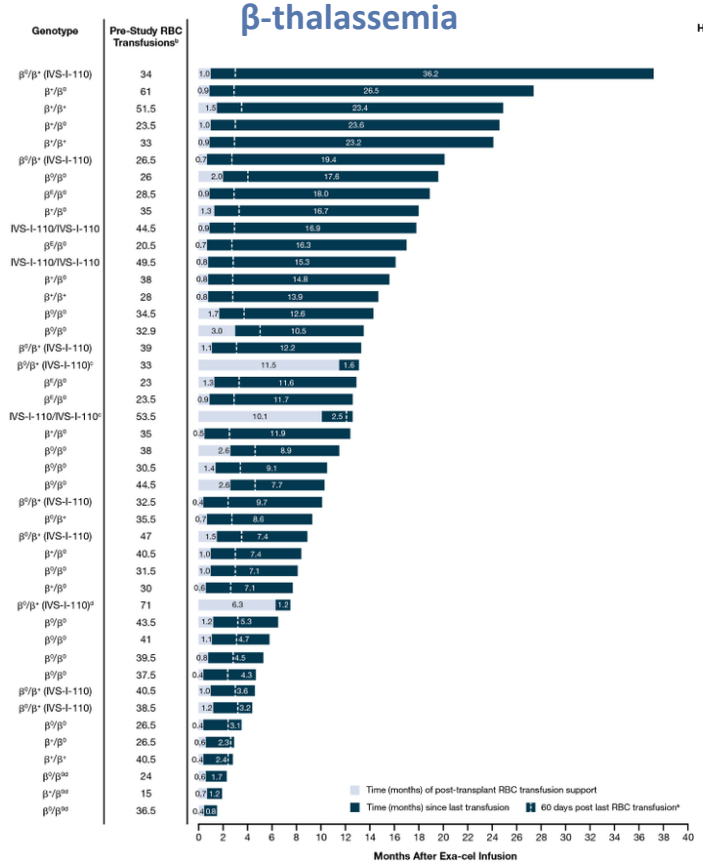
Exa-cel – Groundbreaking Data Across 75 Patients

- **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)



Each row represents an individual patient
RBC, red blood cell; VOC, vaso-occlusive crisis.
[a]Patients are evaluated for elimination of transfusions or VOCs starting 60 days after their last transfusion; [b]Number of transfusion units and pre-study severe VOCs annualized over 2 years; [c]Received RBC transfusions at or after data cut; [d]Patient stopped transfusions after data cut

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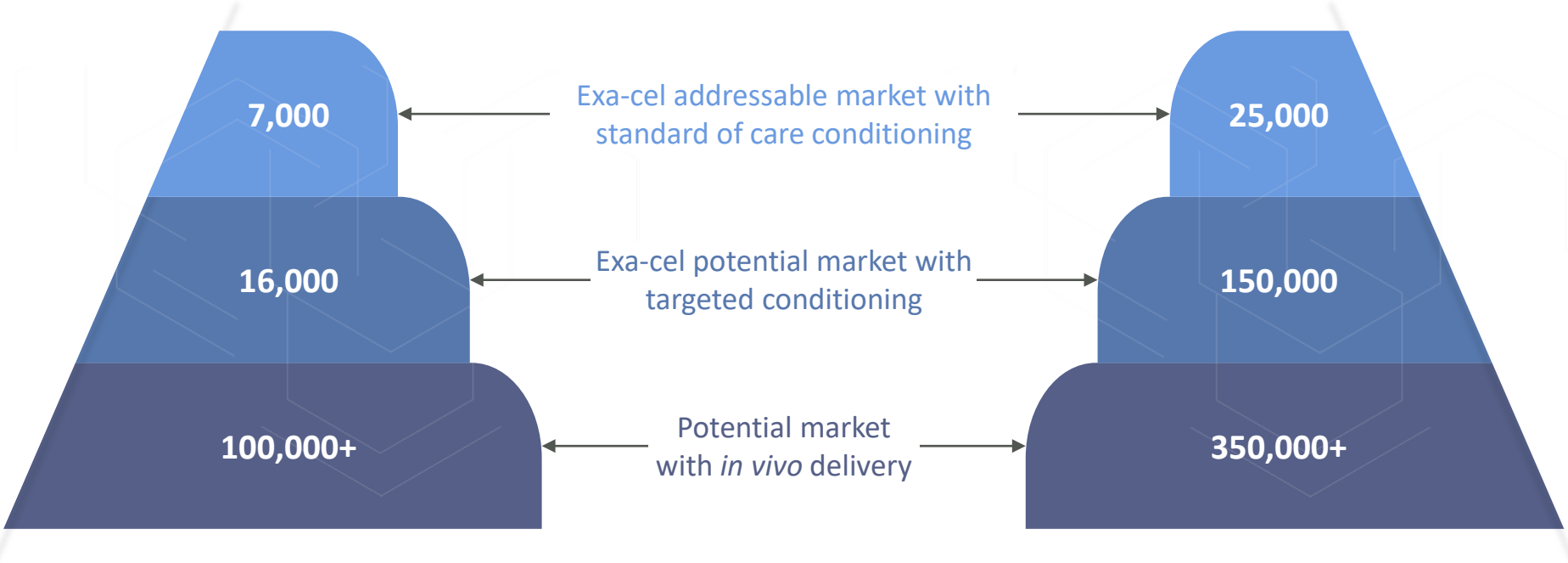
Exa-cel has a Large Addressable Market

Opportunity to broaden market via innovation in conditioning and delivery



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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 products advancing with potency edits** to improve tumor killing capacity and resistance to suppression
- **State-of-the-art internal GMP manufacturing facility**

	Program		Research	IND-enabling	Clinical	Marketed	Status	Partner	Structure
Allo	CD19	CTX110®					Enrolling		Wholly owned
		CTX112™					Enrolling		Wholly owned
	CD70	CTX130™					Enrolling		Wholly owned
		CTX131™							Wholly owned
		Anti-CD70 CAR-NK						nkarta THERAPEUTICS	Collaboration
	Other targets	CTX121™ (anti-BCMA)							Wholly owned
		Other CAR-T programs							Wholly owned
Auto	Novel targets	Anti-CD83 CAR-T						MOFFITT CANCER CENTER	Collaboration[1]
		Anti-GPC3 CAR-T						ROSWELL PARK	Collaboration[1]

(1) CRISPR retains commercial rights

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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

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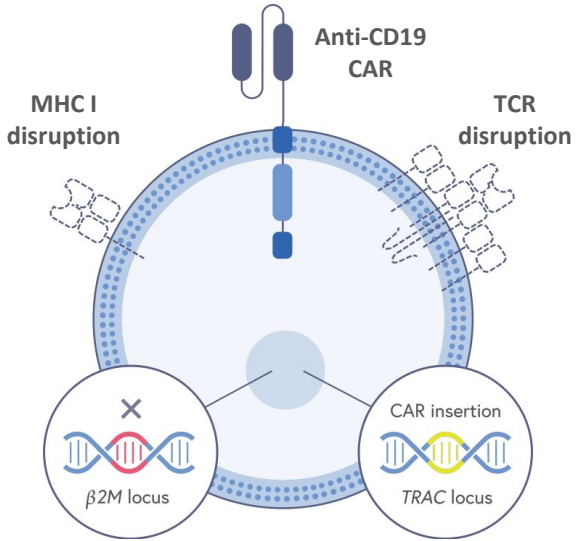
CTX110: Differentiated CRISPR-Edited Allogeneic CAR-T Design

