#AHA23

CTX310: An Investigational *In Vivo* CRISPR-Based Therapy Efficiently and Durably Reduces ANGPTL3 Protein and Triglyceride Levels in Non-Human Primates After a Single Dose

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American Heart Association.

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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

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Disclosure Information

I have the following relevant financial relationships to disclose:

Employee of: CRISPR Therapeutics

Stockholder in: CRISPR Therapeutics

A One-Time CRISPR-Based Therapy Could Transform the Treatment Paradigm for CVD

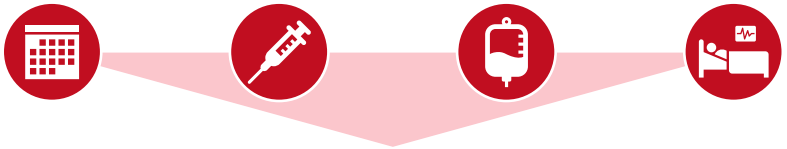
The chronic care model

Daily medications

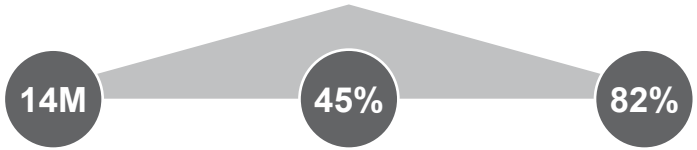
Weekly injections

Multiple infusions annually

Surgical interventions



Heavy burden for patients and the healthcare system



people with very high CV risk[1,2] in U.S. and Europe, including **~4M** with genetic dyslipidemias[3,4]

not adherent to lipid-lowering therapy despite prior major CV events[5]

not at LDL-C target goal[2]

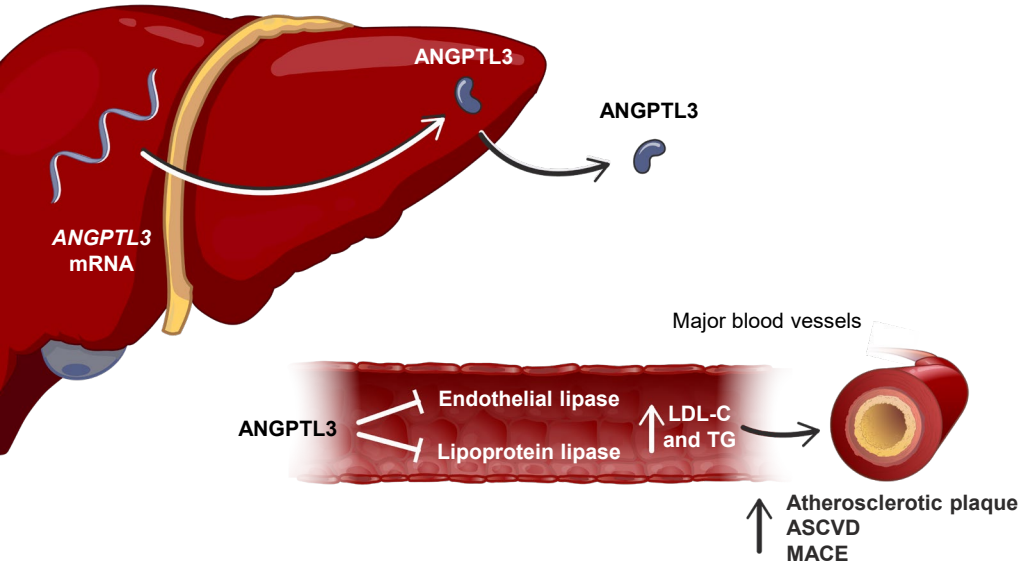
A new treatment paradigm

One-time CRISPR-based therapies with the potential to:

- Recapitulate the protective effect of naturally occurring loss-of-function variants in genes like *ANGPTL3*
- Provide sustained lowering of atherogenic lipoproteins
- Improve long-term cardiovascular outcomes by getting patients' lipid levels lower for longer
- Minimize or eliminate the need for additional treatments

