#AHA23

CTX320: An Investigational *In Vivo* CRISPR-Based Therapy Efficiently And Durably Reduces Lipoprotein(a) Levels In Non-Human Primates After A Single Dose

PK Morrow, M.D. | CMO, CRISPR Therapeutics

Forward-looking Statements

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; (vi) the activities under its collaborations and the expected benefits thereof; (vii) 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; (viii) the sufficiency of its cash resources; and (ix) 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: the potential for initial and preliminary data from any clinical trial and initial data from a limited number of patients not to be indicative of final trial results; the potential that clinical trial results may not be favorable; that one or more of its internal or external product candidate programs will not proceed as planned for technical, scientific or commercial reasons; that future competitive or other market factors may adversely affect the commercial potential for its product candidates; uncertainties inherent in the initiation and completion of preclinical studies and whether results from such studies will be predictive of future results of future studies or clinical trials; 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.

Disclosures

PK MORROW, M.D.

Chief Medical Officer, CRISPR Therapeutics

Disclosure Information

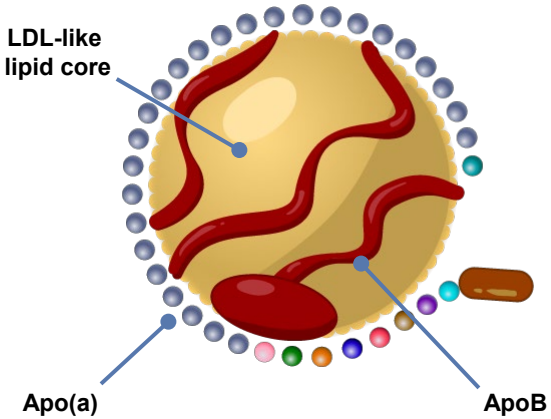
I have the following relevant financial relationships to disclose:

Employee of: CRISPR Therapeutics

Stockholder in: CRISPR Therapeutics

Lipoprotein(a): An Independent Risk Factor for ASCVD

Lp(a) contains a single apo(a) molecule covalently bound by a disulfide bridge to ApoB



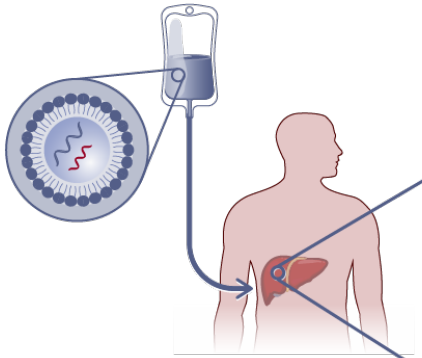
Apo(a) is encoded by the *LPA* gene and determines plasma Lp(a) levels

- Lp(a) is an LDL-like lipoprotein synthesized and secreted by hepatocytes
- Epidemiologic, Mendelian randomization, and genome-wide association studies have shown that elevated Lp(a) levels increase ASCVD risk[1,2,3]
- Over 20% of the global population have circulating Lp(a) concentrations greater than ~125 nmol/L and 5-10% have levels above ~200 nmol/L[4,5]
- In contrast, low expression of Lp(a) (~12.5 nmol/L) is associated with better cardiometabolic outcomes, including 29% reduced risk of coronary heart disease and 37% reduced risk of aortic valve stenosis[6,7]
- Despite the clear association with ASCVD, apheresis is the only proven option for lowering Lp(a) to date
- A one-time, CRISPR-based therapy could recapitulate the protective effect of naturally occurring variants in *LPA* that result in low Lp(a) levels

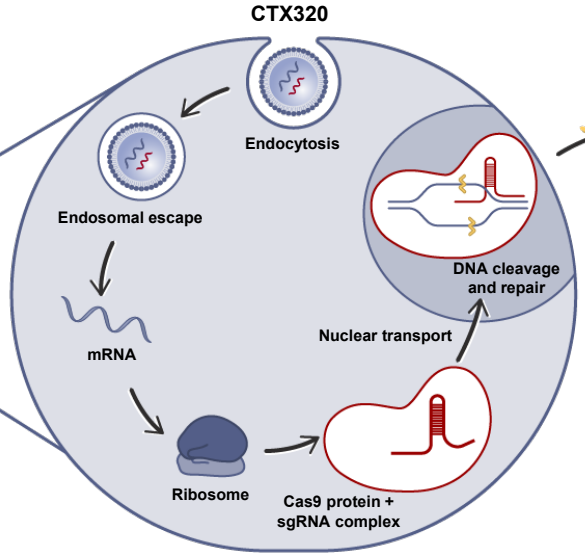
[1]Enas *et al*. 2019; [2]Gurdasani *et al*. 2012; [3]Laschkolnig *et al*. 2014; [4]Nordestgaard *et al*. 2010; [5]Varvel et al. 2016; [6]Langsted *et al*. 2021; [7]Emdin *et al*. 2016