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** (and an anti-CD70 CAR in the case of CTX130 and CTX131)*

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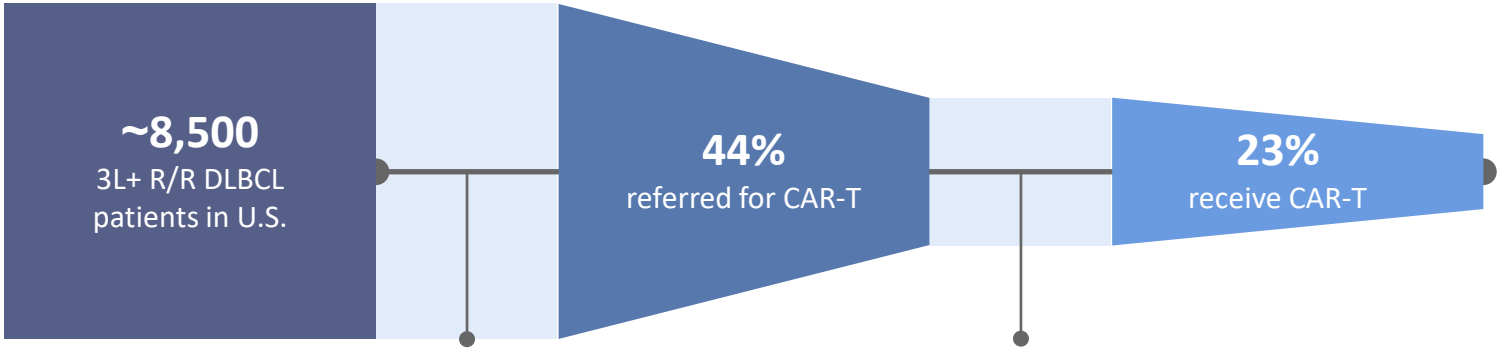
Unlocking the Market with CTX110

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



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
- Treating physician deeming patient ineligible
- Unexpected manufacturing delays
- Patient refusal/discomfort with AE profile

~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

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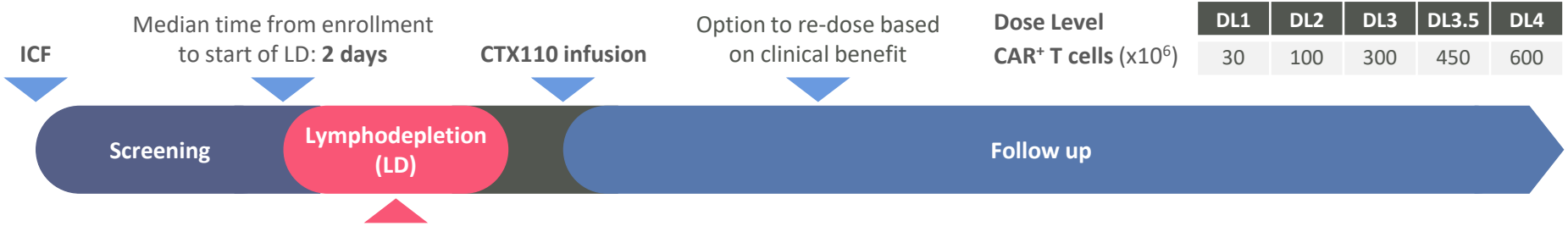
CARBON: Part A Trial Design

CARBON: Single-arm study evaluating the safety and efficacy of CTX110

Allogeneic CAR-T enables simplified trial design:

- Short screening timeframe
- No apheresis
- No bridging chemotherapy
- On-site availability of CAR-T cell product



Dose Level	DL1	DL2	DL3	DL3.5	DL4
CAR+ T cells (x10^6)	30	100	300	450	600

Cyclophosphamide (500 mg/m^2) + **Fludarabine** (30 mg/m^2) for 3 days

NCT04035434

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

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CARBON: Part A Baseline Patient Characteristics

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

N (%) (unless otherwise noted)	All Dose Levels *N=32*
Median age, years (range)	64 (25-75)
Female	10 (31)
ECOG performance status at screening	
0	13 (41)
1	19 (59)
Refractory disease	17 (53)
Prior anticancer therapies	
Median prior therapies, n (range)	2 (2-10)
≥3 prior therapies	15 (47)
Prior stem cell transplant	11 (34)
NHL subtype, n (%)	
DLBCL, NOS	17 (53)
High-grade LBCL	5 (16)
Transformed FL	7 (22)
Other†	3 (9)
Baseline SPD >50 cm^2	11 (34)
Baseline LDH > ULN	17 (53)

*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

Data cutoff date: 6 October 2022

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CARBON: CTX110 Showed Encouraging Efficacy in Part A

Best response per 2014 Lugano criteria[1]	≥1 infusion at DL≥3* *N=27*
Overall response rate (ORR) N (%)	18 (67%)
Complete response (CR) rate N (%)	11 (41%)

- **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)

*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

(1) Cheson, et al. *J Clin Oncol*. 2014;32(27):3059-68.