[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

ANGPTL3 Inhibits Enzymes Critical to Lipoprotein Metabolism



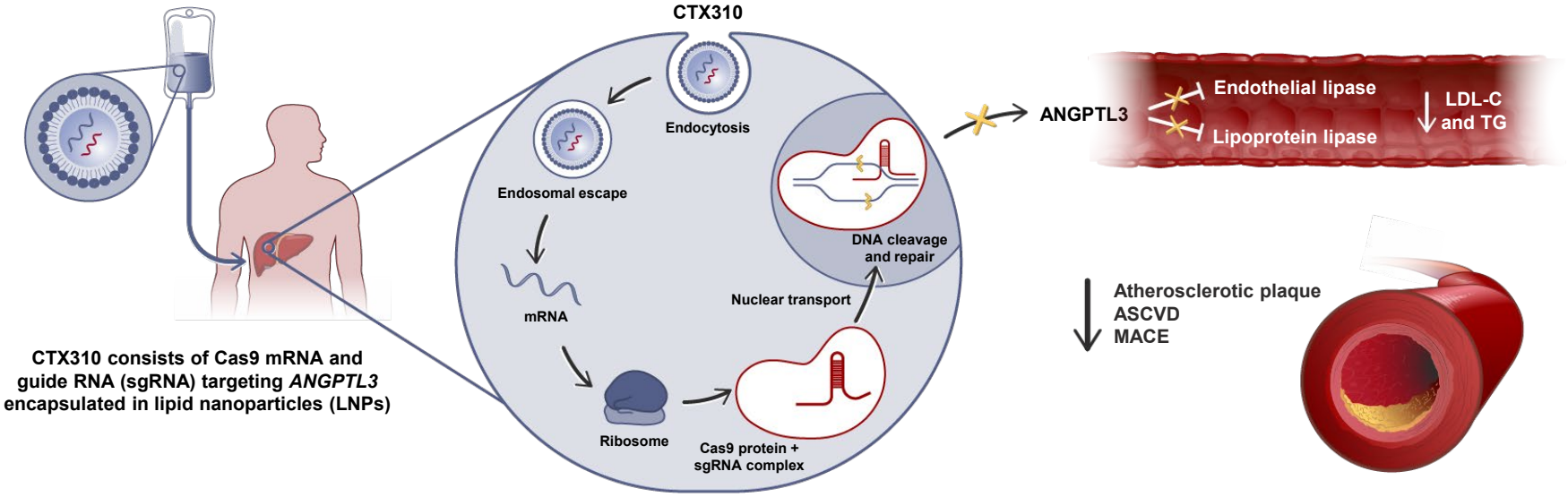
ANGPTL3 inhibits endothelial and lipoprotein lipases which increases circulating LDL-C and TG leading to increases in atherosclerotic plaque formation

- **Angiopoietin-like 3 protein (ANGPTL3)** is synthesized and secreted by hepatocytes and is a key regulator of circulating atherogenic lipoproteins
- **Natural loss-of-function mutations** in *ANGPTL3* have been associated with reduced LDL-C, triglycerides (TG) and ASCVD risk without negative impact on overall health[6,7]
- **Pharmacological inhibition of ANGPTL3** leads to decreases in LDL-C and TG, and thereby has the potential to prevent ASCVD or reduce ASCVD-related events

[6]Minicocci *et al*. 2012; [7]D'Erasmo *et al*. 2023

CTX310: A One-Time Dose Approach to Stop Expression of ANGPTL3

Intravenous delivery to the liver → **CRISPR/Cas9-based editing of *ANGPTL3*** → **Reduced atherogenic lipoprotein concentrations**