CTX320: A Single-Dose Approach to Reduce Lp(a) Levels

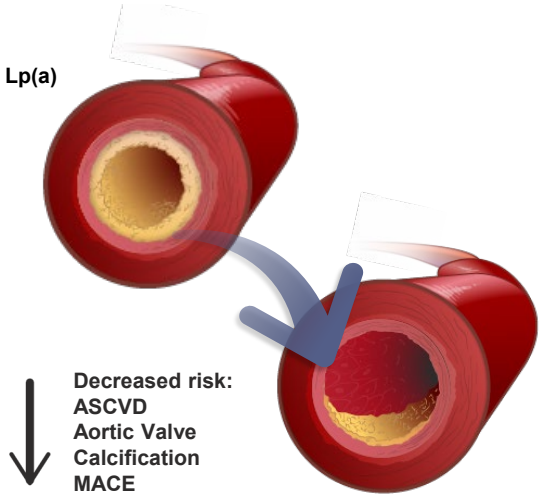
Intravenous delivery to the liver → **CRISPR/Cas9-based editing of *LPA*** → **Reduced plasma Lp(a) levels**



CTX320 consists of Cas9 mRNA and guide RNA (sgRNA) targeting *LPA* encapsulated in lipid nanoparticles (LNPs)



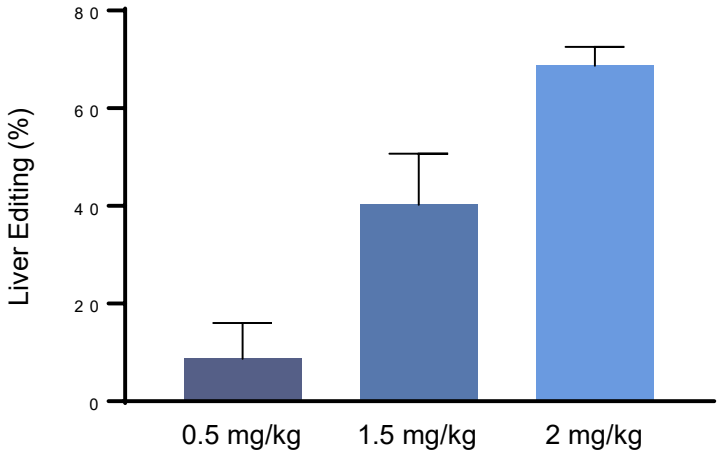
Transient expression of Cas9 and sgRNA in hepatocytes to reduce apo(a) expression permanently



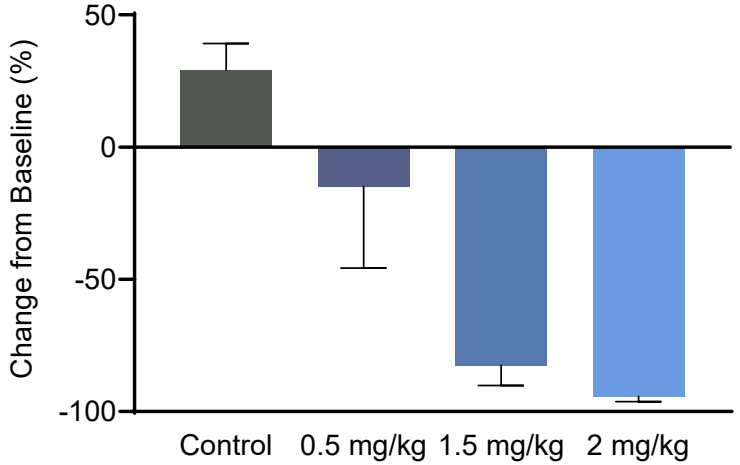
Decreased risk:
ASCVD
Aortic Valve Calcification
MACE

Dose-Dependent Reduction of Lp(a) Observed in Non-Human Primates (NHPs)

