Phase 1 Trial of CRISPR-Cas9 Gene Editing Targeting ANGPTL3

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Background

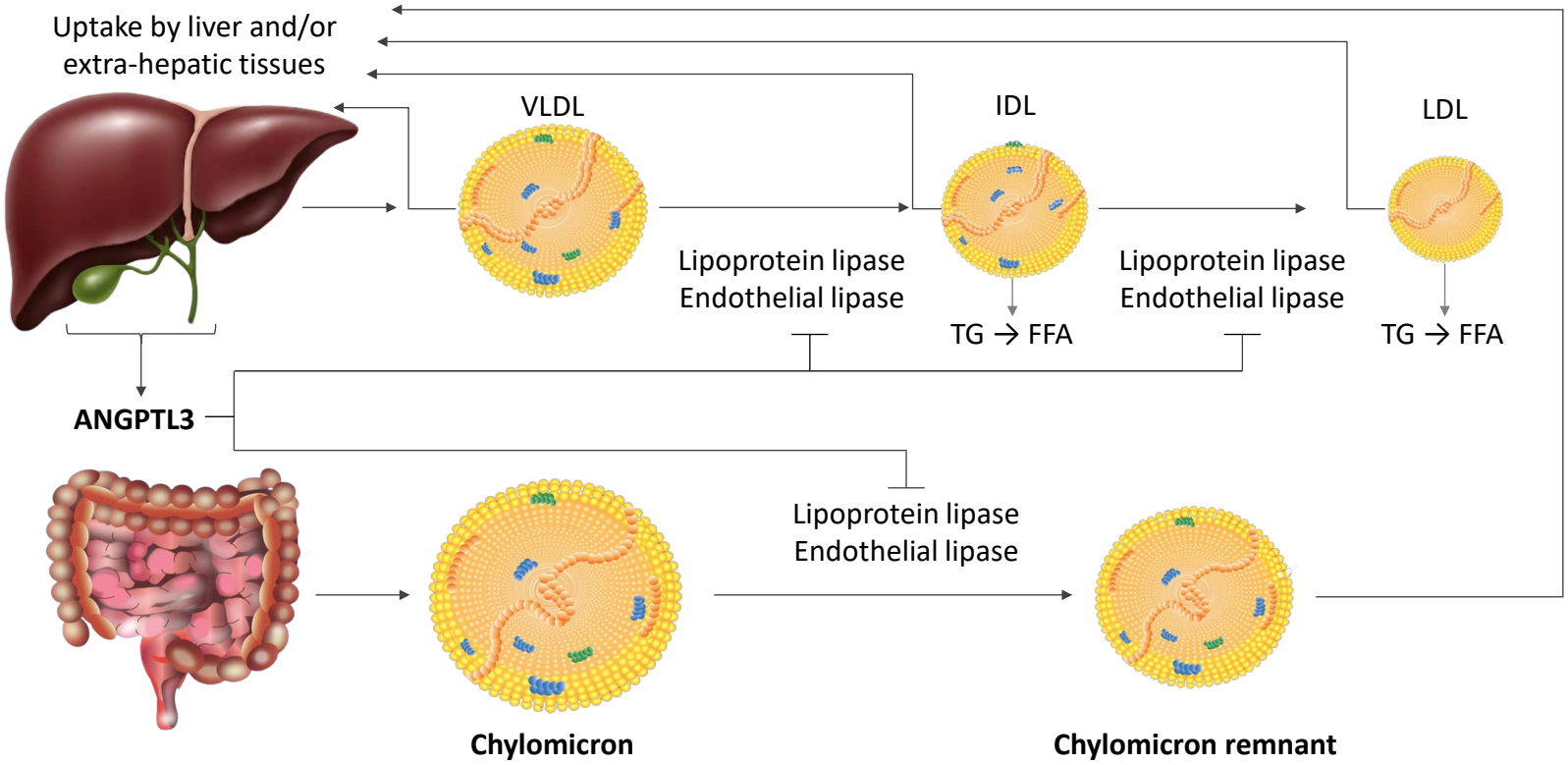
A major limitation of currently available atherogenic lipid-lowering agents is diminishing adherence over time as well as side effects

