Creating transformative gene-based medicines for serious diseases

J.P. Morgan Healthcare Conference

January 9, 2024

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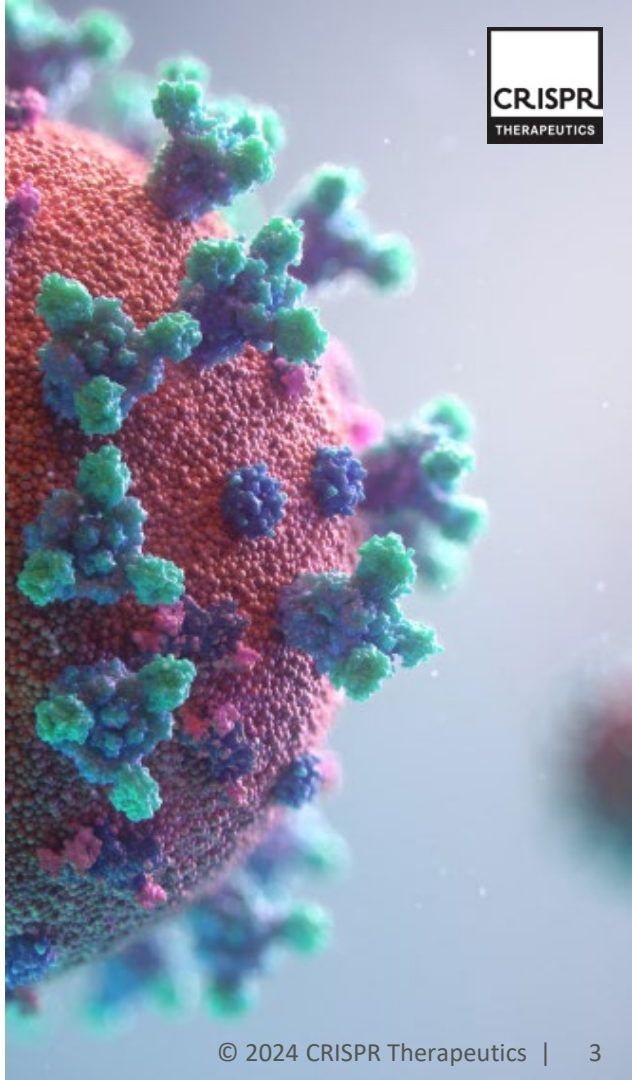
The presentation and other related materials may contain a number of "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding CRISPR Therapeutics' expectations about any or all of the following: (i) its plans and expectations for its preclinical studies, clinical trials and pipeline products and programs; (ii) the safety, efficacy and clinical progress of its various clinical programs; (iii) the status of preclinical studies and clinical trials (including, without limitation, the expected timing of data releases, announcement of additional programs and activities at clinical trial sites, and discussions with regulatory authorities) and expectations regarding the data that is being presented; (iv) the data that will be generated by ongoing and planned preclinical studies and clinical trials and the ability to use that data for the design and initiation of additional preclinical studies and clinical trials; (v) regulatory submissions and authorizations, including timelines for and expectations regarding additional regulatory agency decisions; (vi) manufacturing activities and capabilities; (vii) the activities under its collaborations and the expected benefits thereof; (viii) its intellectual property coverage and positions of its, its licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property; (ix) the sufficiency of its cash resources; and (x) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, including as compared to other therapies. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects" and similar expressions are intended to identify forward-looking statements. You are cautioned that forward-looking statements are inherently uncertain. Although CRISPR Therapeutics believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others, that: the efficacy and safety results from ongoing clinical trials will not continue or be repeated in ongoing or planned clinical trials or may not support regulatory submissions; regulatory authorities may not approve exa-cel on a timely basis or at all; adequate pricing or reimbursement may not be secured to support continued development or commercialization of exa-cel following regulatory approval; the potential that clinical trial results may not be favorable; one or more of its product candidate programs will not proceed as planned for technical, scientific or commercial reasons; future competitive or other market factors may adversely affect the commercial potential for its product candidates; initiation and completion of preclinical studies for its product candidates is uncertain and results from such studies may not be predictive of future results of future studies or clinical trials; regulatory approvals to conduct trials or to market products are uncertain; it may not realize the potential benefits of its collaborations; uncertainties regarding the intellectual property protection for its technology and intellectual property belonging to third parties, and the outcome of proceedings (such as an interference, an opposition or a similar proceeding) involving all or any portion of such intellectual property; and those risks and uncertainties described under the heading "Risk Factors" in its most recent annual report on Form 10-K, quarterly report on Form 10-Q, and in any other subsequent filings made by it with the U.S. Securities and Exchange Commission, which are available on the SEC's website at www.sec.gov. 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. CRISPR Therapeutics disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this presentation, other than to the extent required by law.