Data cutoff date: 6 October 2022

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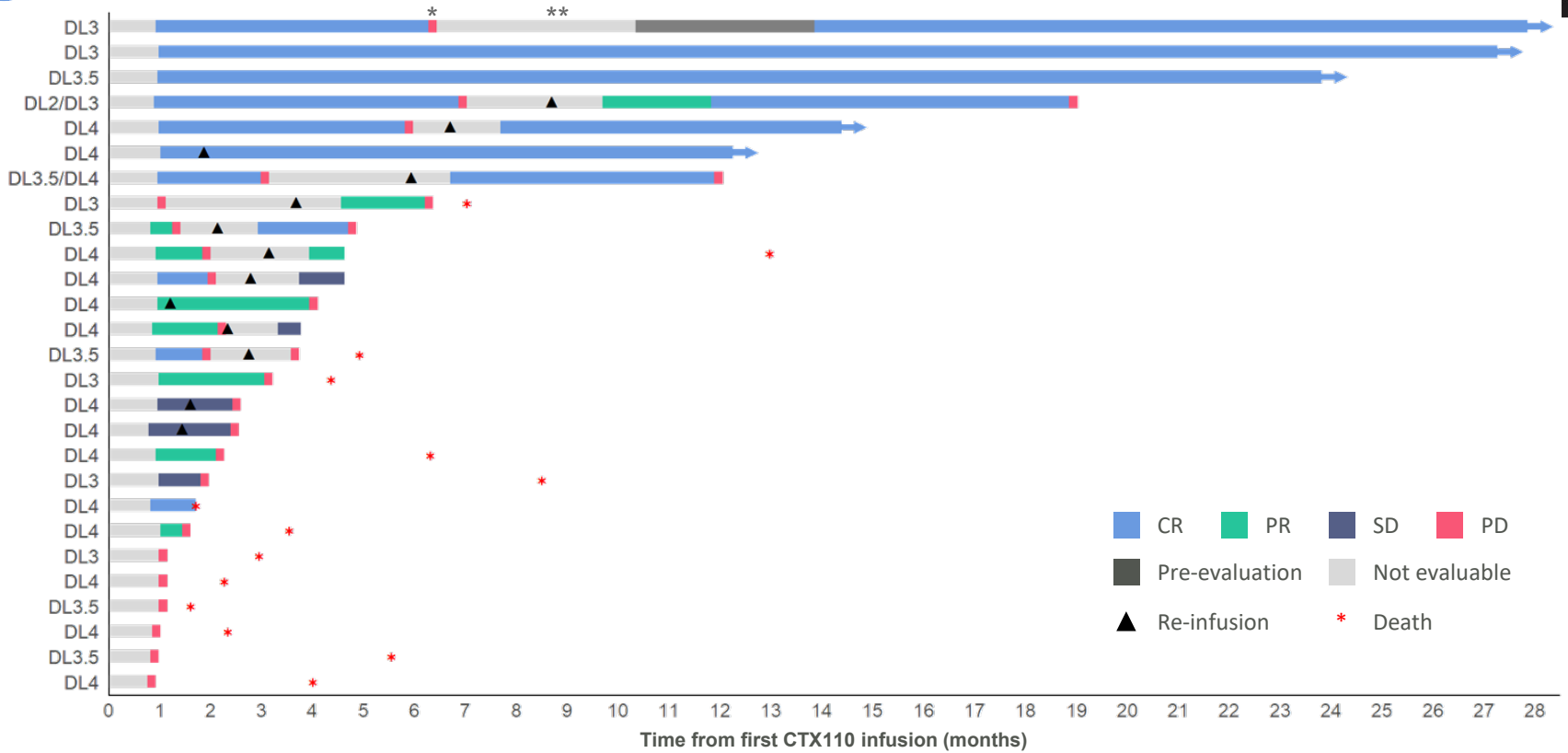
CARBON: Durable Responses Observed with CTX110 in Part A



*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

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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 (%)

	All Dose Levels *N=32*	
	Gr 1-2	Gr 3+
CRS[1]	18 (56)	-
ICANS[2]	1 (3)	2 (6)
GvHD	-	-
Infections[3]	4 (13)	4 (13)

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

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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 – **dosing expected to begin in early 2023** using drug product manufactured with a **commercial-ready process and specifications**

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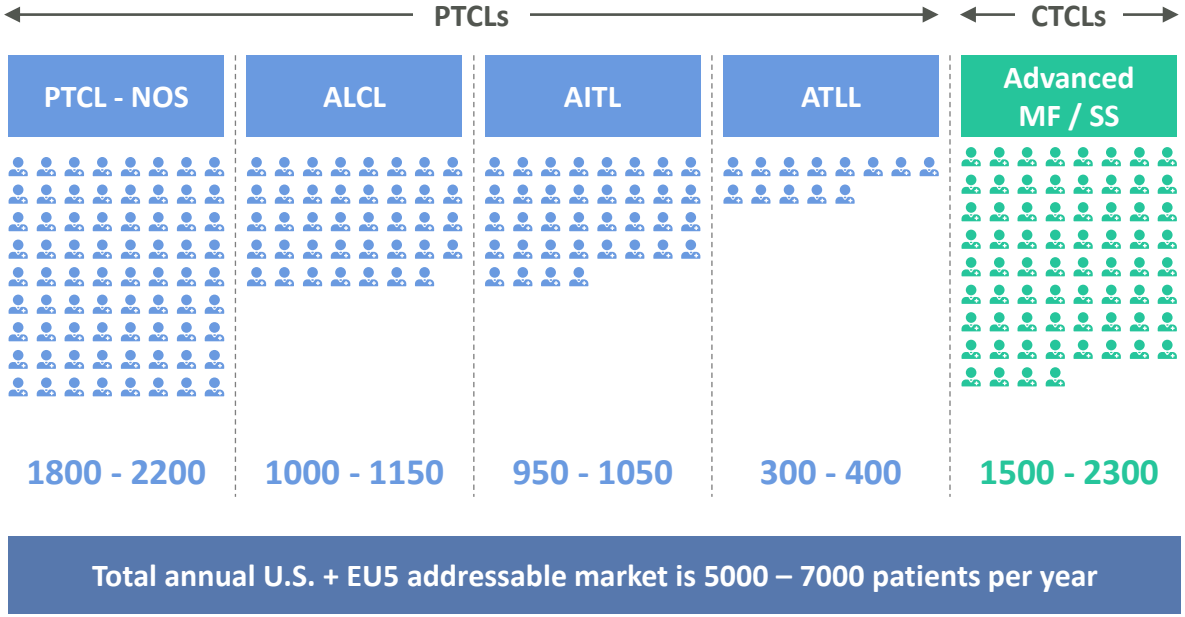
CTX130: Opportunity to Change the Paradigm in T Cell Lymphomas

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



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

PTCL: Peripheral T Cell Lymphoma; CTCL: Cutaneous T Cell Lyphoma; PTCL-NOS: Peripheral T Cell Lymphoma – Not Otherwise Specified; ALCL: Anaplastic Large Cell Lymphoma; AITL: Angioimmunoblastic T cell Lyphoma; ATLL: Adult T cell Leukemia/Lymphoma; MF / SS: Mycosis Fungoides / Sezary Syndrome
Sources: SEER 2021; KOL analysis; Office of National Statistics 2021; Eurostat 2021

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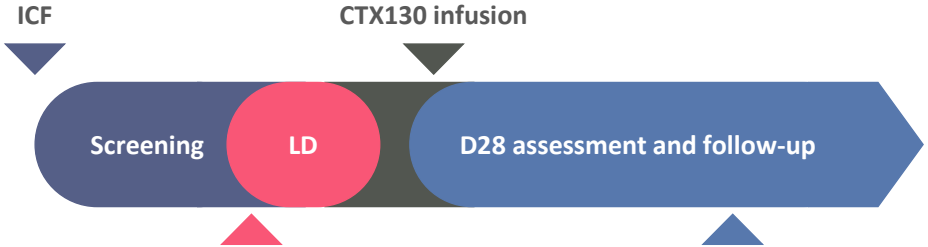
COBALT-LYM: Trial Design and Patient Demographics

Phase 1 study (NCT04502446) evaluating the safety and efficacy of CTX130 in relapsed or refractory T or B cell malignancies



Flu 30mg/m^2 + Cy 500mg/m^2 for 3 days

CTX130 dose levels (CAR+ T cells)

DL1	DL2	DL3	DL4
3×10^7	1×10^8	3×10^8	9×10^8

2nd course of CTX130 can be administered with LD after:

1. Loss of CR within the first 2 years after initial infusion
2. PR, SD, or PD with clinical benefit as determined by the investigator

Patient characteristics, *All Dose Levels N=18*

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

*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

Presented at the European Hematology Association Annual Meeting. 11 June 2022

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COBALT-LYM: CTX130 Safety Profile

Adverse Events of Interest, N (%)