Angiopoietin-like 3 **(ANGPTL3)** is an important regulator of lipid metabolism through inhibition of lipoprotein and endothelial lipase

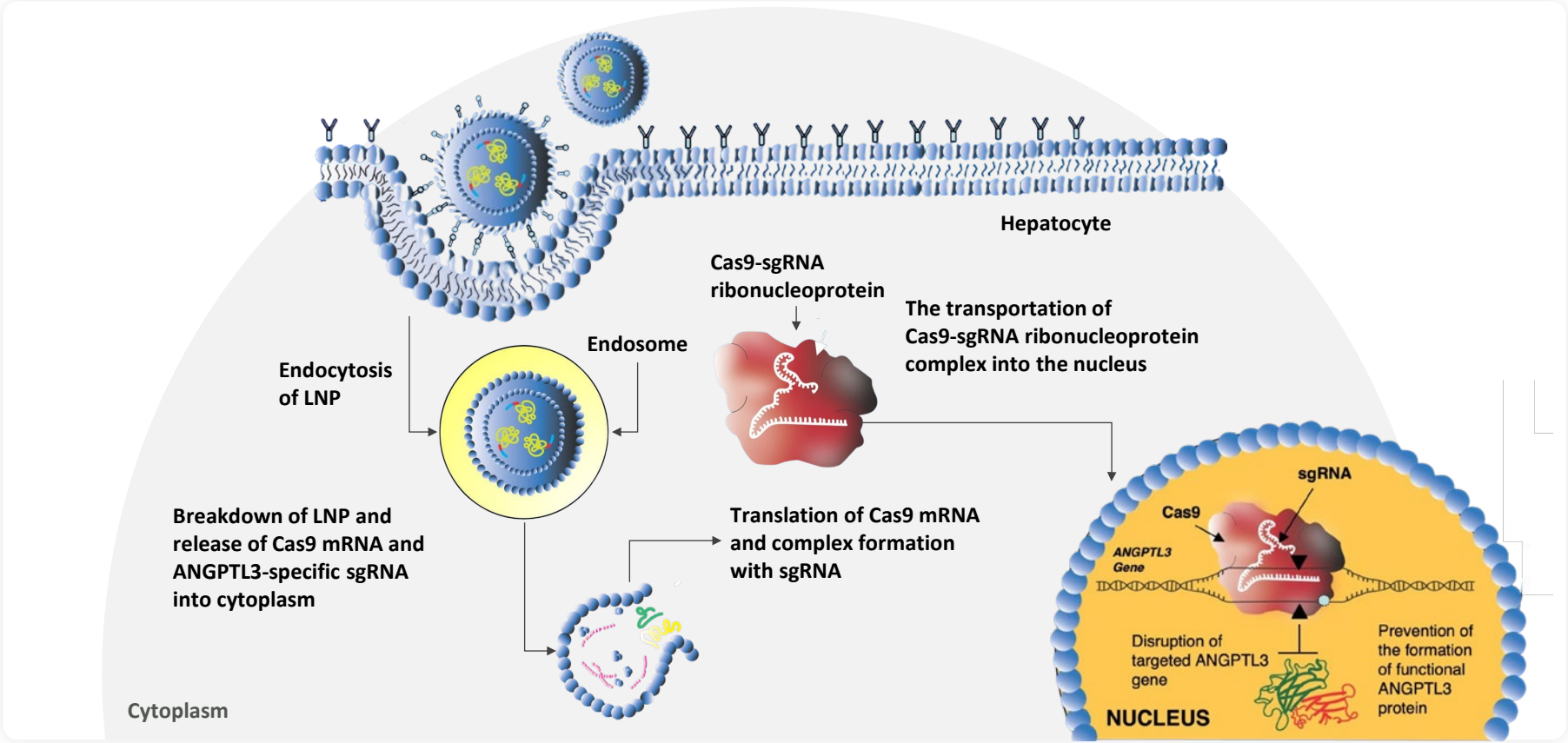
Loss-of-function gene variants for ***ANGPTL3*** result in lifelong reductions in LDL-C, triglycerides and reduced risk of ASCVD

