Creating transformative gene-based medicines for serious diseases

Corporate Overview

Q4 2024

Forward-Looking Statements

Statements contained in this presentation and other related materials regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding any or all of the following: (i) CRISPR Therapeutics preclinical studies, clinical trials and pipeline products and programs, including, without limitation, manufacturing capabilities, status of such studies and trials, potential expansion into new indications and expectations regarding data, safety and efficacy generally; (ii) our strategy, goals, anticipated financial performance and the sufficiency of our cash resources; (iii) regulatory submissions and authorizations, including timelines for and expectations regarding additional regulatory agency decisions; (iv) expected benefits of our collaborations; and (v) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, including as compared to other therapies. Risks that contribute to the uncertain nature of the forward-looking statements include, without limitation, the risks and uncertainties discussed under the heading "Risk Factors" in our most recent annual report on Form 10-K and in any other subsequent filings made by us with the U.S. Securities and Exchange Commission. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. We disclaim any obligation or undertaking to update or revise any forward-looking statements contained in this presentation, other than to the extent required by law.

This presentation discusses CRISPR/Cas9 gene editing investigational therapies and is not intended to convey conclusions about efficacy or safety as to those investigational therapies or uses of such investigational therapies. There is no guarantee that any investigational therapy will successfully complete clinical development or gain approval from applicable regulatory authorities. 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.

CRISPR Therapeutics Highlights

Leading gene editing company with a strong and diversified pipeline, efficient operating model, and proven track record of execution

Hemoglobinopathies	Best-in-class technology, strategy, and execution culminating in the historic approval of CASGEVY™
CAR T	Advancing multiple next-generation allogeneic candidates in IO & autoimmunity; leveraging internal GMP manufacturing
In Vivo	Building scalable portfolio across rare and common diseases, with multiple clinical and pre-clinical programs
T1D	Multiple parallel efforts using edited, stem cell-derived beta cells to address diabetes without chronic immunosuppression
Platform	Continuous innovation across multiple next-generation technologies to enable new therapies

Robust balance sheet of ~$1.9B as of September 30, 2024 to support these efforts

CAR T: Chimeric Antigen Receptor-T cell therapy; T1D: Type 1 Diabetes; GMP: Good Manufacturing Practice

Broad and Diversified Pipeline

	Program	Disease	Research	IND-enabling	Clinical	Approved	Partner	Structure
Heme	CASGEVY[1]	Severe sickle cell disease (SCD)					VERTEX	Collaboration
		Transfusion-dependent β-thalassemia (TDT)						
	Next-generation conditioning	Various						Wholly owned[2]
	In vivo editing of HSCs	Various						Wholly owned[2]
CAR T I/O & Autoimmune	CTX112 Anti-CD19 allogeneic CAR T	B cell malignancies						Wholly owned
		Systemic lupus erythematosus (SLE)						
	CTX131 Anti-CD70 allogeneic CAR T	Renal cell carcinoma and other solid tumors						Wholly owned
		Hematological cancers						
	Anti-GPC3 autologous CAR T	Hepatocellular carcinoma						Collaboration
	Anti-CD70 allogeneic CAR-NK	Solid and hematological cancers						Collaboration
In Vivo Cardiovascular & Rare Disease	CTX310: ANGPTL3	HeFH[3], HoFH[4], Mixed dyslipidemias, and SHTG[5]						Wholly owned
	CTX320: LPA	ASCVD with elevated Lp(a)						Wholly owned
	CTX340: AGT	Refractory hypertension						Wholly owned
	CTX330: PCSK9	HeFH[3]						Wholly owned
	CTX450: ALAS1	Acute hepatic porphyria (AHP)						Wholly owned
T1D	CTX211	Type I diabetes mellitus						Wholly owned
	Deviceless approach	Type I diabetes mellitus						Wholly owned
Other disclosed partnered	Duchenne's muscular dystrophy (DMD)						VERTEX	License
	Myotonic dystrophy type I (DM1)							Collaboration
	Type 1 diabetes mellitus (T1D)							License
	Cystic fibrosis (CF)							License

1. Currently approved in some countries for certain eligible patients with SCD or TDT; 2. Collaboration with Vertex for applications in β-thalassemia and SCDw; 3. Heterozygous familial hypercholesterolemia; 4. Homozygous familial hypercholesterolemia; 5. Severe hypertriglyceridemia

CASGEVY: Historic First Approval of a CRISPR-Based Medicine

Unparalleled speed and execution to a landmark approval[1]

casgevy™ (exagamglogene autotemcel) suspension for IV infusion

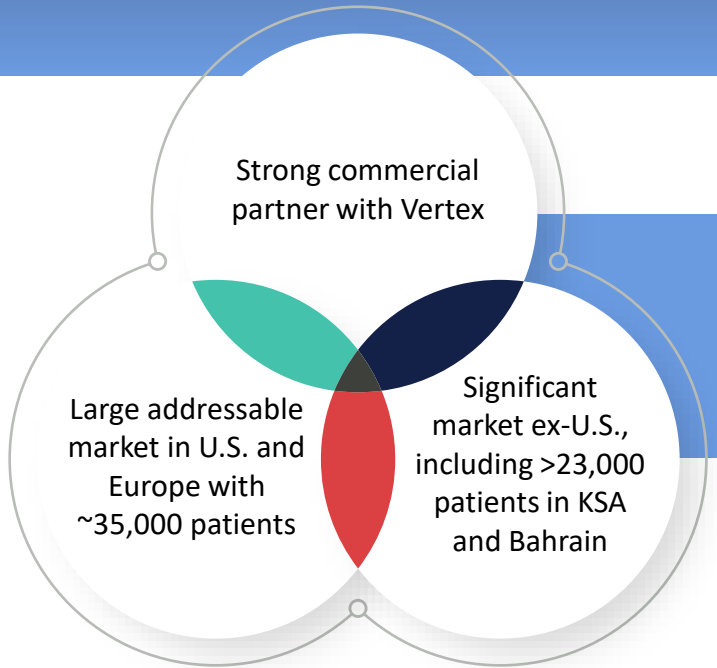
WSJ

FDA Approves World's First Crispr Gene-Editing Drug for Sickle-Cell Disease

Landmark decision heralds a new type of medicine that can tackle genetic conditions that are hard to treat