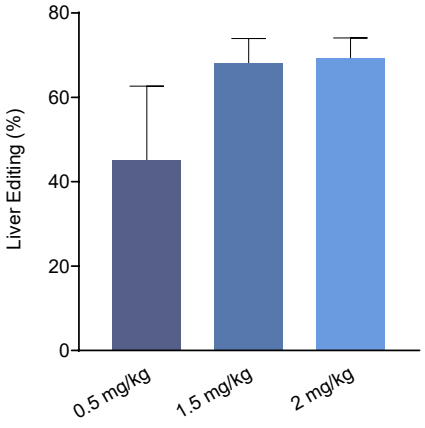


CTX310 consists of Cas9 mRNA and guide RNA (sgRNA) targeting *ANGPTL3* encapsulated in lipid nanoparticles (LNPs)

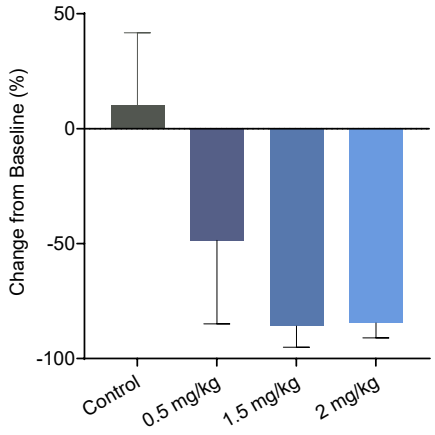
Transient expression of Cas9 and sgRNA in hepatocytes to reduce ANGPTL3 expression permanently

Dose-Dependent Reduction of ANGPTL3 and TG Observed in Non-Human Primates (NHPs)

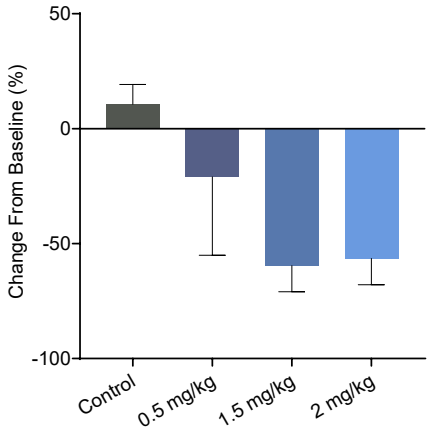
~70% editing of *ANGPTL3*



>85% reduction in plasma ANGPTL3 protein



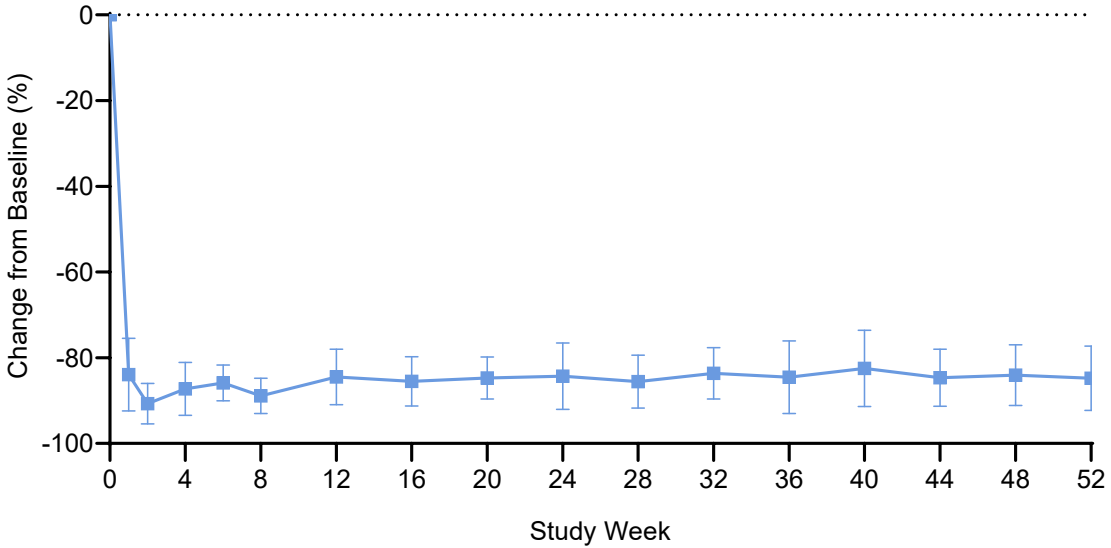
60% reduction in serum triglycerides (TG)