	DL1 $3x10^7$ N=4		DL2 $1x10^8$ N=4		DL3 $3x10^8$ N=5		DL4 $9x10^8$ N=5		DL≥3 N=10	
	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3
CRS	1 (25)	-	1 (25)	-	4 (80)	-	4 (80)	-	**8 (80)**	-
ICANS	-	-	-	-	3 (60)	-	-	-	**3 (30)**	-
GvHD	-	-	-	-	-	-	-	-	-	-
Infections	2 (50)	1 (25)	-	1 (25)	2 (40)	1 (20)	1 (20)	1 (20)	**3 (30)**	**2 (20)**

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

Data cutoff date: 26 April 2022

- **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

Best overall response, n (%)

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

	PTCL		CTCL	
	DL≥3 N=5	Total N=8	DL≥3 N=5	Total N=10
ORR	4 (80)	5 (63)	3 (60)	4 (40)
CR	2 (40)	3 (38)	1 (20)	1 (10)
PR	2 (40)	2 (25)	2 (40)	3 (30)
DCR	4 (80)	5 (63)	5 (100)	8 (80)

*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

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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

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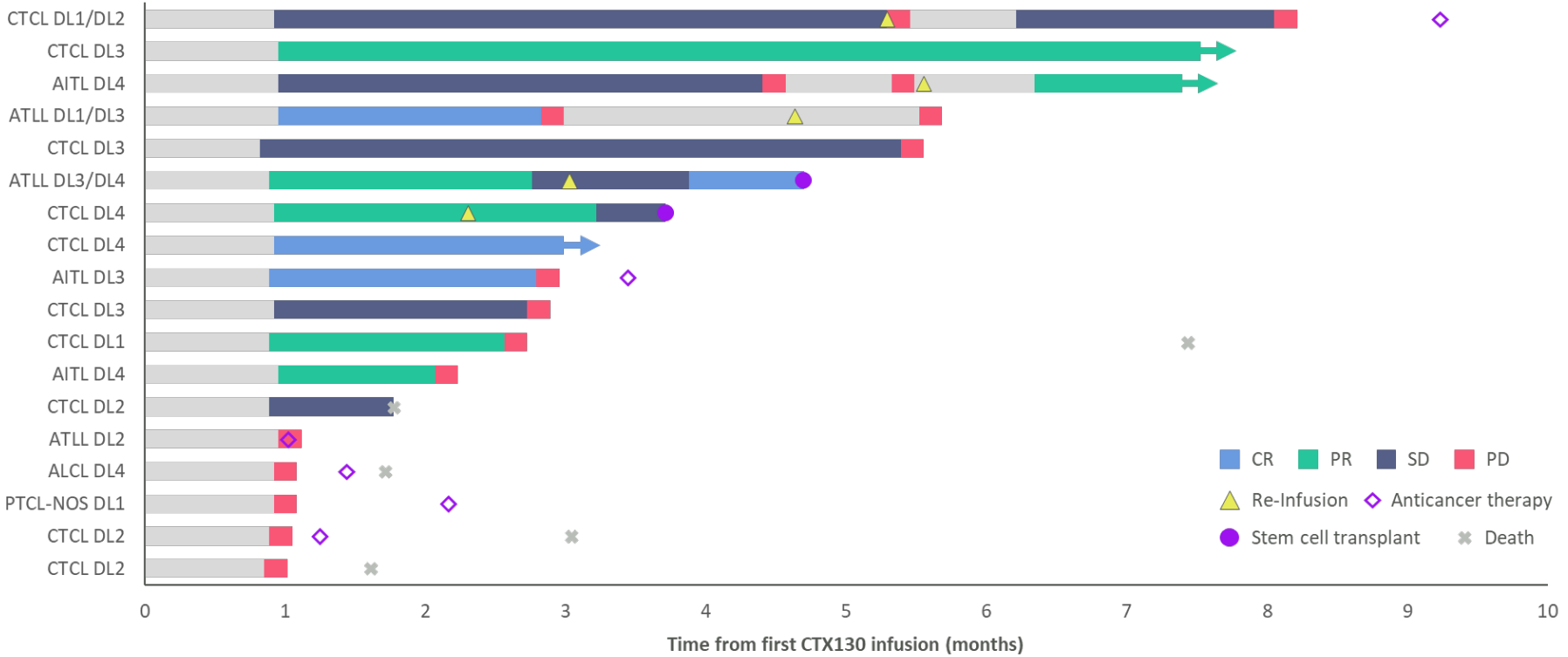
COBALT-LYM: Clinically Meaningful Responses with CTX130



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

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RCC: Large Unmet Need and Significant Addressable Population

Renal Cell Carcinoma (RCC)

Significant worldwide burden

50K US 45K EU5

Annual incidence

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

Sources: SEER 2021; Globocan; WCRFI; ZfKD; Cancer Research UK; Epidemiology of Renal Cell Carcinoma. Powles. *Lancet Oncology*. 2020;21:1563-73. Adam, et al. *Br J of Cancer*. 2006;95(3):298-306.

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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

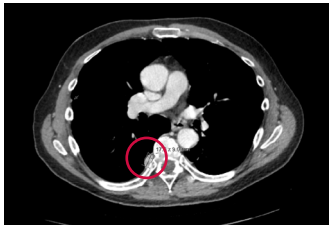
- PR at D42 after a single infusion of $3x10^7$ CAR+ T cells
- CR at M3 and remains in CR at M18

Safety

- Only Gr 1-2 adverse events
- No AEs considered related to CTX130

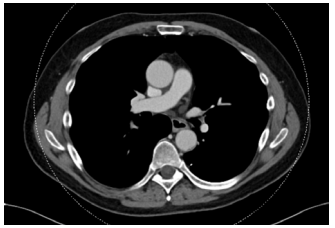
Deepening of response over time

Screening



Day 42

Month 18



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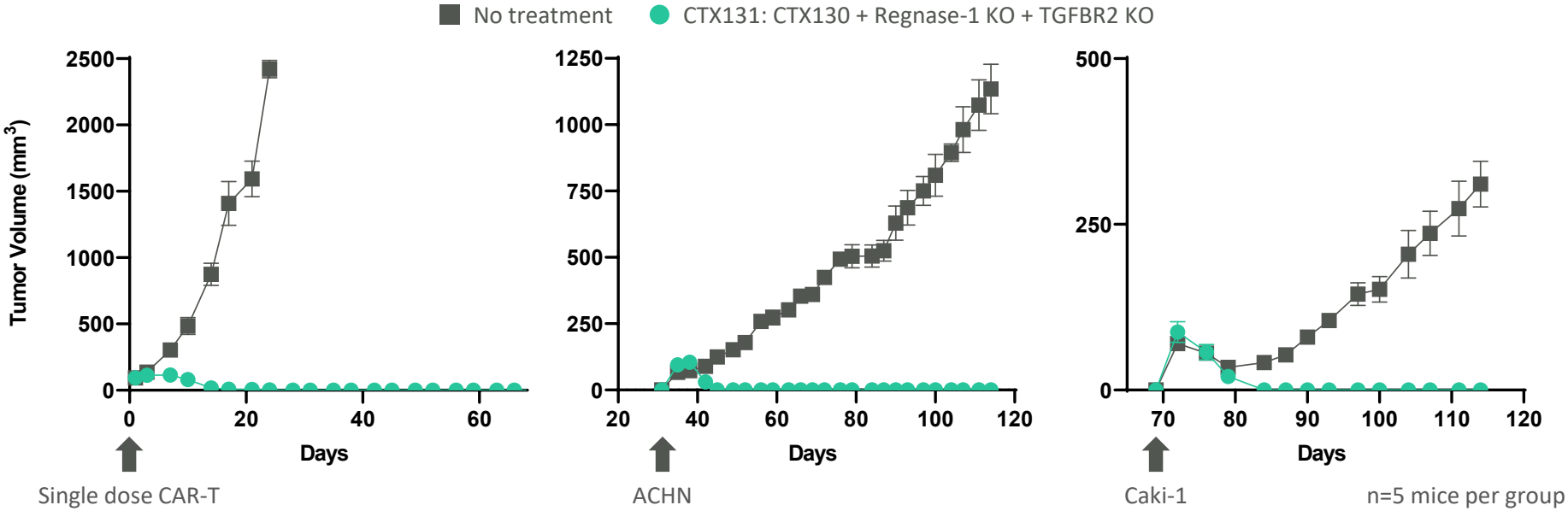
Next-Generation Potency Edits: Regnase-1 and TGFBR2