F.D.A. Approves Sickle Cell Treatments, Including One That Uses CRISPR

Well-positioned for commercial success

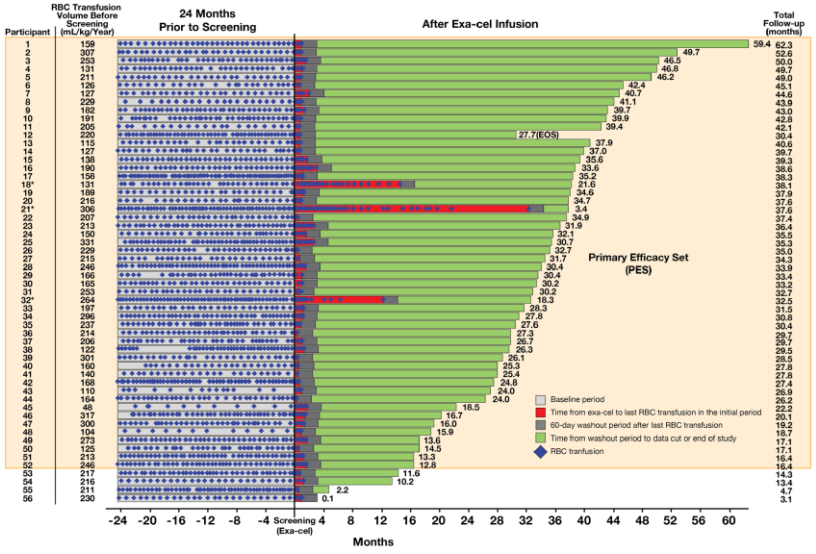


Foundational Year in 2024

1. Approved by the U.S. FDA for the treatment of SCD in patients 12 years and older with recurrent vaso-occlusive crises (VOCs) and TDT;.
Granted conditional marketing authorization by the UK MHRA and Bahrain NHRA for patients 12 years of age and older with SCD with recurrent VOCs or TDT for whom hematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related hematopoietic stem cell donor is not available.
Conditional marketing approval by the EMA and approval by the Saudi Food and Drug Agency for treatment of patients 12 years of age or older with SCD and TDT.

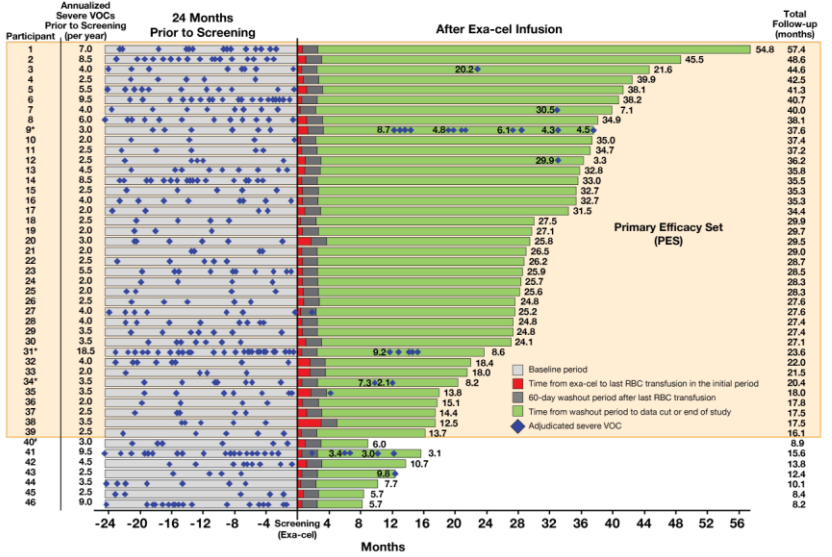
Groundbreaking Data Across >100 Patients

TDT: Transfusion independence achieved out to 59.4 months



Locatelli et al. EHA 2024

SCD: VOC-free and no in-patient hospitalizations for VOCs achieved out to 54.8 months