~70% editing of *LPA*

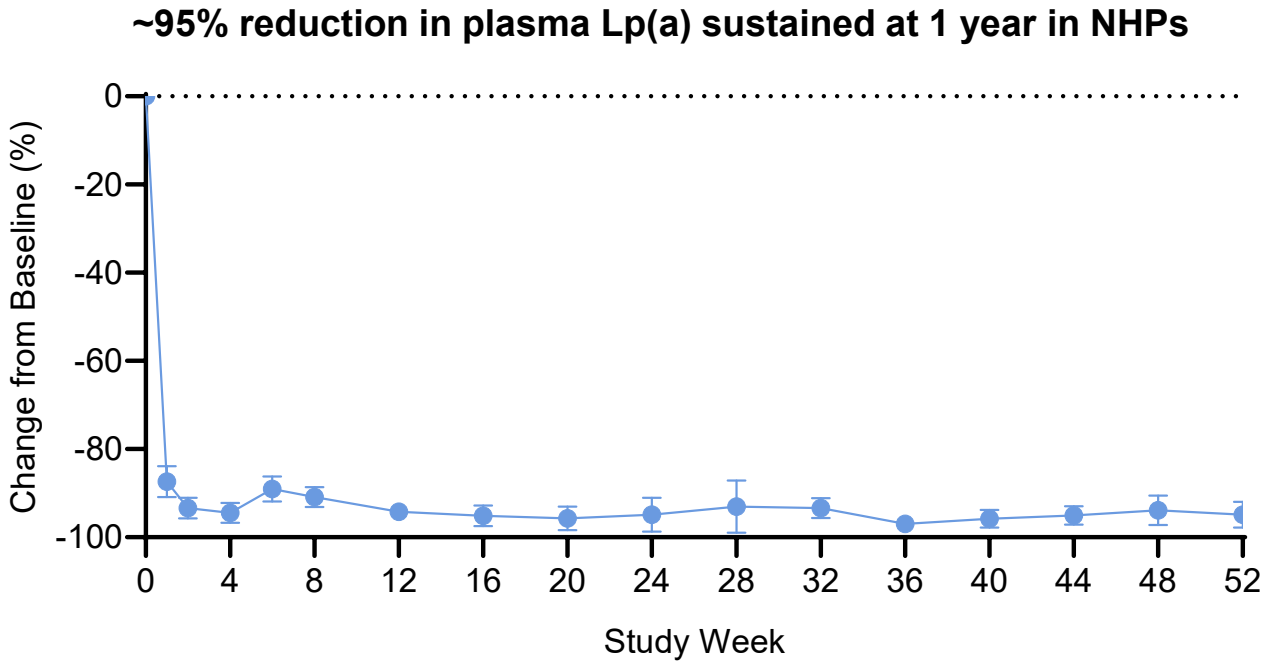


>90% reduction in plasma Lp(a)



Single dose of CTX320 administered to NHPs (N=2 for control, N=4 per treated group) on Day 1; editing for 2 mg/kg assessed at 12 months, all other measurements assessed at 3 months; dose levels reflect mg total RNA

A Single Dose of CTX320 Resulted in Durable Reduction in Lp(a)



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

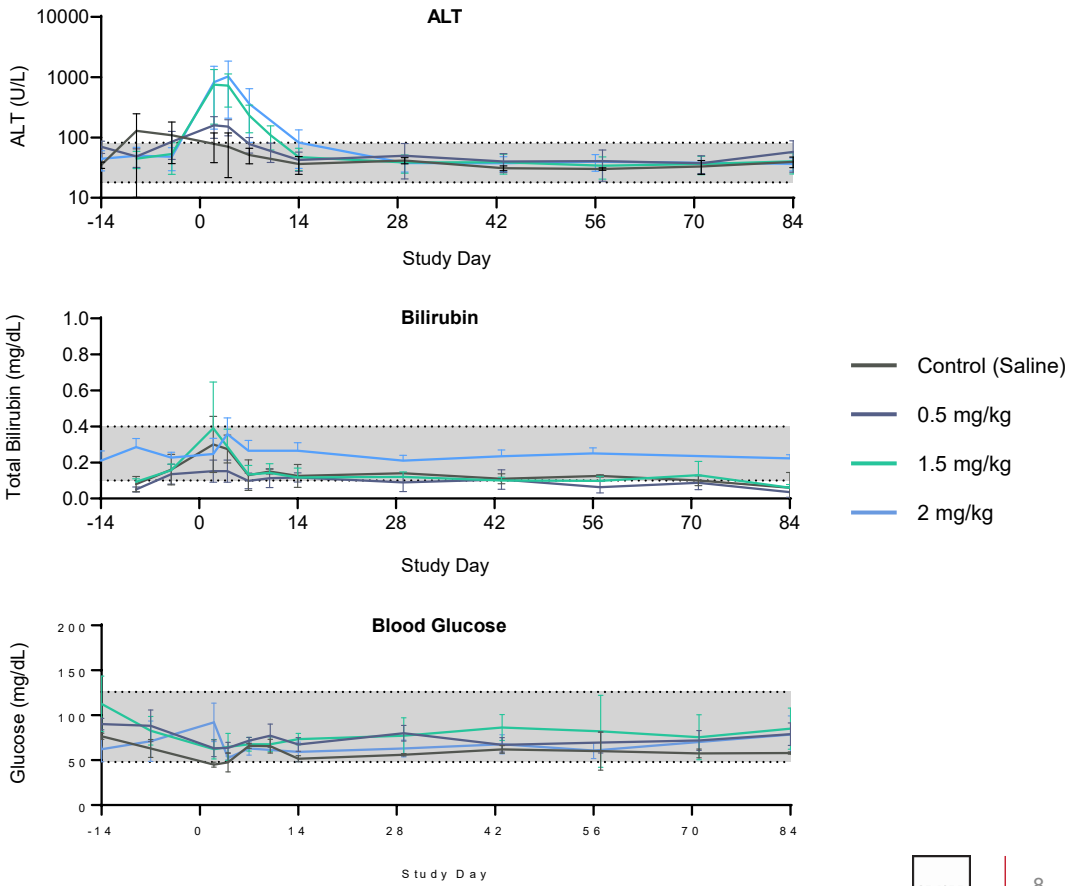
CTX320 Demonstrated an Acceptable Safety Profile in NHPs