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 | ACHN | Caki-1 | n=5 mice per group

Two next-generation constructs moving into the clinic:
CTX112 targeting CD19 and CTX131 targeting CD70 in Solid Tumors

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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

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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
- **CTA cleared 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

Program	Research	IND-enabling	Clinical	Marketed	Status	Partner	Structure
VCTX210™: Type I diabetes mellitus					Enrolling		
VCTX211™: Type I diabetes mellitus					Enrolling	ViaCyte®	Collaboration
VCTX212™: Type I/II diabetes mellitus							

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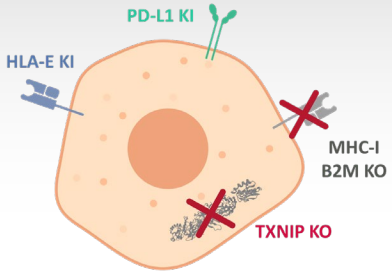
Multi-staged Product Strategy

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

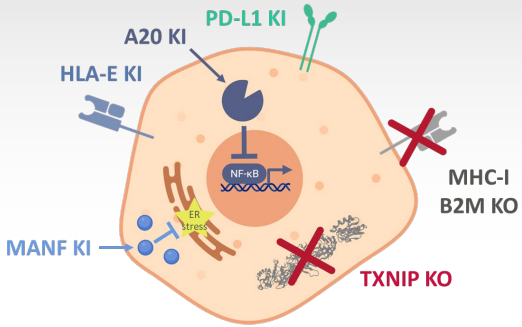
Deviceless approach
- Immature β-cells (stage 6)
- Portal vein injection

210



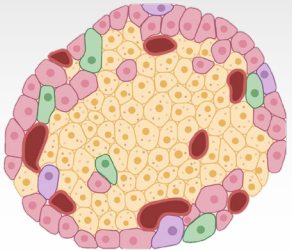
- Entered clinic Nov 2021
- Safety and immune evasion
- Informs 211 trial design

211



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

212



- Unencapsulated, stage 6 cell aggregates containing additional edits beyond 211
- Research stage program

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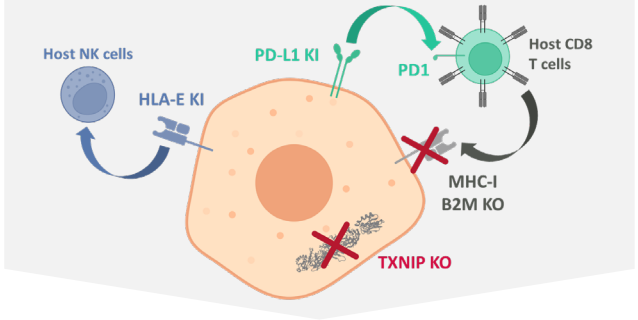
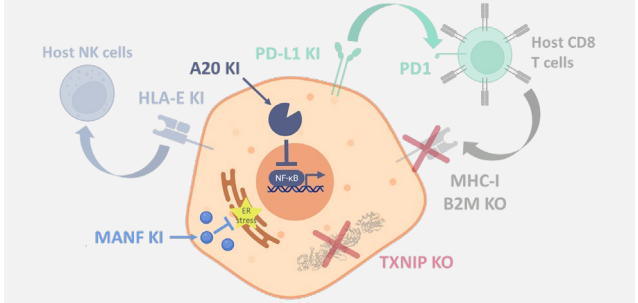
VCTX211: Further Optimized for Cell Fitness

VCTX211 has 2 gene KOs and 4 insertions to improve functionality

VCTX210



VCTX211



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

Sources: Qian, et al. *Immunology*. 1996; 88(1):124-9. Gornalusse, et al. *Nat Biotechnology.* 2017;35(8):765-72. El Khatib, et al. *Gene Therapy*. 2015;22(5):430-8. Chen, et al. *FASEB J.* 2008;22(10):3581-94. Shalev. *Biochem Soc Trans*. 2008;36(5):963-5. Lindahl, et al. *Cell Rep.* 2014;24(7):366-75. Zammit, et al. *JCI Insight.* 2019;4(21).

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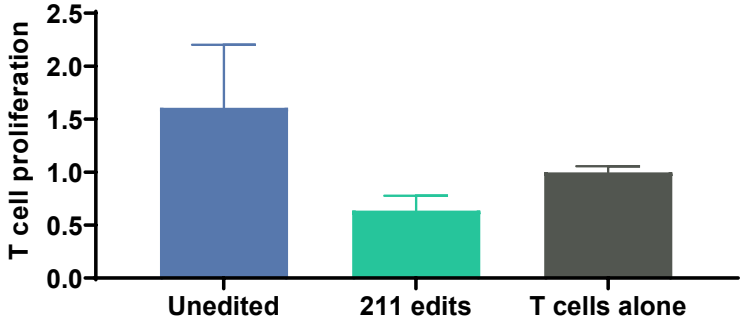
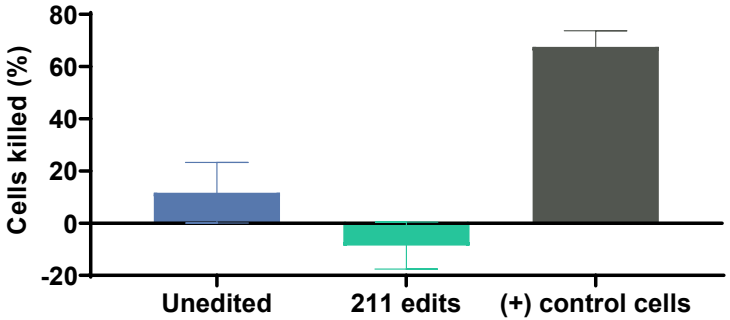
Edited Cells Evade Immunity *In Vitro* and *In Vivo*