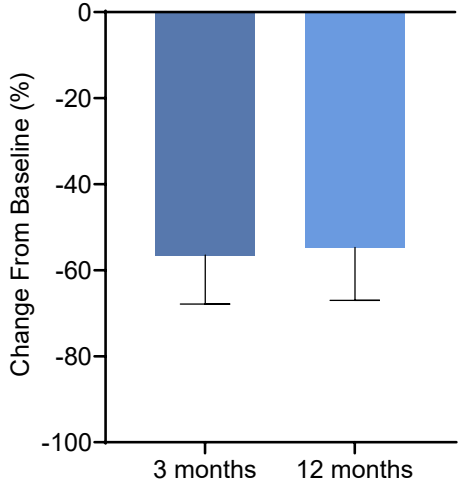
Single dose of CTX310 administered to NHPs (N=2 for control, N=4 for 0.5 and 1.5 mg/kg, N=8 for 2 mg/kg) on Day 1; editing for 2 mg/kg assessed at 12 months, all other measurements assessed at 3 months; dose levels reflect mg total RNA

A Single Dose of CTX310 Resulted in Durable Reduction in ANGPTL3 Protein and TG

Reduction in plasma ANGPTL3 sustained at 1 year in NHPs



Reduction in TG sustained at 1 year



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

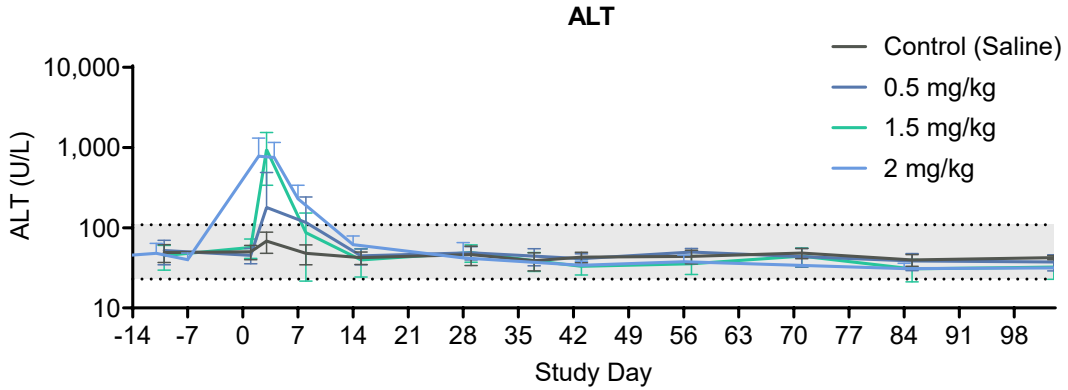
CTX310 Demonstrated an Acceptable Safety Profile in NHPs