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 Today

- Best-in-class technology, strategy, and execution culminating in historic approval of CASGEVY
- 3 additional franchises—oncology, cardiovascular, and diabetes—with multiple catalysts in 2024
- Continuous platform innovation across multiple next-gen technologies to enable new therapies
- Disciplined operating model and capital efficiency



Advancing to the Next Phase of Growth for the Company

Stage 1
2013-2017

- Relentless focus on bringing first asset to clinical POC
- Parlay established capabilities to broaden pipeline
- Industry-leading deals to validate platform

Stage 2
2018-2025

- Build out diversified pipeline (I/O, CV, T1D) and rapidly advance to the clinic
- Establish efficient operating model to support and capture synergies across all verticals
- Establish in-house manufacturing competencies

Stage 3
2026+

- Establish a fully-integrated, sustainable biotech company
- Productive innovation engine with 1-2 INDs per year
- Opportunistic M&A to supplement portfolio

Sector-leading operating efficiency[1], minimal dilution, and strong balance sheet of ~$1.9B *pro forma*

1. Based on analysis of trailing twelve-month operating expenses less non-cash items per clinical candidate

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

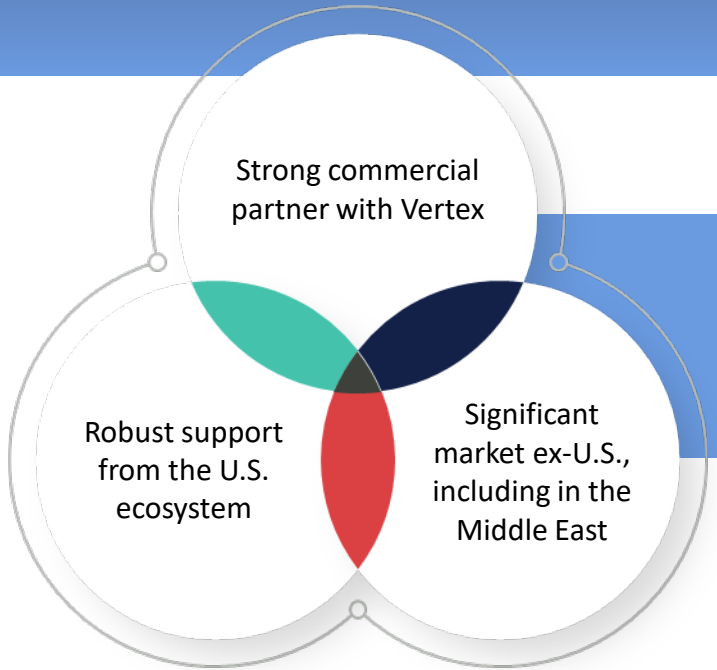
FDA Approves World's First Crispr Gene-Editing Drug for Sickle-Cell Disease

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

T

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

Well-positioned for commercial success



Additional regulatory milestones upcoming 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); PDUFA target action date for TDT of March 30, 2024. 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. Currently under review by the EMA (positive opinion received from the CHMP) and Saudi Food and Drug Agency for SCD and TDT.