CTX310 is a lipid nanoparticle CRISPR Cas9 formulation to induce permanent loss of function in the ***ANGPTL3*** gene developed as a one-time treatment for elevated LDL-C and triglycerides

Role of ANGPTL3 in Lipid Metabolism



CTX310: CRISPR-Cas9 Editing of **ANGPTL3**



Study Design

- Single ascending doses of CTX310 administered intravenously to 15 participants with HoFH, HeFH, elevated TGs or mixed dyslipidemia on maximally tolerated medical therapy
- Participants premedicated with corticosteroids and antihistamines randomized to 0.1, 0.3, 0.6, 0.7 or 0.8 mg/kg of CTX310 infused over several hours
- Safety and tolerability assessed during follow up with biomarkers collected to assess lipid effects and liver safety
- Biomarkers available for ≥ 30 days for the current report

Primary Safety and Efficacy Endpoints

Safety outcomes, including dose limiting toxicities, graded using the Common Terminology Criteria for Adverse Events

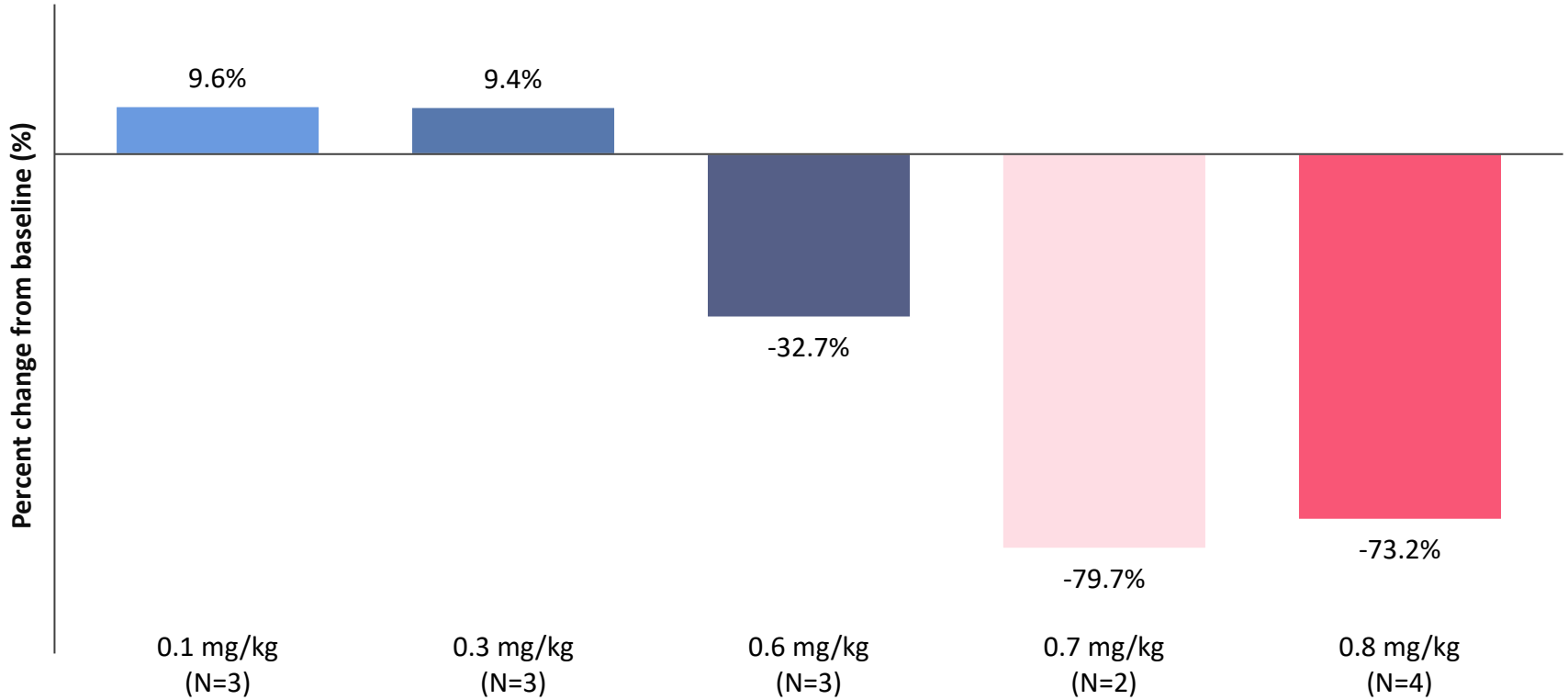
Efficacy endpoints included percent changes over time for