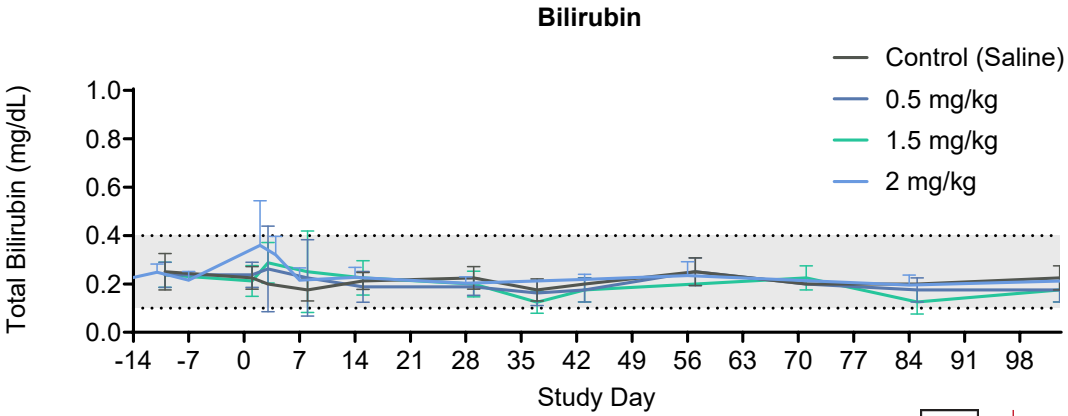
Transient liver enzyme elevations commonly seen with LNP delivery to NHPs