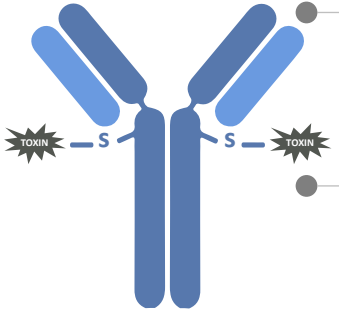
Expanding the Number of Patients Who Can Benefit

Targeted conditioning

Optimal attributes

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

Our approach: Antibody-drug conjugate (ADC) targeting cKit



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

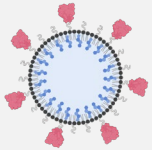
Validated **GMP** toxin with **HSC activity** and **reduced hydrophobicity** to limit non-specific toxicity

In vivo editing of HSCs

- 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
- Received $14.5M grant from the Bill & Melinda Gates Foundation in Oct 2023 for this work

Achieving editing of HSCs *in vivo* requires delivery AND editing expertise

DELIVERY



Targeted LNP

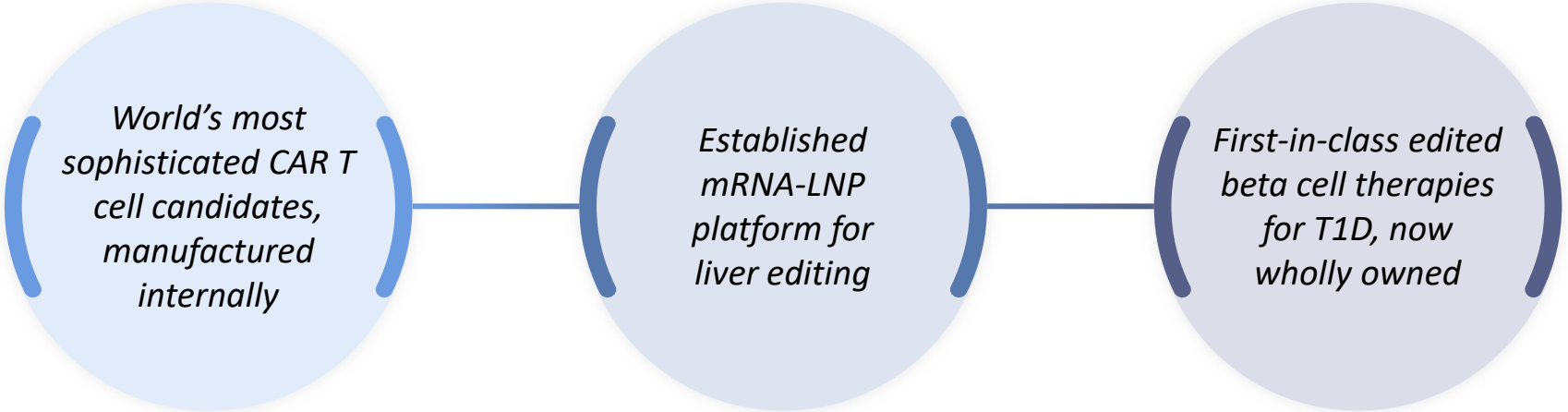
AAV