- LDL cholesterol
- Triglycerides
- Apolipoprotein B, Apolipoprotein CIII
- Non-HDL cholesterol
- Remnant cholesterol

Baseline Characteristics

	All participants (n=15)
Median Age	53 years
Male	87%
Clinical ASCVD	40%
Familial hypercholesterolemia	40%
Severe hypertriglyceridemia	13%
Mixed dyslipidemia	40%
Mean LDL-C	155 mg/dL
Median triglycerides	192 mg/dL

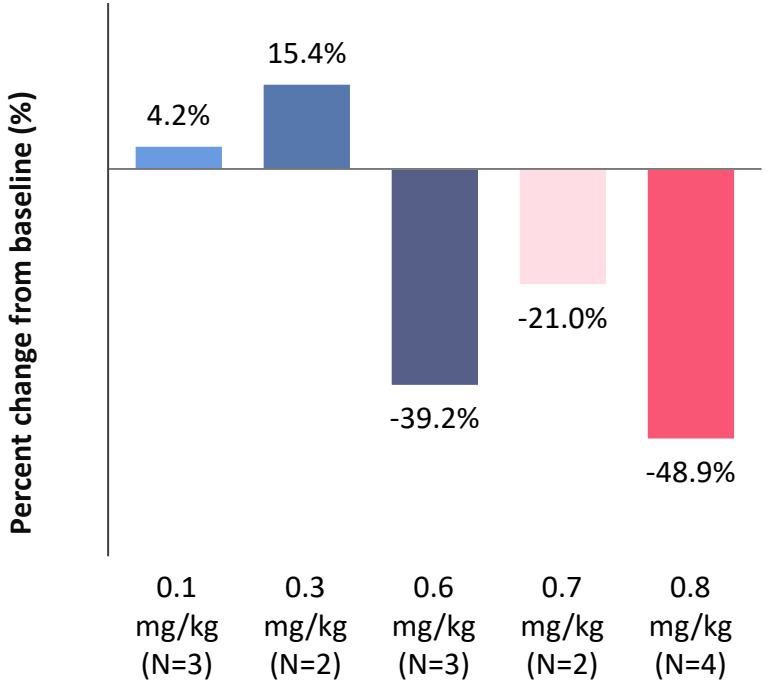
Mean Percent Change from Baseline in ANGPTL3



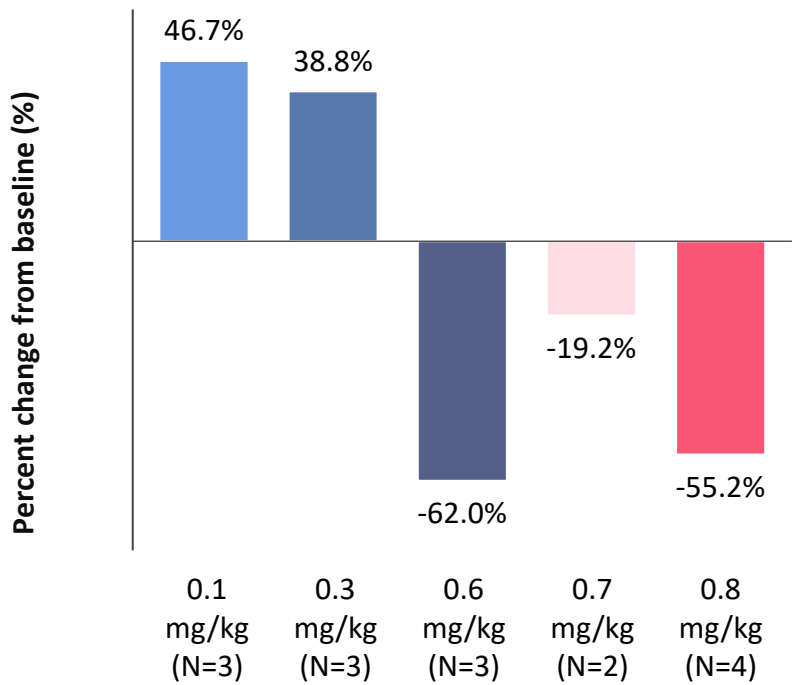
*Mean percent change from baseline are reported at 30 days for all subjects.