- 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 ANGPTL3 editing

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

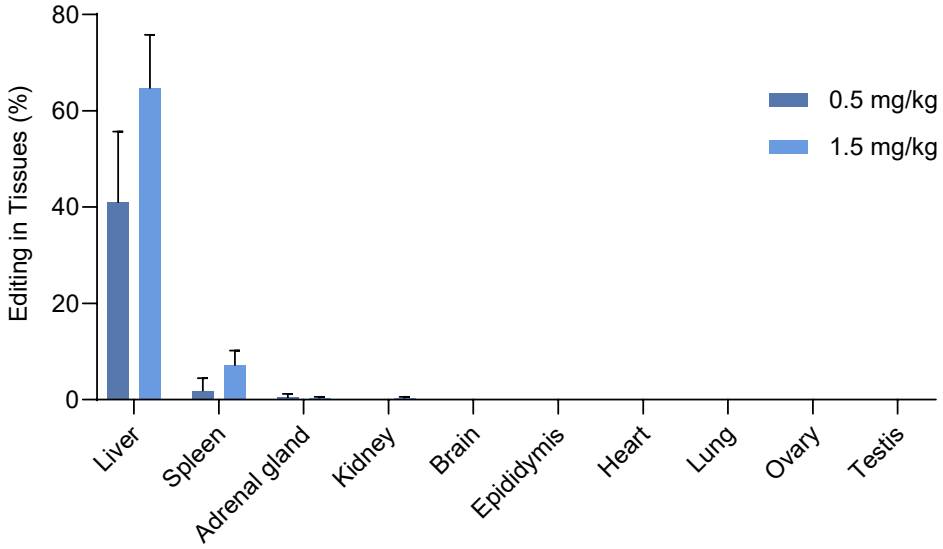




Graphs: Shaded areas indicate normal range

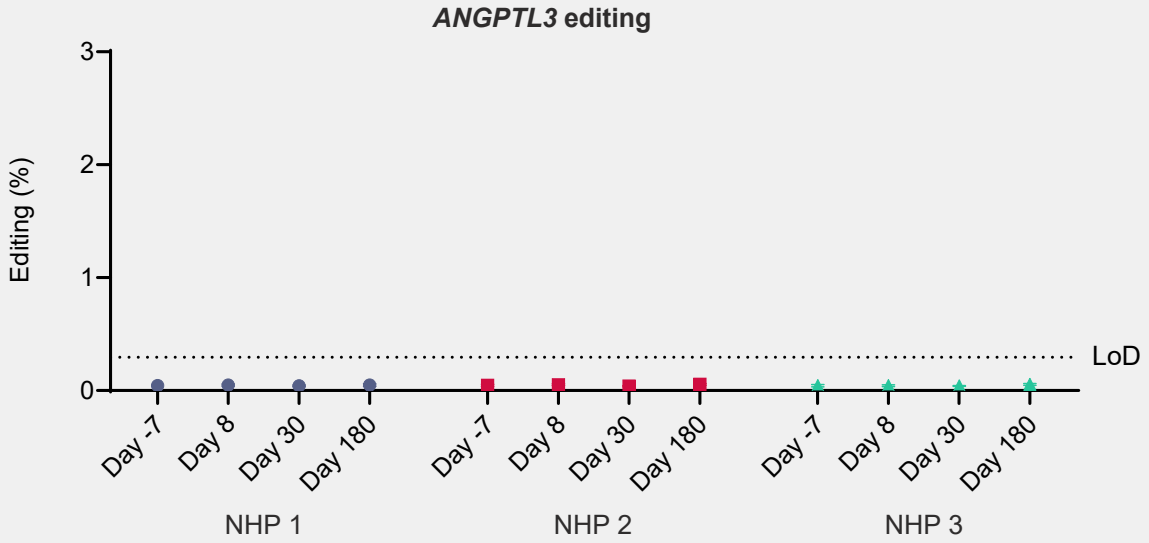
CTX310 Is Highly Directed to the Liver

- No editing above limit of detection (0.295%) observed in most extrahepatic tissues
- No adverse events related to extrahepatic editing observed



Single dose of CTX310 administered to NHPs (N=4, 2 male, 2 female) on Day 1

No Germline Editing Observed in Sexually Mature Male NHPs



- Assessment of on-target editing in sperm from a pharmacology study of CTX310 in sexually mature cynomolgus monkeys
- No editing above the limit of detection observed for the duration of the study

Single dose of CTX310 (1 mg/kg) administered to sexually mature (10-year-old) male NHPs (N=3) on Day 1; n=6 technical replicates per sample; Limit of Detection (LoD) = 0.295%

No Unintended Genomic Alterations Observed Following Extensive Assessment

Off-target editing

Nomination of potential off-target sites

~550 sites identified from computational homology search

~60 sites identified from empirical homology-independent assay[1]

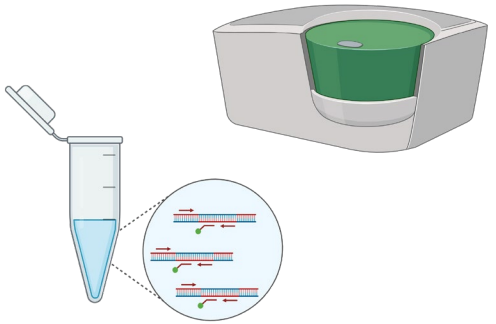
Validation of nominated off-target sites

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)