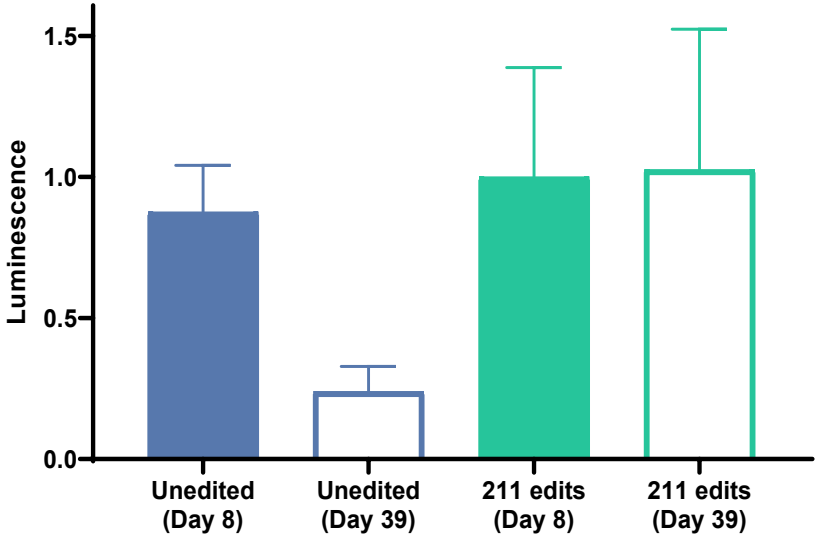
Adaptive – T cells do not respond to 211 cells *in vitro*



Innate – 211 cells resist NK attack *in vitro*



Adaptive & Innate – 211 cells survive in humanized mouse model



Demonstrates broad immune evasive potential of 211 cells – humanized mouse model contains human DC, B cells, T cells, NK cells, and monocytes

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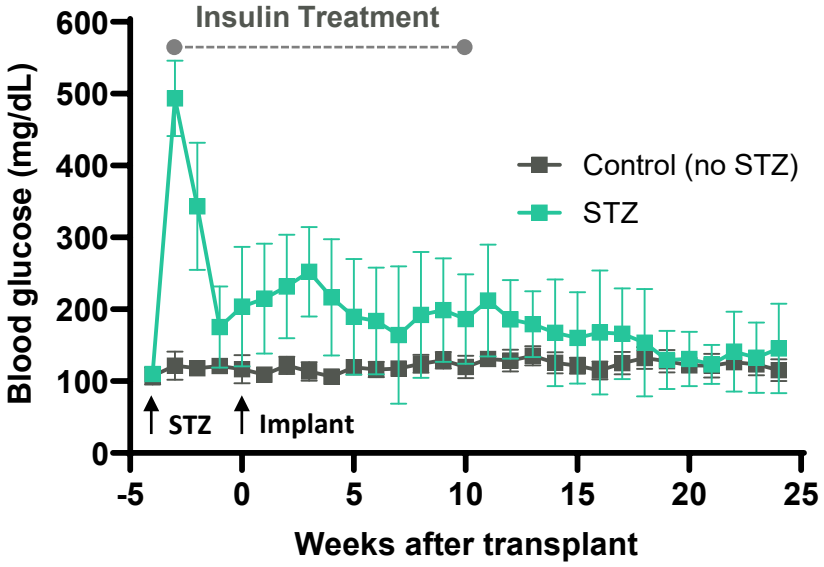
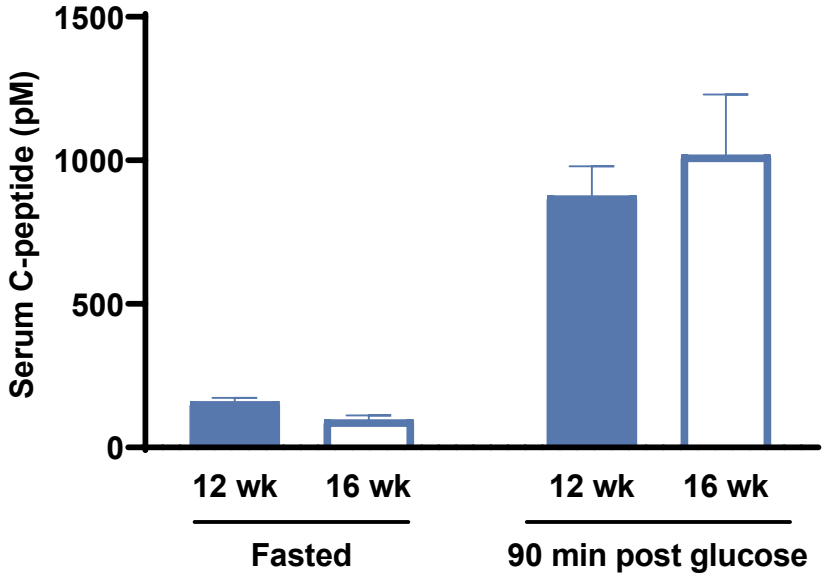
VCTX211 Reverses Hyperglycemia in Diabetic Rat Model

Normalization of blood glucose by 12-16 weeks



Treated rats maintain glucose sensitivity



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

STZ: Streptozotocin (β-cell toxin)

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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

	Program		Research	IND-enabling	Clinical	Marketed	Partner	Structure
LNP	Disruption or deletion	CTX310™: ANGPTL3						Wholly-owned
		CTX320™: Lp(a)						Wholly-owned
		CTX330™: PCSK9						Wholly-owned
		Undisclosed CV programs						Wholly-owned
		Other gene disruption programs						Wholly-owned
		Undisclosed ocular program					Bayer	Collaboration
	Insertion	Hemophilia A						
		Undisclosed insertion program						Wholly-owned
AAV	Disruption or deletion	Friedreich's ataxia (FA)					Capsida Biotherapeutics	Collaboration
		Amyotrophic lateral sclerosis (ALS)						

Partnered with Vertex on several additional disease areas, including Duchenne muscular dystrophy (DMD), myotonic dystrophy type 1 (DM1), and cystic fibrosis (CF)

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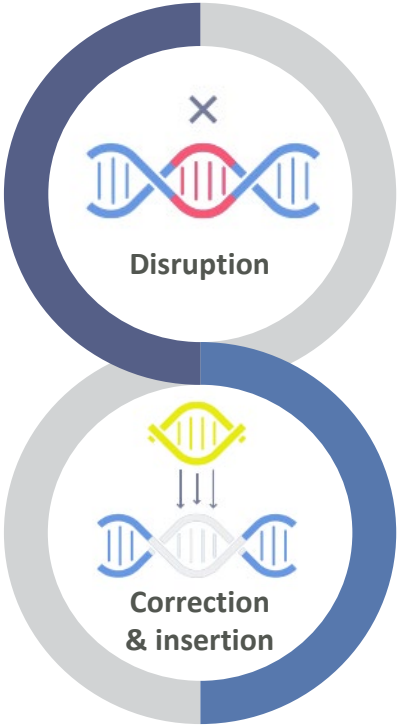
Becoming an *In Vivo* Leader – Our Strategy