Mean Percent Change from Baseline in LDL-C and Triglycerides

LDL Cholesterol



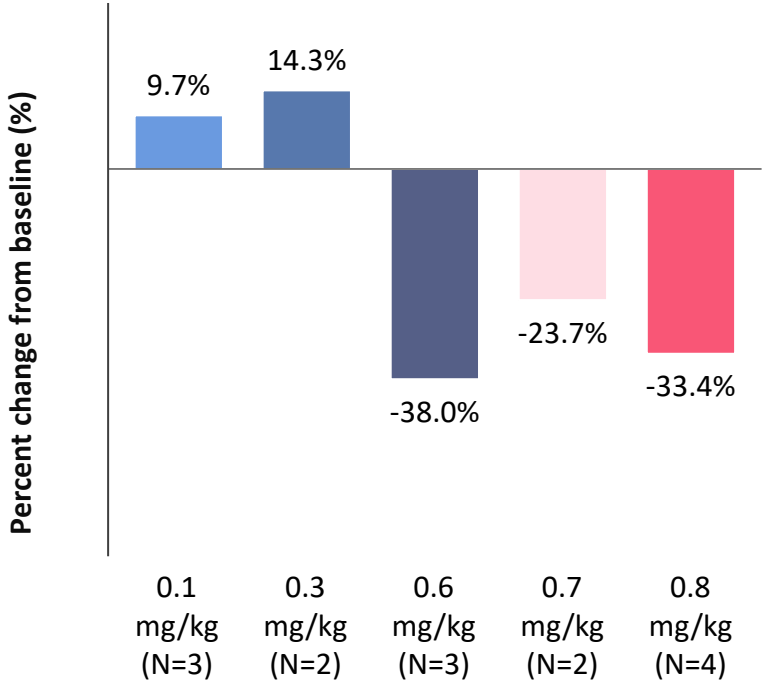
Triglycerides



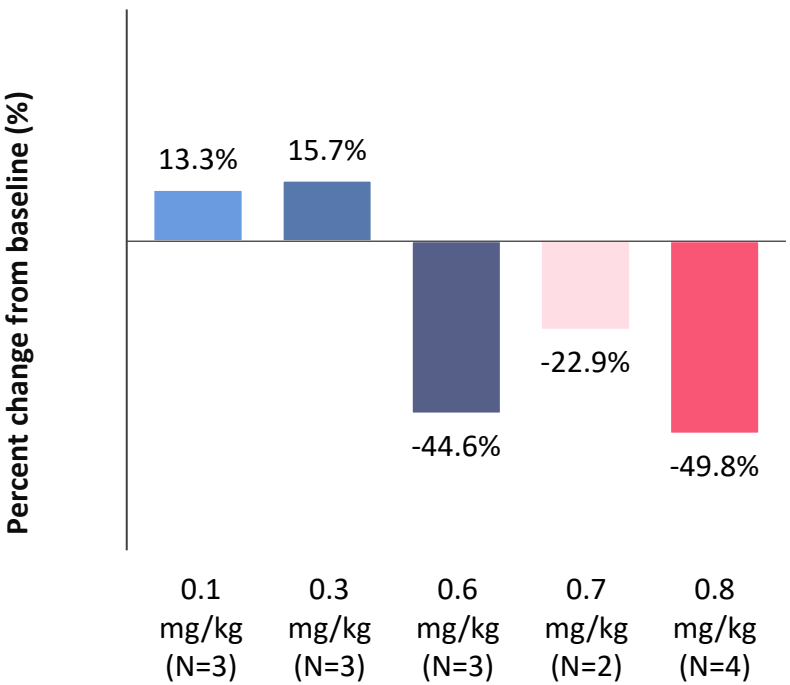
Mean percent change from baseline are reported at 90 days following 0.1, 0.3, 0.6 mg/kg CTX310 doses and at 60 days following 0.7 and 0.8 mg/kg CTX310 doses.