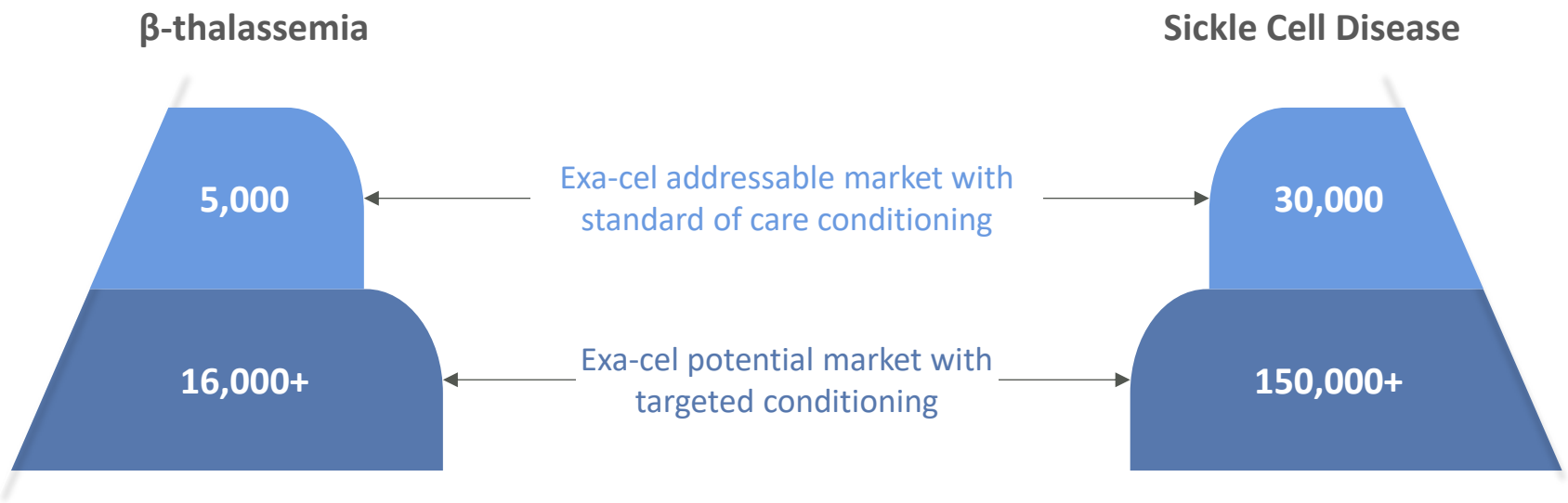
Frangoul et al. EHA 2024

Exa-cel treatment resulted in early and sustained increases in Hb and HbF leading to **transfusion independence (TI12) in 94.2% of patients** with TDT and **elimination of VOCs (VF12) and inpatient hospitalization for VOCs (HF12) in 92.3% and 97.4% of patients** with SCD, respectively

* Participant who did not achieve TI12 (TDT) or VF12 (SCD); #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.
Some subjects had VOCs after the washout period; numerical values before the VOC indicate the number of months a subject was VOC-free since the washout period/previous VOC.
EOS, end of study; exa-cel, exagamglogene autotemcel; RBC, red blood cell; TI12; proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL; VF12, proportion of participants free of severe VOCs for ≥12 consecutive months; RBC, red blood cell; VOC, vaso-occlusive crisis.

CASGEVY Has a Large Addressable Market

Significant opportunity in US and Europe, with potential to expand further with targeted conditioning



Additionally Middle East represents substantial potential addressable market and key focus area for early commercialization

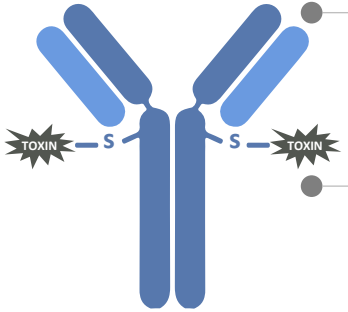
Represents estimated number of addressable patients in U.S., Europe

Expanding the Addressable Patient Population

Near-Term: Targeted conditioning using Antibody-drug conjugate against c-Kit to expand addressable population for CASGEVY

Optimal Attributes

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



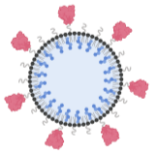
Proprietary **GMP monoclonal antibody** with **short half-life** targeting **c-Kit (CD117)**

Validated **GMP** toxin with **HSC activity** and **reduced hydrophobicity** to limit non-specific toxicity

Long-Term: Targeted LNP and AAV based delivery systems to enable *in vivo* editing of HSCs[1]

- Could enable a global cure for SCD and TDT and unlock the ability to address new indications
- Progressing multiple approaches that could solve this challenge
- Ongoing grant from the Bill & Melinda Gates Foundation

DELIVERY

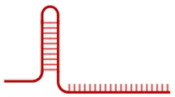


Targeted LNP

AAV

EDITING

mRNA optimization



gRNA modification

1 Hematopoietic stem cells

Three Additional Franchises Beyond CASGEVY

CAR T
I/O and Autoimmune

World's most sophisticated CAR T cell candidates, manufactured internally

Multiple opportunities across heme and solid cancers, plus autoimmune indications

In Vivo
Common and Rare Disease

Established mRNA-LNP platform for liver editing

Validated targets for CV, plus additional programs across both **common and rare diseases**

Type 1 Diabetes

First-in-class edited beta cell therapies for T1D

Multiple approaches for a beta cell replacement product without long-term immunosuppression

Platform
Next-generation editing and delivery

Our Gene-Edited Allogeneic CAR T Franchise

Advancing the most sophisticated CAR T cell candidates in the clinic against multiple opportunities across heme and solid cancers, plus autoimmune indications

First-generation: CTX110 and CTX130	Next-generation: CTX112 and CTX131	Additional indications and targets
Proof-of-concept that **allogeneic CAR T cells can produce durable remissions** following a standard lymphodepletion regimen	Preliminary clinical data suggest **next-generation programs may improve upon the clinical profile of the first-generation**	**Advancing in new areas**, e.g., autoimmune disease and autologous CAR T in solid tumors

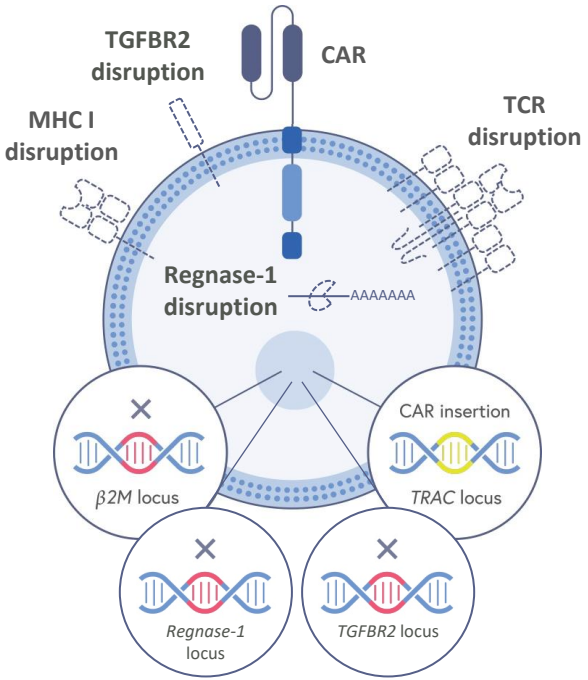
Program	Indication(s)	Research	IND-enabling	Clinical	Partner
CTX112 Anti-CD19 allogeneic CAR T	B cell malignancies				
	Systemic lupus erythematosus (SLE)				
CTX131 Anti-CD70 allogeneic CAR T	Renal cell carcinoma and other solid tumors				
	Hematological cancers				
Anti-GPC3 Autologous CAR T	Hepatocellular carcinoma				Roswell Park
Anti-CD70 Allogeneic CAR-NK	Solid and hematological cancers				nkarta Therapeutics