Transient liver enzyme elevations commonly seen with LNP delivery to NHPs

- At anticipated clinical dose levels, one-time, dose-dependent elevations in liver enzymes observed, which resolve fully
- After transient elevation, liver enzymes remain in normal range out to 12 months
- Clinical studies with LNP-based therapies indicate that humans experience low or no enzyme elevations at comparable doses

No adverse effects observed due to *LPA* editing

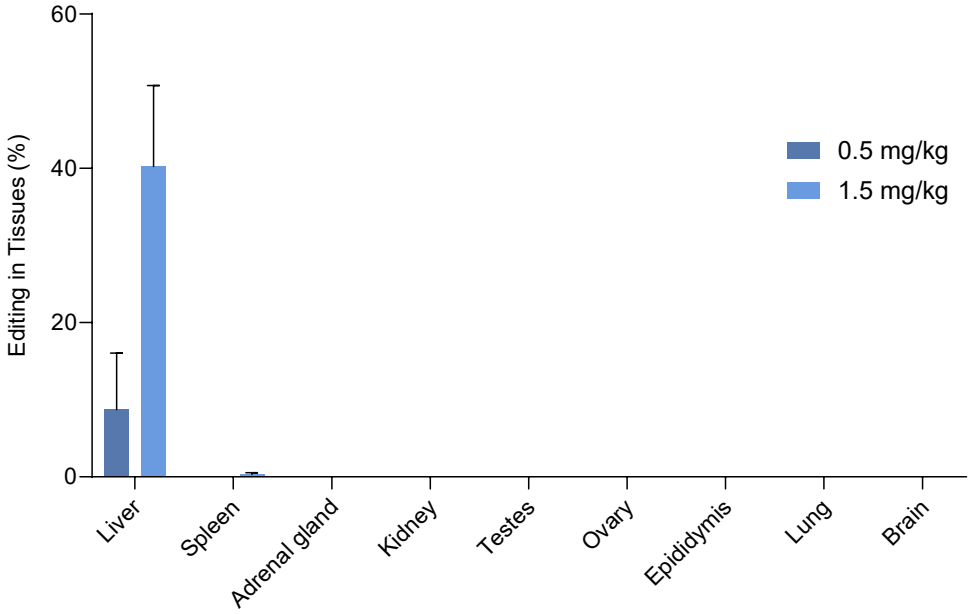
- No related changes in histopathology, clinical signs, body weight, or safety pharmacology evaluations (ocular, neurologic, respiratory)
- No related changes in hematology, including coagulation
- No changes to blood glucose