Mean Percent Change in ApoB and Non-HDL-C

Apolipoprotein B



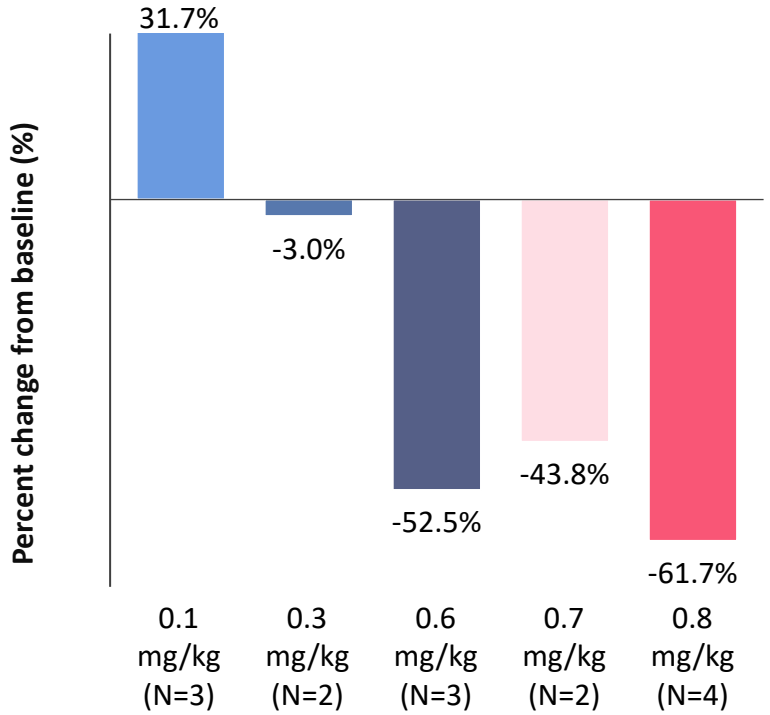
Non-HDL Cholesterol



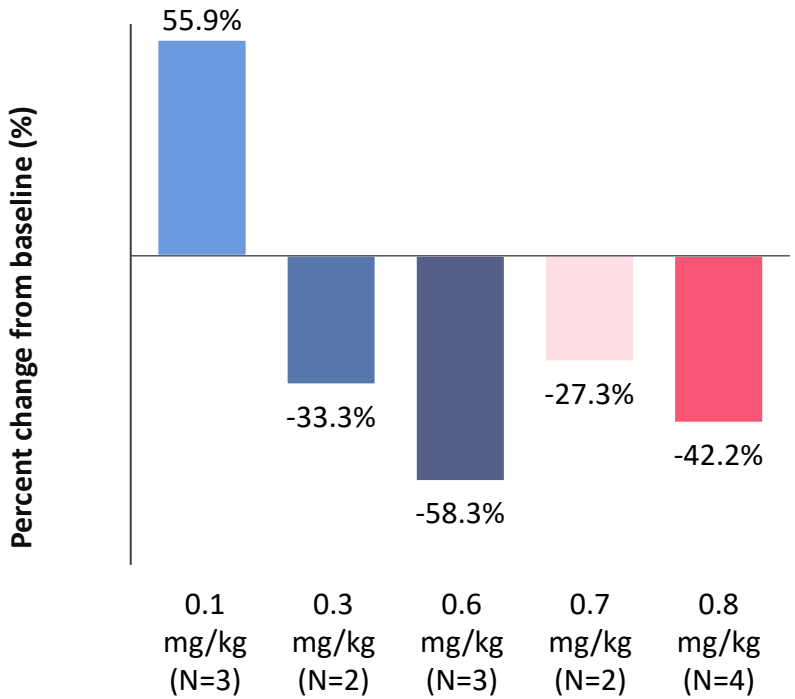
Mean percent change from baseline are reported at 90 days following 0.1, 0.3, 0.6 mg/kg CTX310 doses and at 60 days following 0.7 and 0.8 mg/kg CTX310 doses.