CTX112 and CTX131 Incorporate Novel Potency Edits

Next-generation CRISPR gene-edited allogeneic CAR T chassis

Novel Potency Edits

- **Regnase-1 KO:** Increase functional persistence, cytokine secretion and sensitivity, and effector function
- **TGFBR2 KO:** Reduce tumor microenvironment inhibition of multiple CAR T cell functions



- **TCR KO:** Prevent GvHD
- **CAR KI:** Site-specific insertion into TRAC locus without using lentivirus
- **MHC I KO:** Improve persistence in the allogeneic setting and avoid need for more toxic lymphodepletion

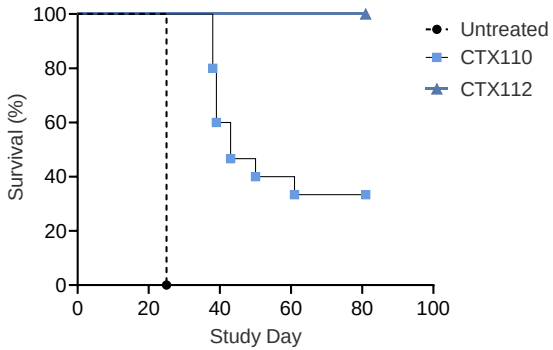
CTX112 and CTX131 utilize the same CRISPR-edited allogeneic T cell chassis, *but CTX112 incorporates a CD19-targeted CAR while CTX131 incorporates a CD70-targeted CAR and knock-out of CD70*

CTX112 and CTX131 Build Upon First Gen CAR T's in Oncology

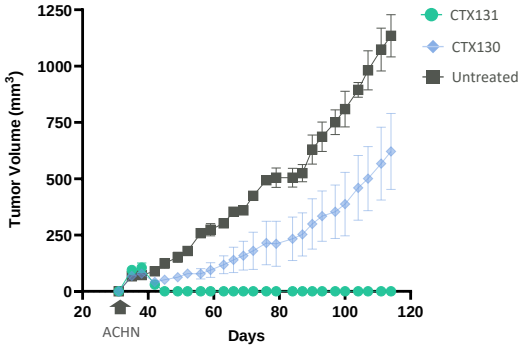
First-generation CAR Ts, CTX110 & CTX130

Proof-of-concept that our allogeneic CAR T cells can produce durable remissions following a standard LD regimen in hematological malignancies as well as solid tumors

Potency edits in CTX112 lead to extended survival in Nalm6-Luc mice compared to CTX110



CTX131 eliminates different xenograft tumor models upon rechallenge without exhaustion



Preliminary clinical data in next generation CAR T suggests improvement on first generation clinical profile, including significantly higher CAR T cell expansion & functional persistence

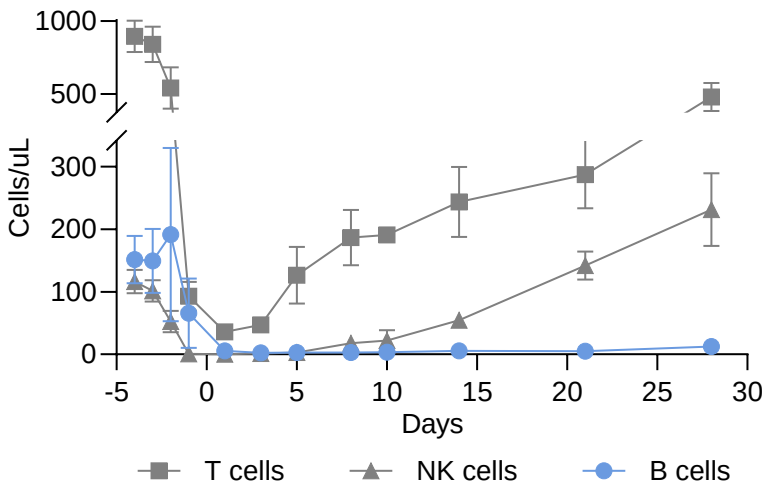
N=15 mice per treated group
N=5 mice for untreated group

N=5 mice per group

CTX112: Significant Opportunity in Autoimmune Diseases

- **Allogeneic CAR T cells produce deep B cell depletion** in B cell malignancies, as observed with CTX110
- **CD19-directed autologous CAR T cells have produced durable remissions in multiple autoimmune indications** in early clinical studies (e.g., Mueller et al. ASH 2023)
- **CTX112 has the potential to provide similar results with several potential advantages:**
  - Increased scalability
  - Dramatically decreased COGS
  - Reduced risk of CRS, ICANS, and prolonged B cell aplasia
  - Improved patient experience with no need for apheresis

B cell depletion following CTX110 infusion among patients with detectable B cells at baseline (N=9)



Median time to B cell recovery: 178 days (range: 44-465)

CTX112 clinical trial in systemic lupus erythematosus (SLE) is ongoing,
with potential expansion opportunities in additional autoimmune indications