EDITING

mRNA optimization

gRNA modification

2024: A Pivotal Year to Define the Next Phase of Growth



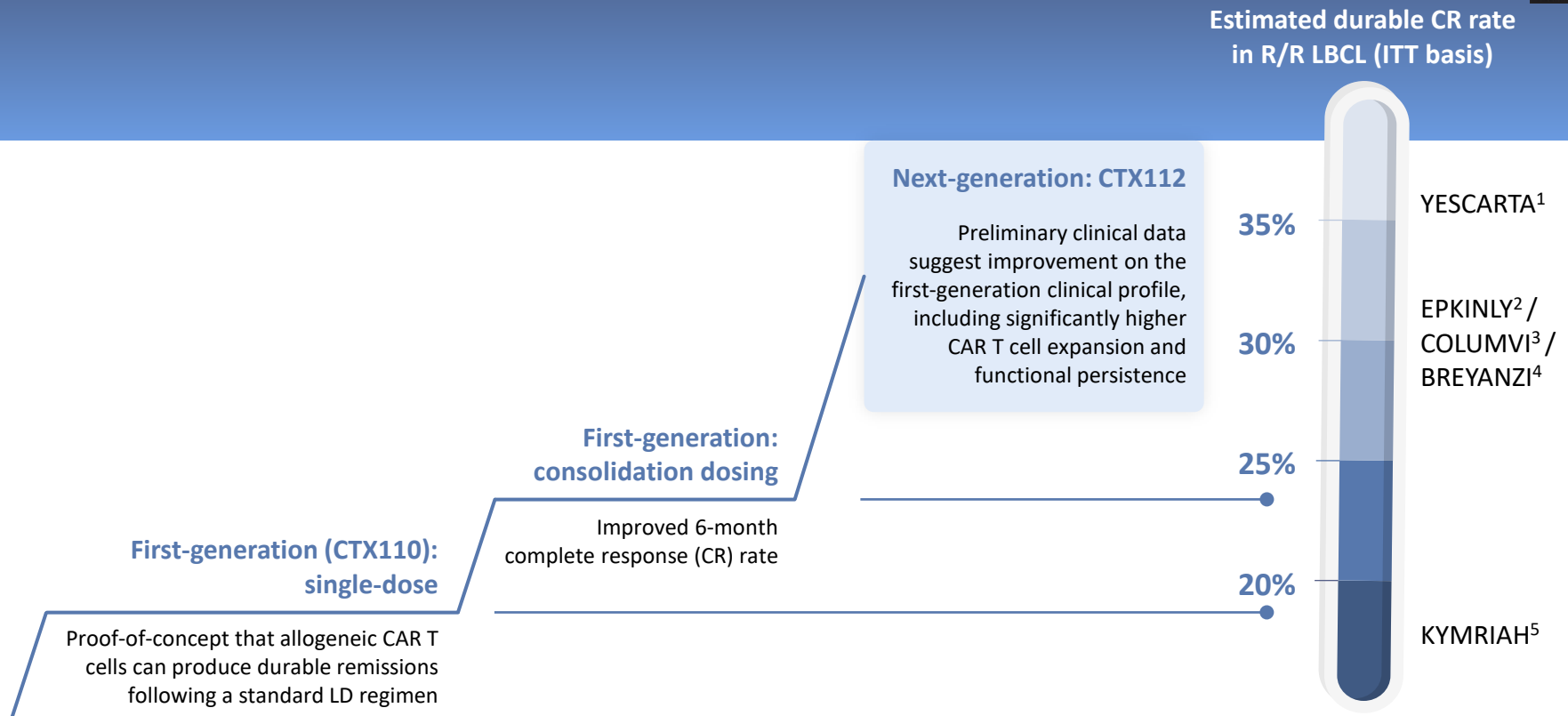
Multiple opportunities across heme and solid cancers, plus autoimmune indications

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

Multiple shots to achieve a beta cell replacement product without long-term immunosuppression

Platform
Next-generation editing and delivery

Next-Generation CD19 CAR T: CTX112 Builds Upon CTX110



Opportunity to expedite development of CTX112 based on clinical and regulatory learnings from first-generation candidates

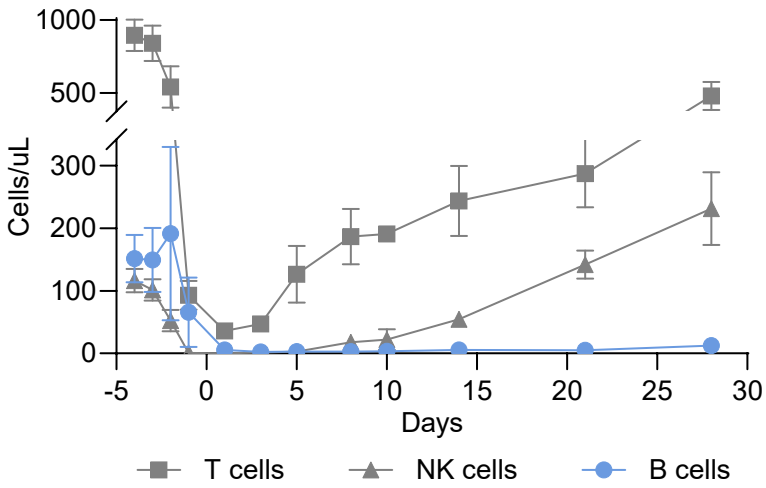
1. YESCARTA USPI, Locke et al. 2019; 2. EPKINLY USPI; 3. COLUMVI USPI, Dickinson et al. 2022; 4. BREYANZI USPI; 5. KYMRIAH USPI and EPAR