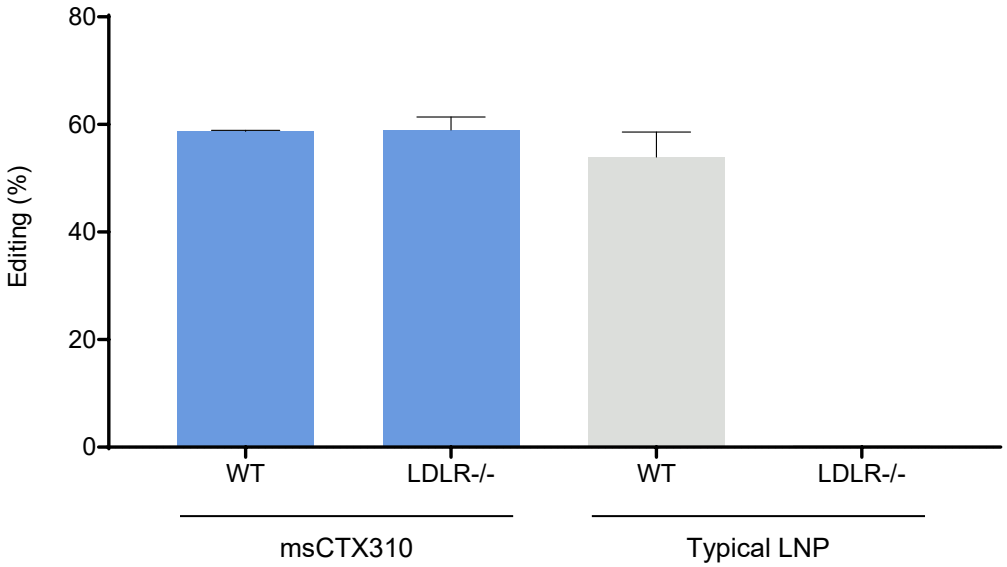
No translocations observed

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

[1]Digenome-seq

CTX310 Does Not Require LDL Receptor For Uptake in Hepatocytes

Comparable editing of *Angptl3* observed in wild type (WT) and LDLR-/- mice using a mouse surrogate gRNA (msCTX310)



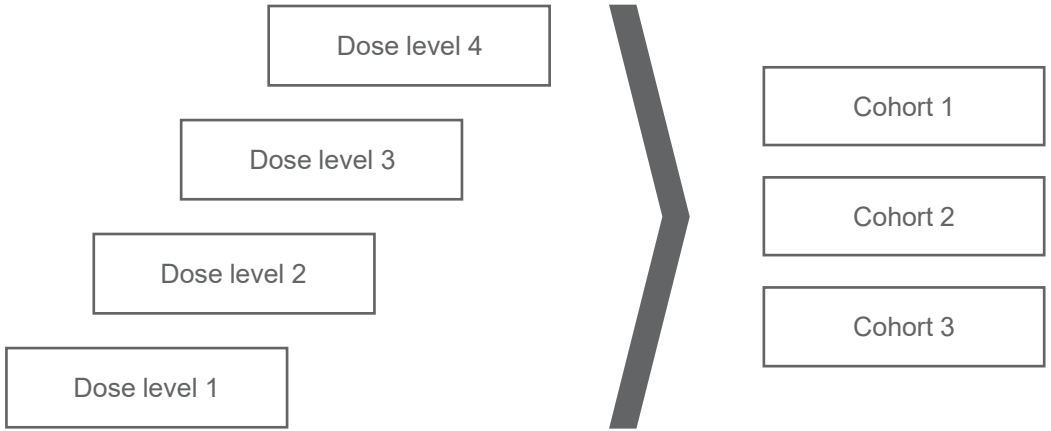
- Most patients with homozygous familial hypercholesterolemia (HoFH) have dysfunctional LDL receptor (LDLR), making delivery with typical LNP formulations ineffective
- CTX310 has a next-generation LNP formulation that enables hepatic delivery independent of LDLR expression, without the need for additional conjugations like GalNAc
- A pilot study in an LDLR-/- HoFH disease mouse model demonstrated the expected reductions in atherogenic lipoproteins, including LDL-C, following *Angptl3* editing

N=3 mice per group

Phase 1 Study Evaluating the Safety and Efficacy of CTX310

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

Phase 1b/2: Expansion cohorts at optimal biological dose



Key eligibility criteria

- Age ≥18-70 years
- Persistent mixed dyslipidemia, HoFH, HeFH, MCS and other undefined dyslipidemias
- Refractory or lack of access to available therapies
- 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 ANGPTL3 compared to baseline
- Change in lipid levels compared to baseline
- Pharmacokinetics

Summary

- **CTX310 is an investigational CRISPR-based gene editing therapy designed to reduce expression of ANGPTL3,** which should thereby lower levels of atherogenic lipoproteins
- A single dose of CTX310 leads to **efficient editing and durable reductions in plasma ANGPTL3 and circulating triglycerides in NHPs** in a dose-dependent manner
- **Extensive preclinical analysis of CTX310 supports the safety of a CRISPR/Cas9-based therapeutic** to disrupt ANGPTL3 expression
- CTX310 has the potential to permanently reduce atherogenic lipoproteins following a one-time treatment, which could **shift the treatment paradigm for cardiovascular disease** away from the chronic care model
- **A Phase I trial evaluating CTX310 has been initiated** in patients with hypercholesterolemia (HeFH/HoFH) or hypertriglyceridemia

THANK YOU

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