CTX112 is Positively Differentiated From Other CD19 Therapies

CTX112 vs. Autologous CAR T	• **Off-the-shelf benefits** are critical in context of autoimmune patients (e.g., removing requirement for apheresis allows patients to continue use of concurrent medications) • Potential to **expand addressable patient population** due to **dramatically lower COGS, increased scalability** and **improved patient experience** (i.e., reduced time off immunosuppressive therapy)
CTX112 vs. T cell engagers (TCEs)	• **CAR Ts drive deep B cell depletion in tissues**[1], likely critical for immune reset • **Long term data in oncology**[2] and **early clinical results in autoimmune support superior clinical responses** for CAR Ts vs. TCEs
CTX112 vs. Other Allo CAR T / NK	• **Early clinical results**[3] from other allo CAR T **provides supporting rationale for CTX112** given similar PK and B cell depletion profile • CTX112 has empirically designed potency edits that lead to **significantly higher CAR T cell expansion and functional persistence**

1. Tur C, et al. Ann Rheum Dis. 2024; 2. Kim J, et. al. Blood. 2024; 3. Wang X, et al. Cell. 2024

Owning Manufacturing Gives Us Flexibility

- Manufacturing CTX112 and CTX131 at our internal GMP facility
- These candidates exhibit increased manufacturing robustness, with a higher and more consistent number of CAR T cells produced per batch
- Potential for significantly lower COGS and greater scalability
- Capacity and flexibility to manufacture additional programs and modalities (e.g., mRNA, iPSC)

Advancing Plug-and-Play *In Vivo* Platform Across Multiple Diseases

Established plug-and-play LNP/ mRNA platform for *in vivo* gene disruption, starting in the liver

~60-70% whole liver editing across multiple targets, which translates to near-complete editing in hepatocytes[1]

Potential to transform the treatment paradigm for CV with CTX310, CTX320, CTX330 and CTX340

First two programs in the clinic with CTX310 targeting ANGPTL3 and CTX320 targeting Lp(a)

Preclinical programs CTX340 targeting AGT and CTX330 targeting PCSK9

Advancing *in vivo* programs in additional rare diseases

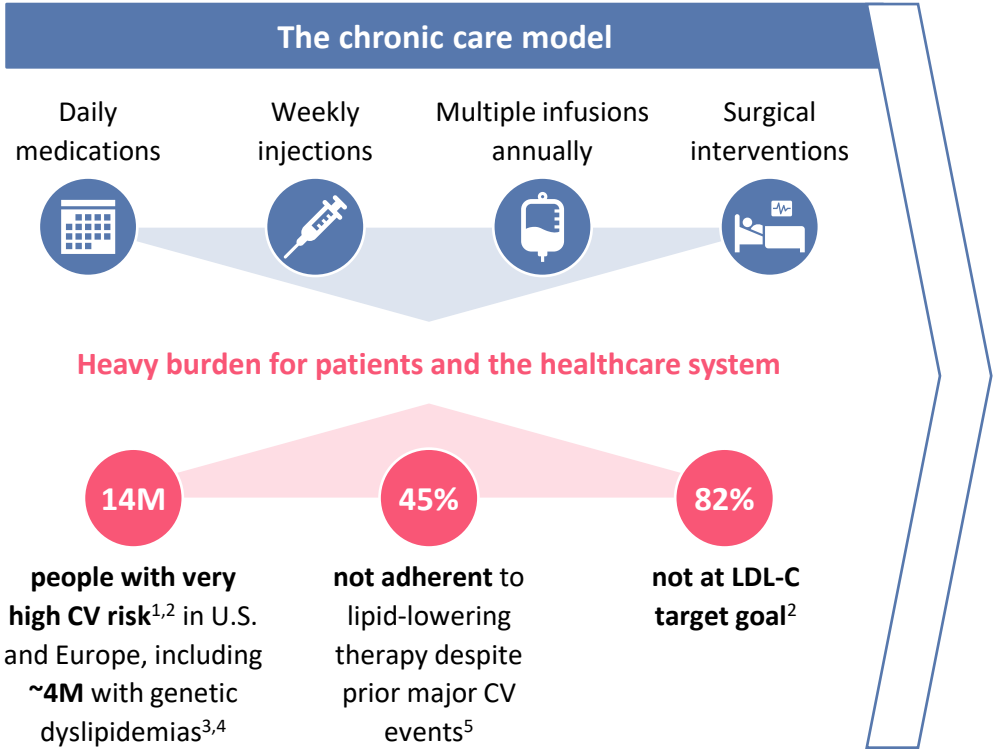
One-time therapies that could recapitulate the proven benefit of targets validated by human genetics and other modalities

Preclinical program CTX450 targeting ALAS1

Program	Indication(s)	Research	IND-enabling	Clinical
CTX310: ANGPTL3	HeFH[2], HoFH[3], Mixed dyslipidemias, and SHTG[4]			
CTX320: Lp(a)	ASCVD with elevated Lp(a)			
CTX340: AGT	Refractory hypertension			
CTX330: PCSK9	HeFH[2]			
CTX450: ALAS1	Acute hepatic porphyria			

1. Gao et al. 2008; 2. Heterozygous familial hypercholesterolemia; 3. Homozygous familial hypercholesterolemia; 4. Severe hypertriglyceridemia

CTX310 and CTX320 Could Transform the Treatment Paradigm for ASCVD



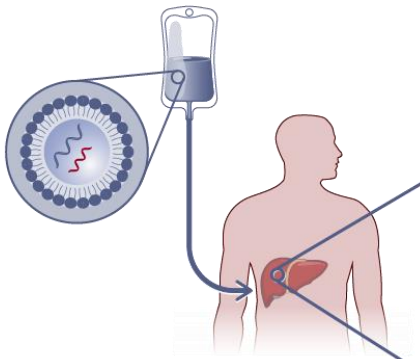
A new treatment paradigm: one-time CRISPR-based therapies with the potential to…

- Recapitulate the proven benefit of targets like ANGPTL3, as validated by natural human genetics and other therapeutic modalities
- Improve long-term cardiovascular outcomes by durably lowering atherogenic lipoproteins for a patient's lifetime
- Minimize or eliminate the need for additional treatments
- Treat both severe disease and much larger ASCVD patient populations