Expanding CTX112 into Autoimmune Disease

CTX112 has a 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)

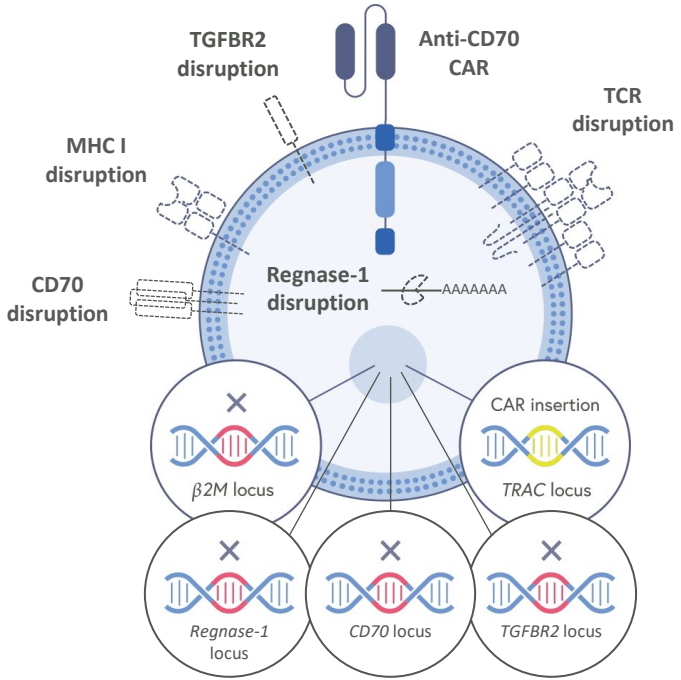


Median time to B cell recovery: 178 days (range: 44-465)

Planning to initiate trial in 1H 2024 starting in systemic lupus erythematosus (SLE)
with expansion opportunities in additional autoimmune indications

Next-Generation CAR T: Cracking Solid Tumors

CTX131 next-generation CAR T chassis: Most sophisticated CAR T cell candidate in the clinic



Regnase-1 and TGFBR2 edits synergistically increase CAR T potency

Solid tumor CAR T pipeline

Program	Indications
CTX131 Anti-CD70 allogeneic CAR T	▪ Phase I trial in RCC and other solid tumors ▪ Expanding into hematologic malignancies as well
Anti-GPC3 autologous CAR T with TGFβRII KO	▪ IND filing in HCC planned in next ~12 months ▪ Roswell Park conducts manufacturing and initial trial ▪ CRISPR retains commercial rights
Anti-PTK7 allogeneic CAR T	▪ Potential for numerous, including breast, ovarian, and lung
Anti-LIV1 allogeneic CAR T	▪ Expressed across all breast cancer subtypes, including TNBC

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)