Graphs: Shaded areas indicate normal range

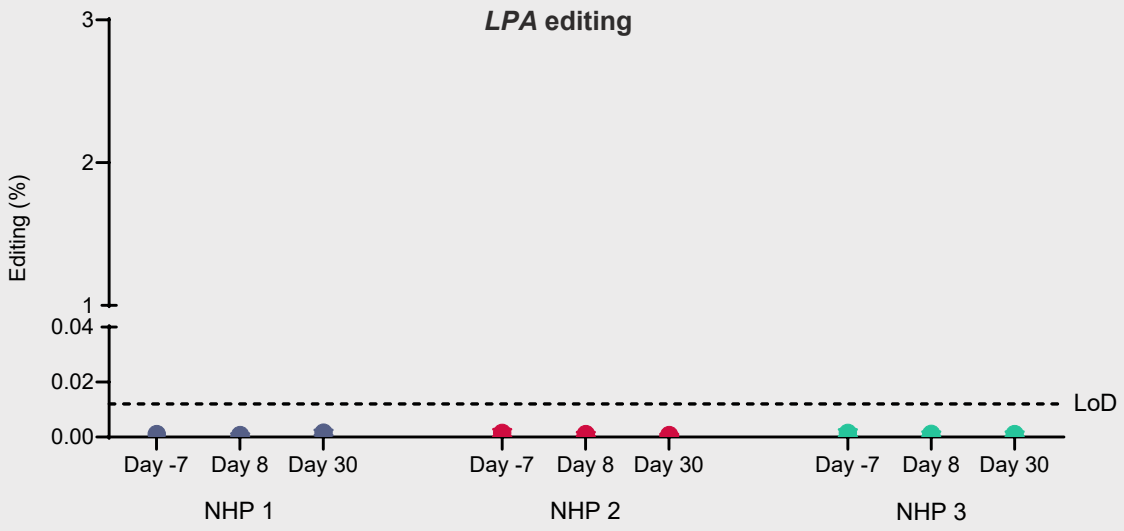
CTX320 Is Highly Directed to the Liver

- No editing above limit of detection (0.012%) observed in most extrahepatic tissues
- No adverse events related to extrahepatic editing observed



Single dose of CTX320 administered to NHPs (N=4, 2 male, 2 female) on Day 1

No Germline Editing Observed in Sexually Mature Male NHPs



- Assessment of CTX320 on-target editing in male sperm from a pharmacology study of CTX320 in cynomolgus monkeys
- No editing above the limit of detection observed to date

Single dose of CTX320 (1 mg/kg) administered to sexually mature (>10 years old) male NHPs (N=3) on Day 1; n=5 technical replicates per sample; Limit of Detection (LoD) = 0.012%; study ongoing

No Unintended Genomic Alterations Observed Following Extensive Assessment

Off-target editing

Nomination of potential off-target sites

~420 sites identified from computational homology search

~20 sites identified from empirical homology-independent assay[1]

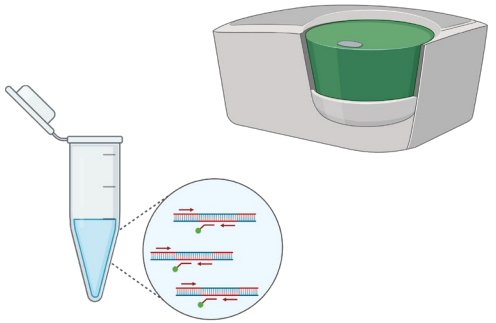
Validation of nominated off-target sites

Nominated sites assessed using deep sequencing of liver, spleen, and adrenal primary cells from 10 human donors

No off-target editing observed

Translocation analysis

Highly sensitive ddPCR assay to measure homologous translocations at the on-target site in primary human hepatocytes (PHH)



No translocations observed

Follows framework highlighted in the FDA Advisory Committee meeting on October 31, 2023

[1]Digenome-seq

Phase 1 Study Evaluating the Safety and Efficacy of CTX320

Phase 1: Single ascending dose escalation to identify optimal biological dose

- Dose level 4
- Dose level 3
- Dose level 2
- Dose level 1

Key eligibility criteria

- Age ≥18-65 years
- Elevated levels of Lp(a) and CVD
- Adequate renal, liver, cardiac, and pulmonary organ function
- No significant co-morbidities

Primary endpoints

- Incidence of adverse events, defined as DLTs

Key secondary endpoints

- Change in Lp(a) compared to baseline
- Pharmacokinetics

Phase 2

- Patients with elevated levels of Lp(a)
- Phase 2 dose informed by Phase 1

Summary

- Lp(a) is an atherogenic lipoprotein associated with an **increased risk of ASCVD and MACE;** there are currently **no therapies approved for lowering Lp(a)**
- **CTX320 is an investigational CRISPR-based gene editing therapy designed to reduce expression of LPA**
- A single dose of CTX320 leads to **efficient editing and durable reductions in plasma Lp(a) in NHPs** in a dose-dependent manner
- **Extensive preclinical analysis of CTX320 supports the safety of a CRISPR/Cas9-based therapeutic** to lower Lp(a)
- CTX320 has the potential to permanently reduce Lp(a) following a one-time treatment, which could **address the significant unmet need for patients with high levels of Lp(a)**
- **A Phase I trial evaluating CTX320 is on track to start in 2024** for the treatment of patients with elevated Lp(a)

THANK YOU

American Heart Association.

Scientific Sessions

#AHA23