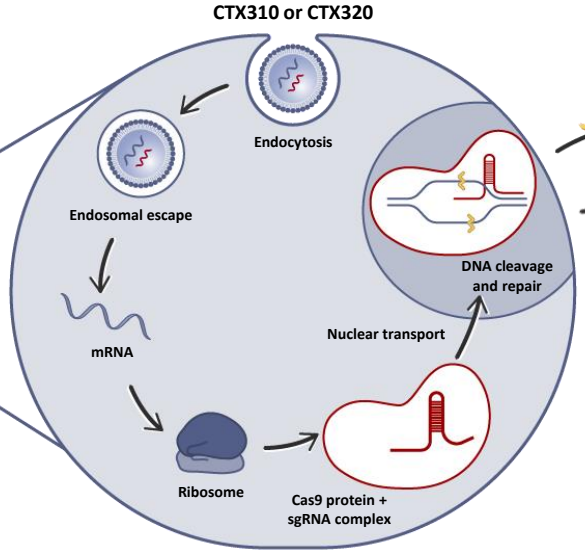
ASCVD: atherosclerotic cardiovascular disease; 1. Gu et al. 2022; 2. Ray et al. 2021; 3. Hu et al. 2020; 4. Dron et al. 2018; 5. Guglielmi et al. 2017

CTX310 and CTX320: A One-Time Dose to Treat CV Diseases

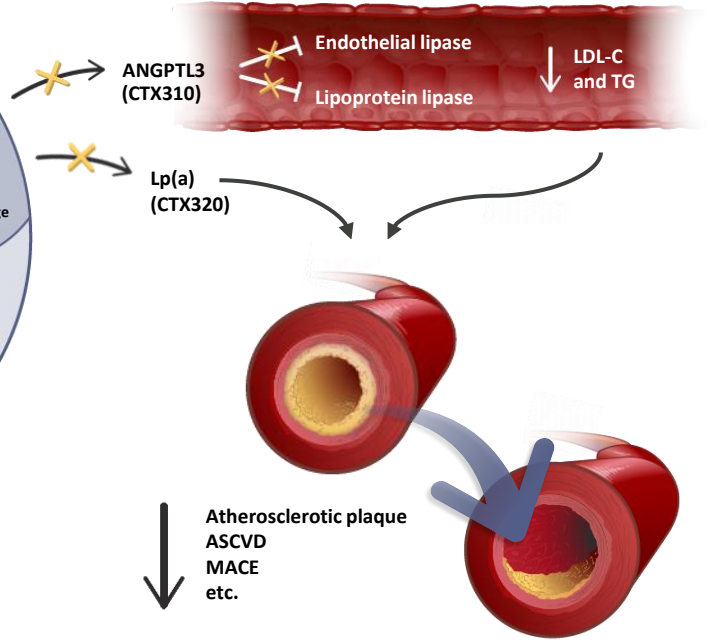
Intravenous delivery targeting the liver → **CRISPR/Cas9-based editing** → **Reduced atherogenic lipoprotein concentrations**



CTX310 and CTX320 consist of Cas9 mRNA and guide RNA (sgRNA) targeting *ANGPTL3* or *LPA*, respectively, encapsulated in lipid nanoparticles (LNPs)



Transient expression of Cas9 and sgRNA in hepatocytes to reduce target protein expression permanently



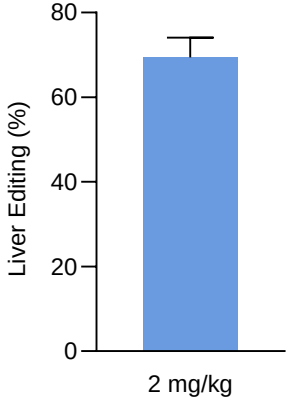
CTX310 Targeting ANGPTL3 for Cardiovascular Disease

Natural loss-of-function mutations in *ANGPTL3* are associated with reduced LDL-C, triglycerides (TG), and ASCVD risk without any negative impact on overall health[1,2]

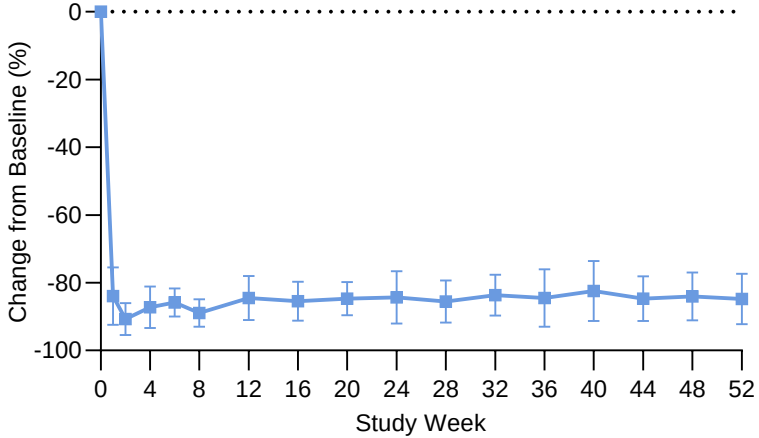
A one-time, CRISPR-based therapy could recapitulate the protective effect of naturally occurring loss-of-function variants in *ANGPTL3*

A single dose of CTX310 durably reduced ANGPTL3 and triglycerides in NHPs out to 1 year

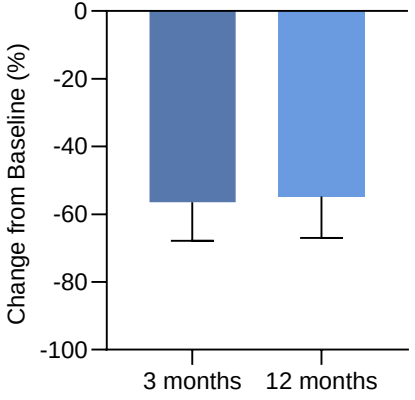
~70% editing of *ANGPTL3*



Sustained reduction in plasma ANGPTL3



Sustained reduction in TG



Presented at the American Heart Association Scientific Sessions. 11 Nov 2023

Note: Single dose of CTX310 (2 mg/kg) administered to non-human primates (NHPs) (N=8) on Day 1; study ongoing