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

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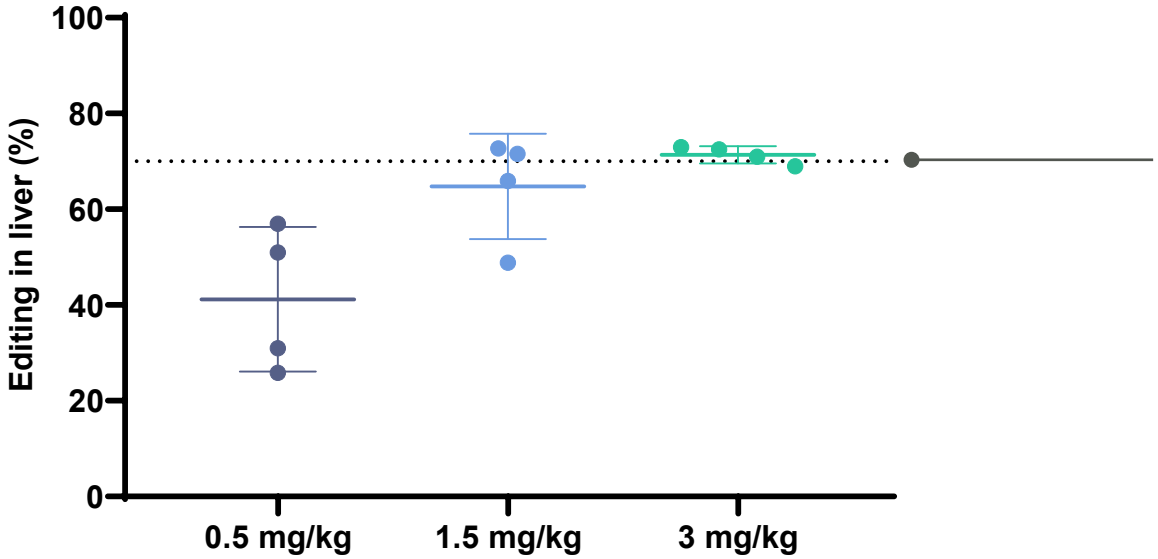
Established a Leading mRNA/LNP Platform for Gene Disruption

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

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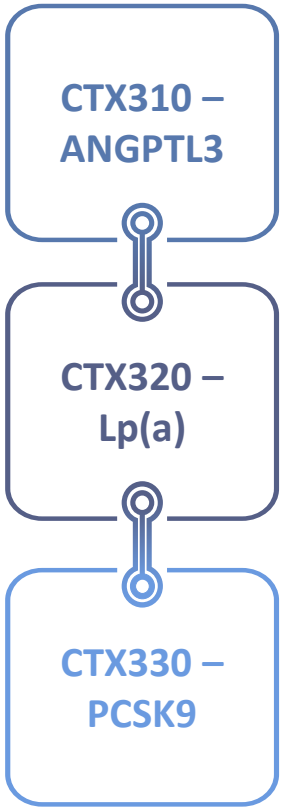
ASCVD Programs: Proven Benefit in a Once-and-Done Format



- Proven benefit based on natural human genetics (similar to BCL11A) and antibody / small RNA therapeutics
- Paradigm shift possible with single-dose, potentially lifetime durable editing approach
- 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

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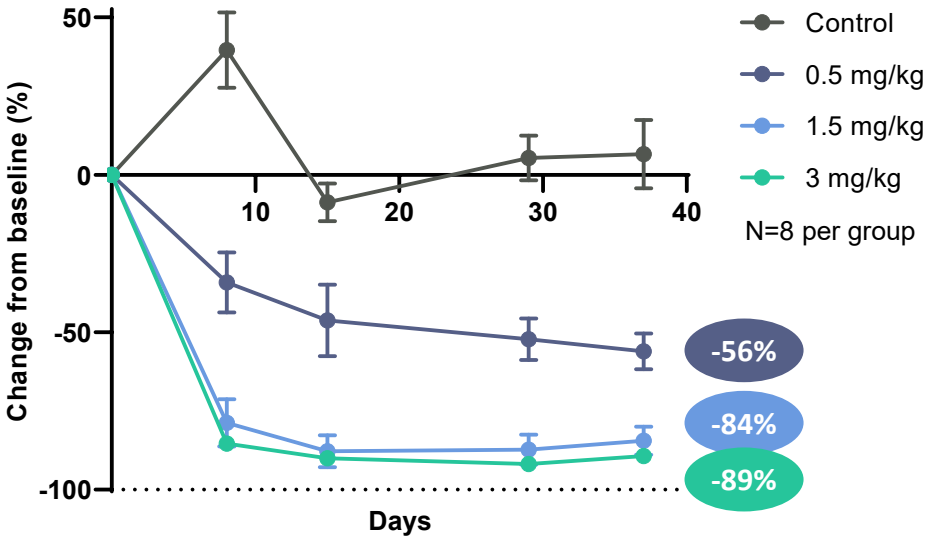
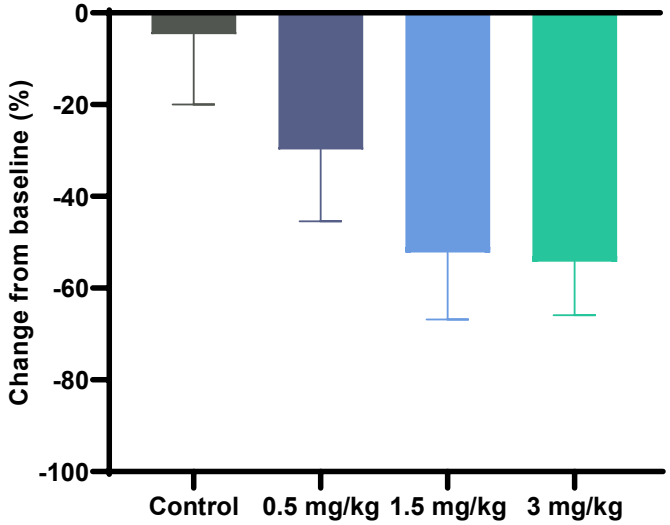
CTX310: Potentially Transformative for Cardiovascular Disease