Applying 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

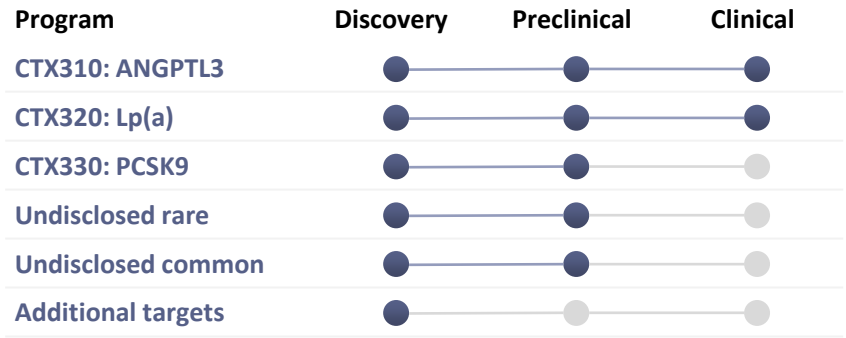
70% whole liver editing across multiple targets in NHPs, which translates to near-complete editing in hepatocytes[1]

Advancing broad portfolio of wholly-owned *in vivo* programs across rare and common diseases

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

Potential to transform the treatment paradigm for CVD with CTX310 and CTX320

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



New targets to be disclosed in mid-2024

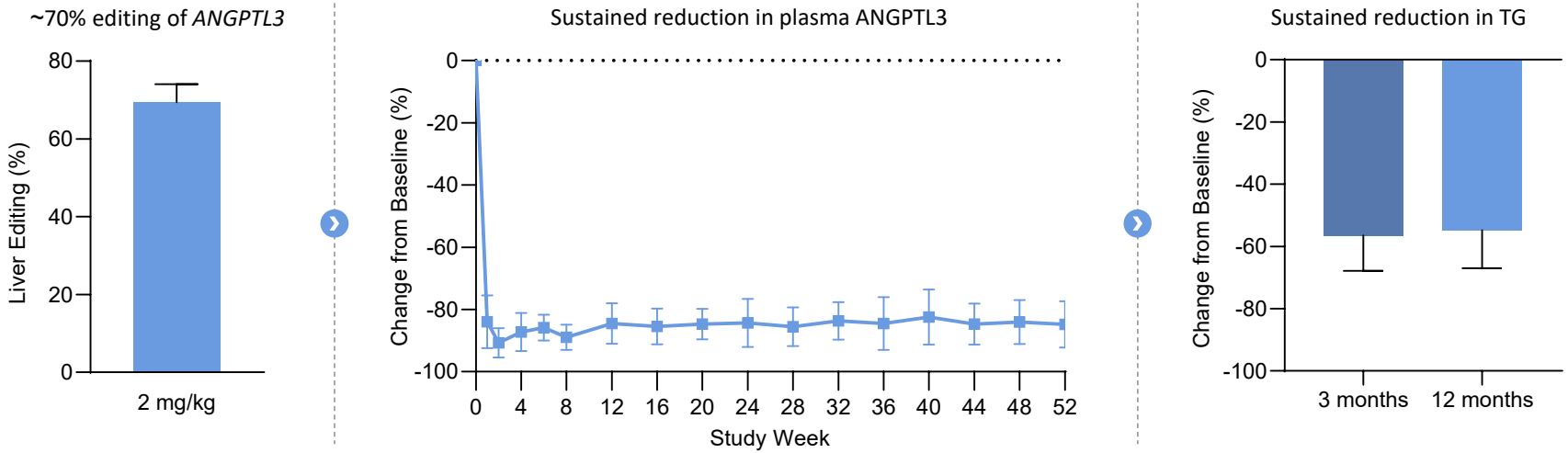
1. Gao et al. 2008

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



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

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

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

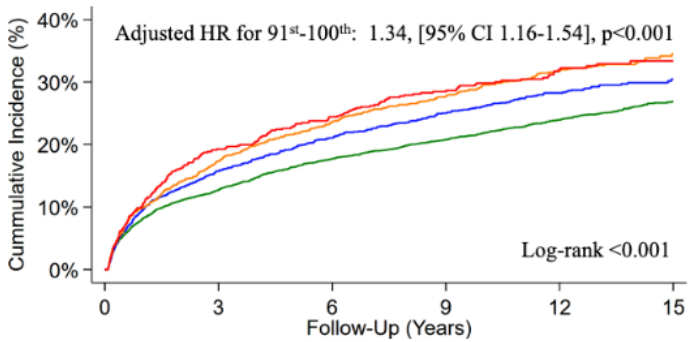
Elevated lipoprotein(a) [Lp(a)] levels increase ASCVD risk, as observed across numerous studies[1,2,3,4,5]