1. Minicocci et al. 2012; 2. D'Erasmo et al. 2023

CTX320 Targeting Lp(a), an Independent Risk Factor for ASCVD

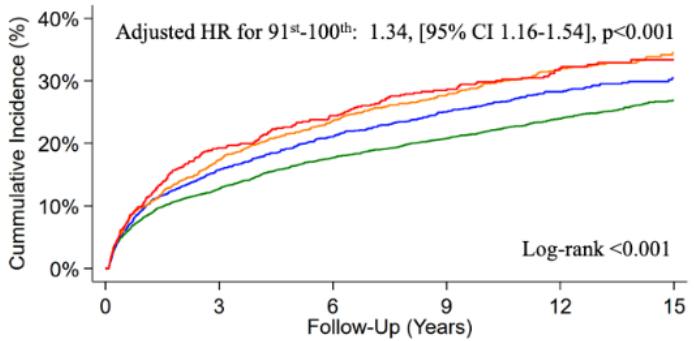
Elevated lipoprotein(a) [Lp(a)] levels increase ASCVD risk, as observed across numerous studies[1,2,3,4,5]

Up to 20% of the global population has elevated Lp(a)[6,7], primarily determined by genetics[8]

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

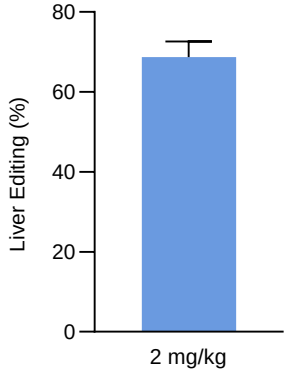
Lp(a) shows an independent association with MACE[5]

- **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

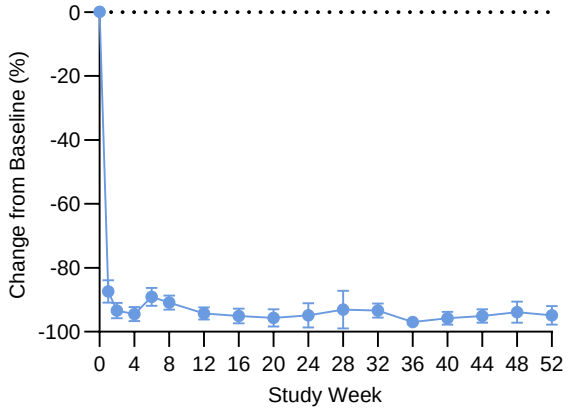


A single dose of CTX320 durably reduced Lp(a) in NHPs out to 1 year

~70% editing of *LPA*



~95% reduction in plasma Lp(a)



Note: Single dose of CTX320 (2 mg/kg) administered to non-human primates (NHPs) (N=4) on Day 1; study ongoing

1. Enas et al. 2019; 2. Gurdasani et al. 2012; 3. Laschkolnig et al. 2014; 4. Emdin et al. 2016; 5. Berman et al. 2023; 6. Nordestgaard et al. 2010; 7. Varvel et al. 2016; 8. Langsted et al. 2021

Presented at the American Heart Association Scientific Sessions. 11 Nov 2023

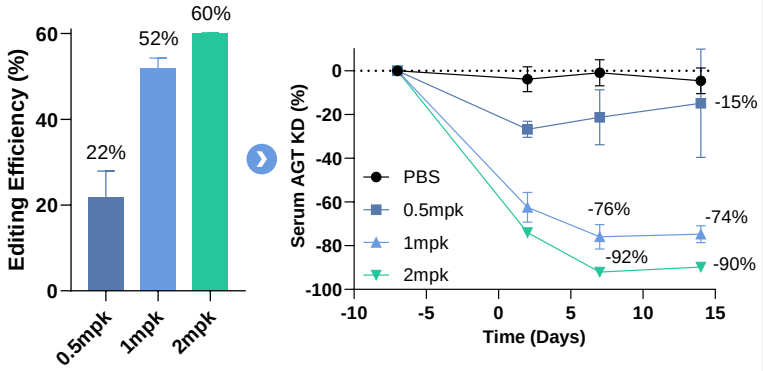
CTX340 Targeting AGT For Refractory Hypertension

Hypertension is the leading cause of cardiovascular morbidity and mortality worldwide[1,2]

Refractory hypertension defined as uncontrolled blood pressure despite use of ≥5 or more antihypertensives at maximal tolerated doses[3]

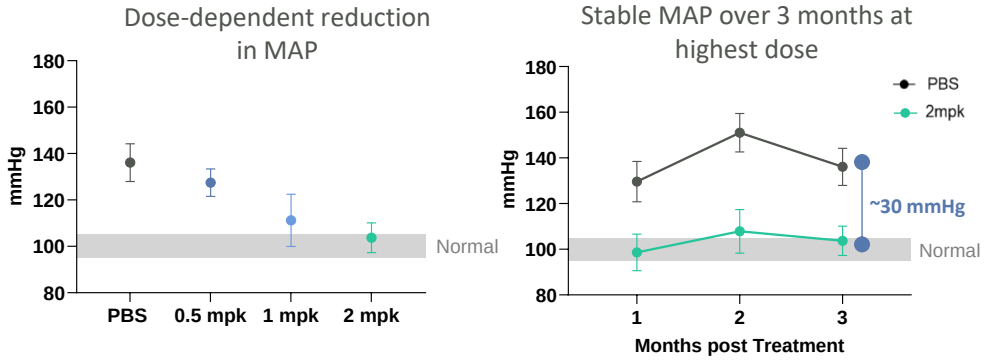
A one-time, CRISPR-based therapy targeting angiotensinogen (AGT) could durably lower blood pressure