~90% reduction in serum ANGPTL3 protein in NHPs



>50% reduction in serum triglycerides at one month



Progressing CTX310 program to the clinic in 2023

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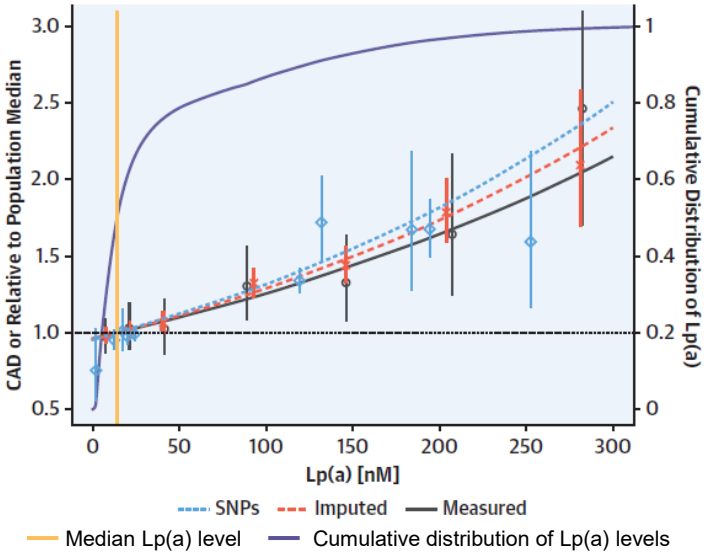
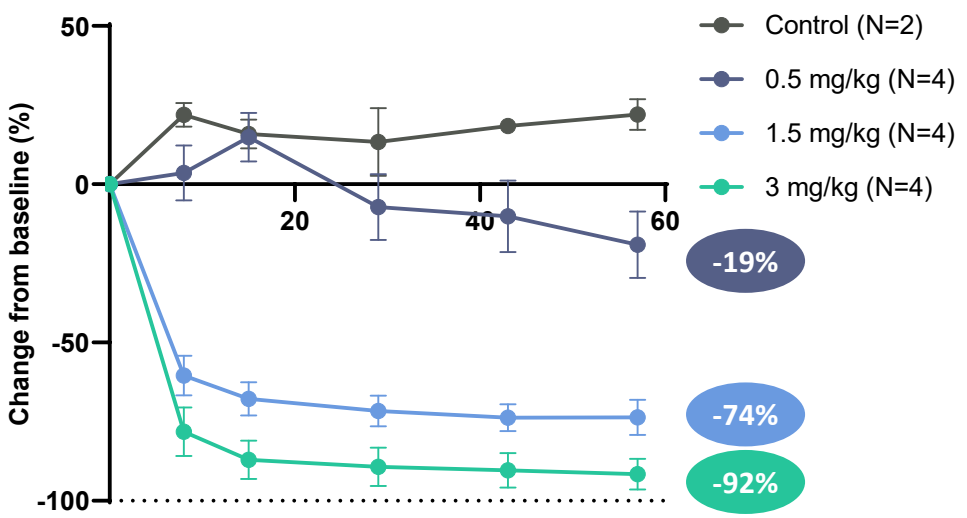
CTX320: Lp(a) is Emerging as an Ideal Target for ASCVD

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



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



Progressing CTX320 program to the clinic after CTX310

Sources: Gudbjartsson, et al. *J Am Coll Cardiol*. 2019;74(24):2982–94.

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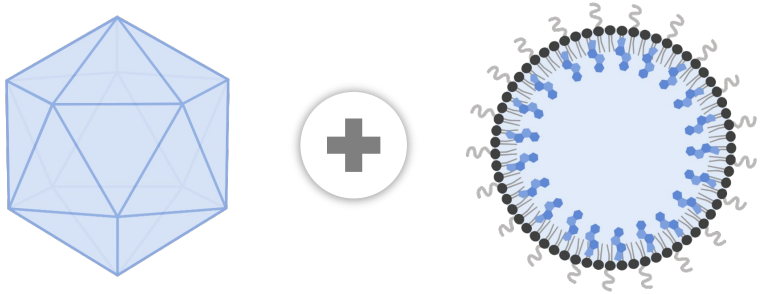
Unlocking Whole Gene Correction and Insertion

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

CRISPRx

- 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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Strong U.S. and Global Foundational IP Position

United States

CVC granted patents of broad scope; multiple applications progressing

- **50+** Patents of broad scope granted
- **15+** Additional patent applications moving forward in parallel with both broad and narrow claims
- PTAB decision in Broad interference appealed to the CAFC; separate interferences declared between CVC and Toolgen & Sigma, and Broad and Toolgen & Sigma on same subject matter as the Broad vs. CVC interference

Europe and Global

CVC granted foundational patents, including use in eukaryotes

- **2** Patents of broad scope granted in the EU; one EP patent revoked and decision appealed
- **35+** 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

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

As of Q3 2022

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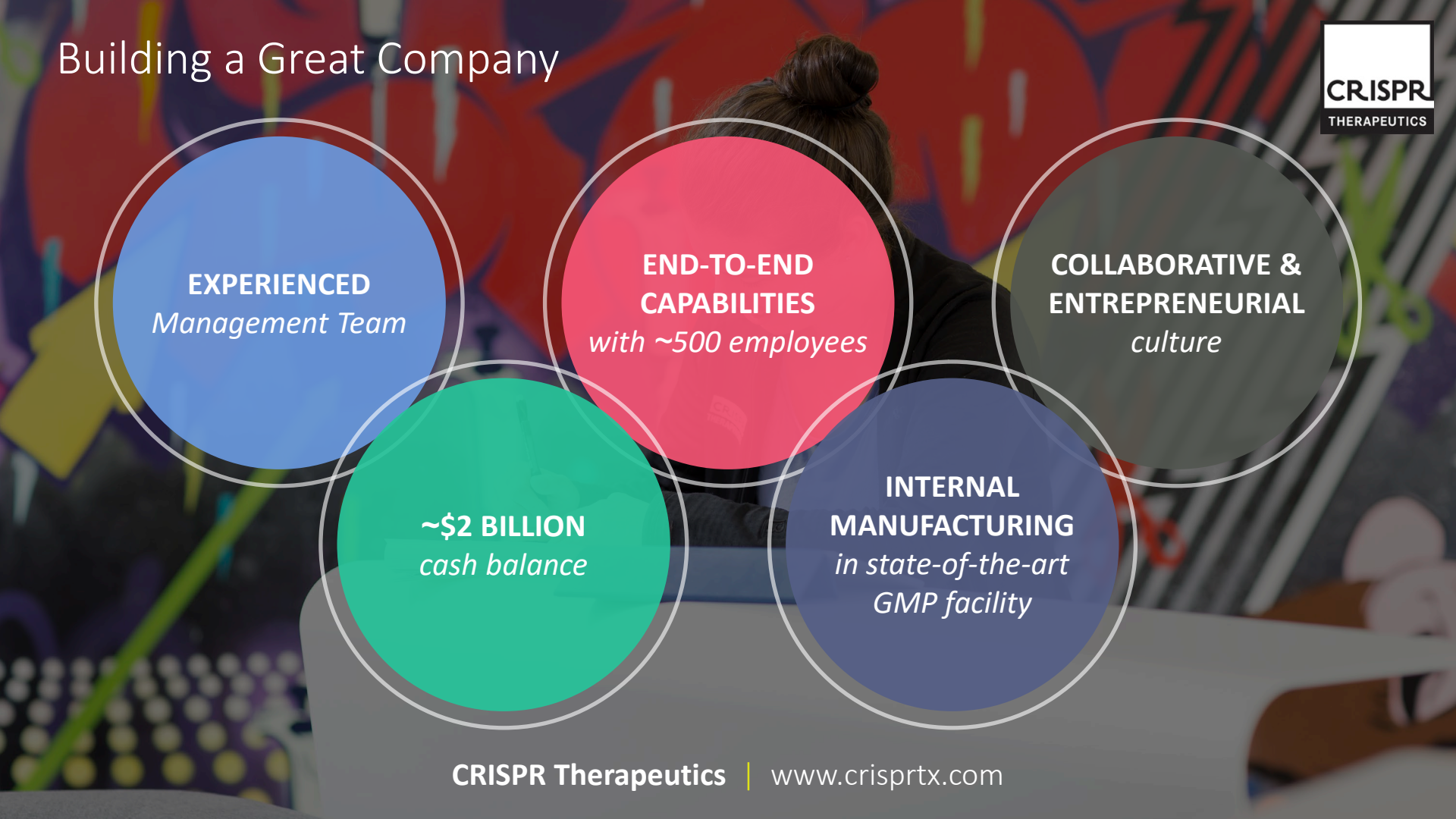
Building a Great Company