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)

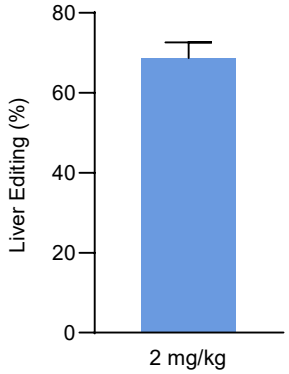
Lp(a) shows an independent association with MACE[5]

- **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

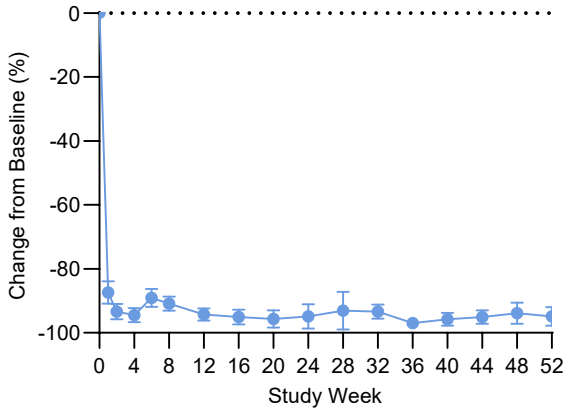


A single dose of CTX320 durably reduced Lp(a) in NHPs out to 1 year

~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

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 (formerly VCTX211)

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 following Vertex opt-out, with ability to leverage ViaCyte cell lines and IP

Next-Generation Editing: Poised to Continue Our Leading Role

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**

In Summary, We Have a 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]
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					ROSWELL PARK	Collaboration[3]
	Anti-CD70 allogeneic CAR-NK	Solid and hematological cancers					nkarta THERAPEUTICS	Collaboration
	Other CAR T	Various						
In Vivo	CTX310: ANGPTL3	Mixed dyslipidemias, HoFH[4], and SHTG[5]						Wholly owned
	CTX320: Lp(a)	ASCVD with elevated Lp(a)						Wholly owned
	CTX330: PCSK9	HeFH[6]						Wholly owned
	Undisclosed rare	-						Wholly owned
	Undisclosed common	-						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)							License
	Myotonic dystrophy type I (DM1)						VERTEX	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 SCD; 3. CRISPR retains commercial rights; (4) Homozygous familial hypercholesterolemia; (5) Severe hypertriglyceridemia; (6) Heterozygous familial hypercholesterolemia

…with Several Upcoming Catalysts in the Next 12 months

	Program	Disease	Status
Heme	CASGEVY	SCD and TDT	EMA approval decision; TDT PDUFA date March 30, 2024
I/O & Autoimmune	CTX112	B-cell malignancies	Trial ongoing – data update in 2024
		SLE	Trial to be initiated 1H 2024
	CTX131	Solid tumors	Trial in RCC ongoing – accruing data from early cohorts
		Heme malignancies	Trial to be initiated 1H 2024
In Vivo	CTX310	Dyslipidemias	Trial initiated – targeting completion of dose escalation in 2024
	CTX320	ASCVD with elevated Lp(a)	Trial initiated – targeting completion of dose escalation in 2024
	Undisclosed	Multiple	New targets to be disclosed in 2024
T1D	CTX211	Type 1 diabetes	Trial ongoing – adding patients to initial cohort

From Our First Decade to the Next One

- Unparalleled strategy and execution to translate our revolutionary CRISPR technology into the **first-ever approved gene-editing therapy**
- **Strong and diversified pipeline, effective operating engine, and robust balance sheet** to support our next phase of growth as a company
- Exciting year for the company coming in 2024, with **multiple catalysts across different disease areas**
- Well-positioned to **establish a sustainable competitive advantage and extend our leadership** in the field