Up to 60% editing and 90% reduction in serum AGT in SHR[4] model



N=4 per group; mean ± SEM

A single dose of CTX340 led to dose-dependent, durable reduction in blood pressure



N=8 per group; mean ± SEM
MAP = mean arterial pressure

1. Zhou et al. 2021; 2. Danaei et al. 2009; 3. Acelajado et al. 2019; 4. SHR: spontaneous hypertensive rat

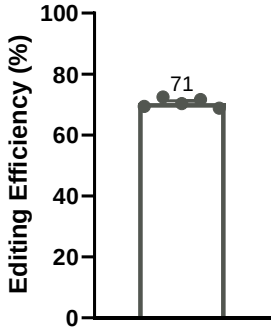
CTX450 Targeting ALAS1 for AHP

Acute hepatic porphyrias (AHP) are inherited metabolic disorders caused by deficiencies of specific enzymes in the heme biosynthesis pathway.[1,2] The rate-limiting enzyme of the heme biosynthetic pathway is hepatic 5-aminolevulinic acid synthase (ALAS1)[3,4,5]

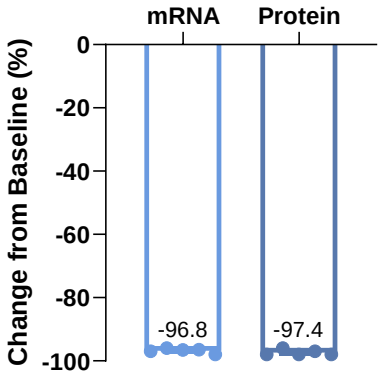
A one-time, CRISPR-based therapy could durably reduce disease-associated biomarkers, potentially leading to an amelioration of AHP attacks

A single dose of CTX450 showed deep reductions in ALAS1 mRNA and protein leading to normalization of ALA/PBG in a disease model

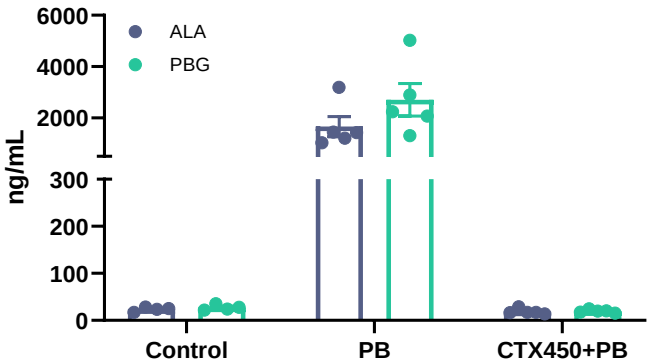
~70% editing of *ALAS1*



~97% mean mRNA and protein reduction



Leading to reduction of ALA[6] and PBG[7] biomarkers in PB[8] challenge model



N=5 per group; mean ±SEM

1. Anderson et al. 2001; 2. Chan et al. 2015; 3. Granick S. 1963; 4. deMatteis 1967; 5. Handschin et al. 2005; 6. 5-aminolevulinic acid (ALA), 7. porphobilinogen (PBG), 8. phenobarbital (PB)

Three Parallel Efforts in Type 1 Diabetes (T1D)

Gene-editing is key to achieving the goal of developing a beta-cell replacement product to treat diabetes without requiring long-term immunosuppression

1

CTX211

First-in-class edited beta-cell replacement therapy: Encapsulated pancreatic progenitor cells derived from pluripotent stem cells with gene-edits for immune evasion and cell survival

Phase 1 clinical trial ongoing

2

Deviceless approach

Unencapsulated pancreatic progenitor cells derived from edited pluripotent stem cells

Advancing through research phases

3

Non-exclusive license with Vertex

Covers Vertex's gene-edited hypoimmune programs for T1D

$170M in upfront and milestone payments to CRISPR in 2023

Up to $160M in additional research and development milestones, plus royalties on future products

Wholly owned, with ability to leverage ViaCyte cell lines and IP

Next-Generation Editing and Proprietary LNP Platform

The race to bring next-generation gene-editing technologies to the clinic has just begun

Both editing and delivery expertise needed to make the required edit in the required location

No one editing approach will dominate – each disease will have its own optimal approach

CRISPR-X

Dedicated internal research group focused on emerging technologies for gene correction and insertion, including non-viral DNA delivery and all-RNA systems

LNP

Dedicated LNP group supporting liver-directed and extrahepatic *in vivo* programs with novel lipids and formulations, targeting moieties, etc.

Most next-generation editing technologies combine the RNA-guided endonuclease activity of Cas9 with a fused effector domain, e.g., a reverse transcriptase – **we have issued foundational IP covering such fusions**

Several Upcoming Catalysts Across Portfolio

	Program	Disease	Status
Heme	**CASGEVY**	SCD and TDT	Ongoing launch – 2024 is a foundational year
I/O & Autoimmune	**CTX112** - allo CD19 CAR T	B-cell malignancies	Trial ongoing – update in 2024
		SLE	Trial ongoing
	CTX131 - allo CD70 CAR T	Solid tumors	Trial in RCC ongoing – update in 2025
		Heme malignancies	Trial ongoing
In Vivo	**CTX310** - ANGPTL3	Dyslipidemias	Trial ongoing – update in 2025
	CTX320 - Lp(a)	ASCVD with elevated Lp(a)	Trial ongoing – update in 2025
	CTX340 - AGT	Refractory Hypertension	Trial targeting initiation in 2H 2025
	CTX450 - ALAS1	Acute Hepatic Porphyria	Trial targeting initiation in 2H 2025
T1D	**CTX211** – gene-edited beta cell replacement	Type 1 diabetes	Trial ongoing

Building an Industry-Leading Company