Mean Percent Change in Remnant Cholesterol and Apo CIII

Apolipoprotein CIII

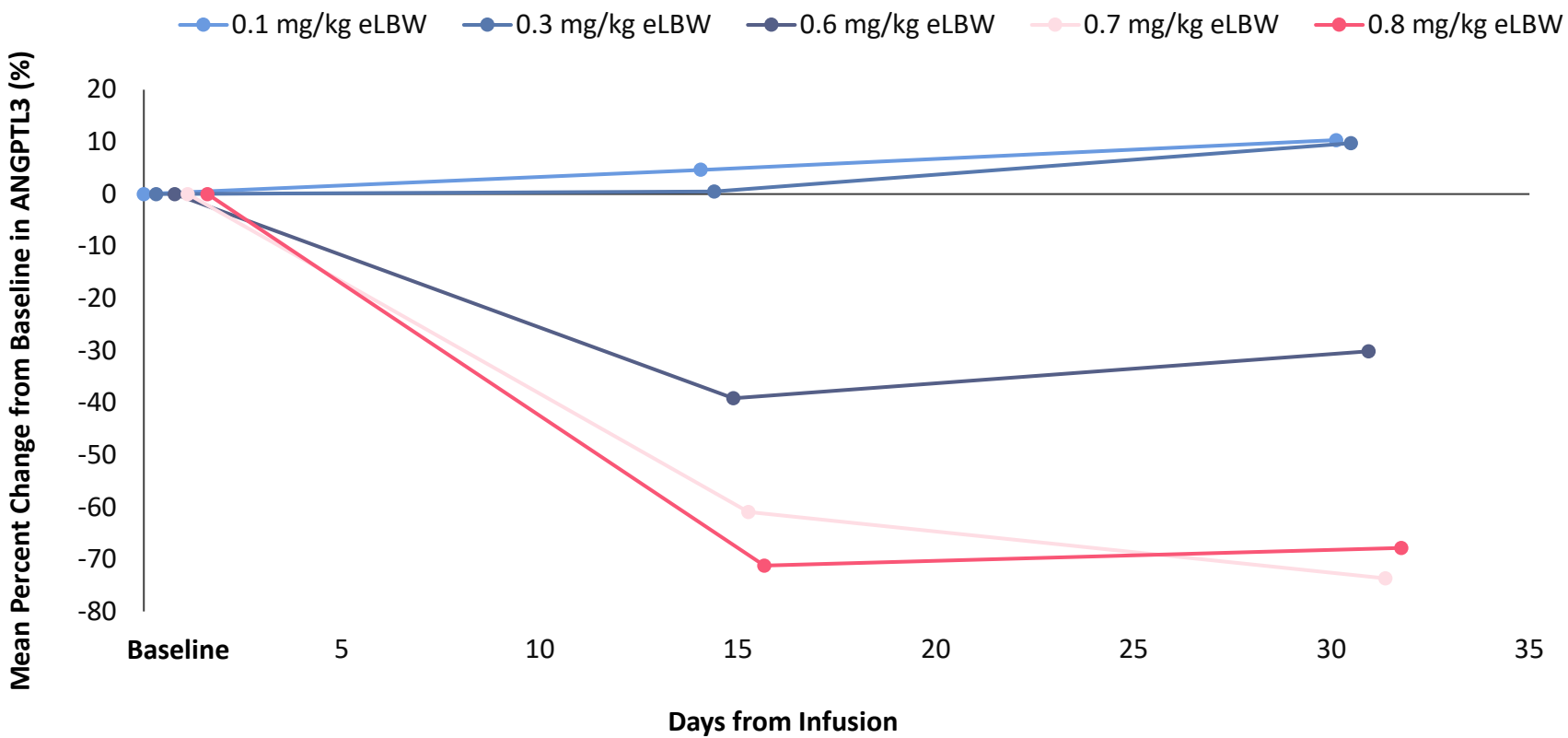


Remnant Cholesterol

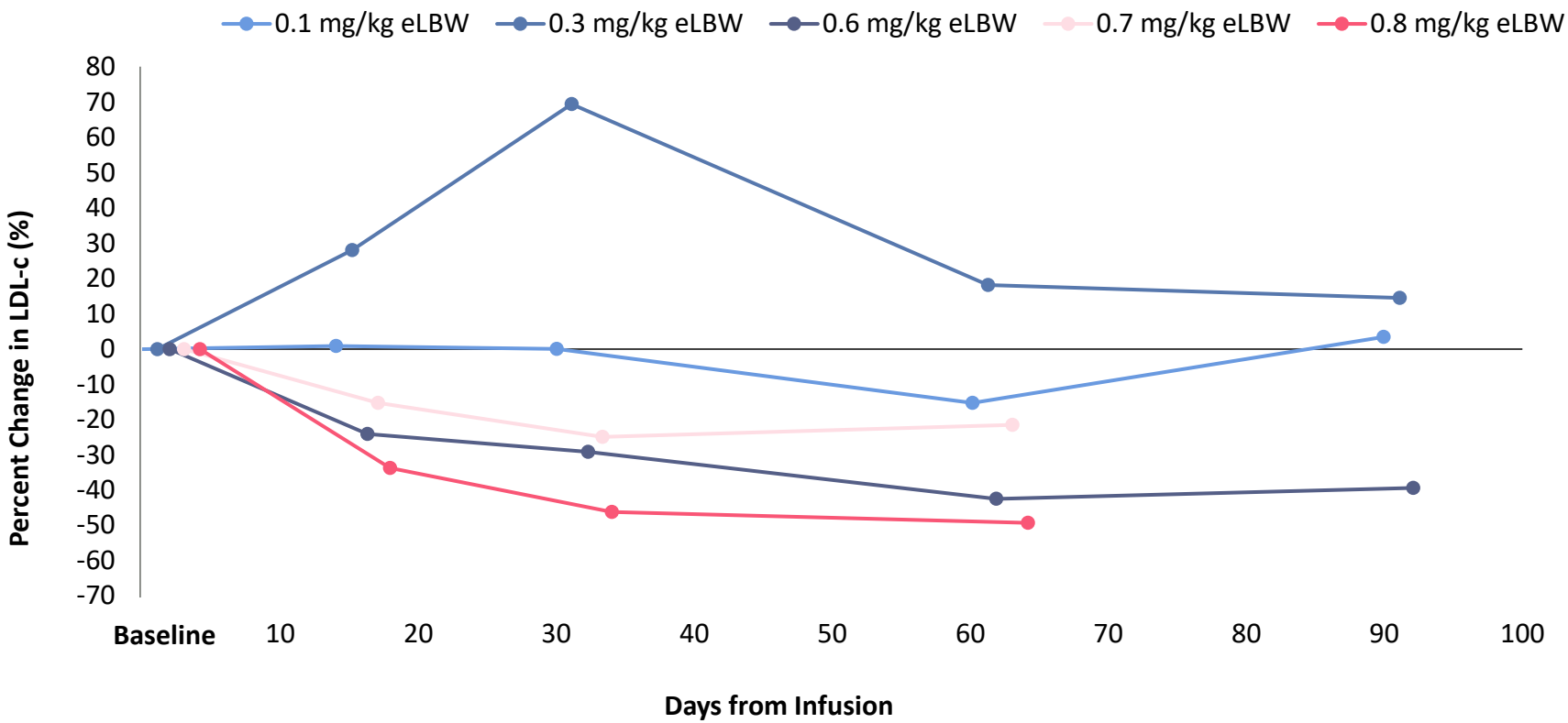


Mean percent change from baseline are reported at 90 days following 0.1, 0.3, 0.6 mg/kg CTX310 doses and at 60 days following 0.7 and 0.8 mg/kg CTX310 doses.

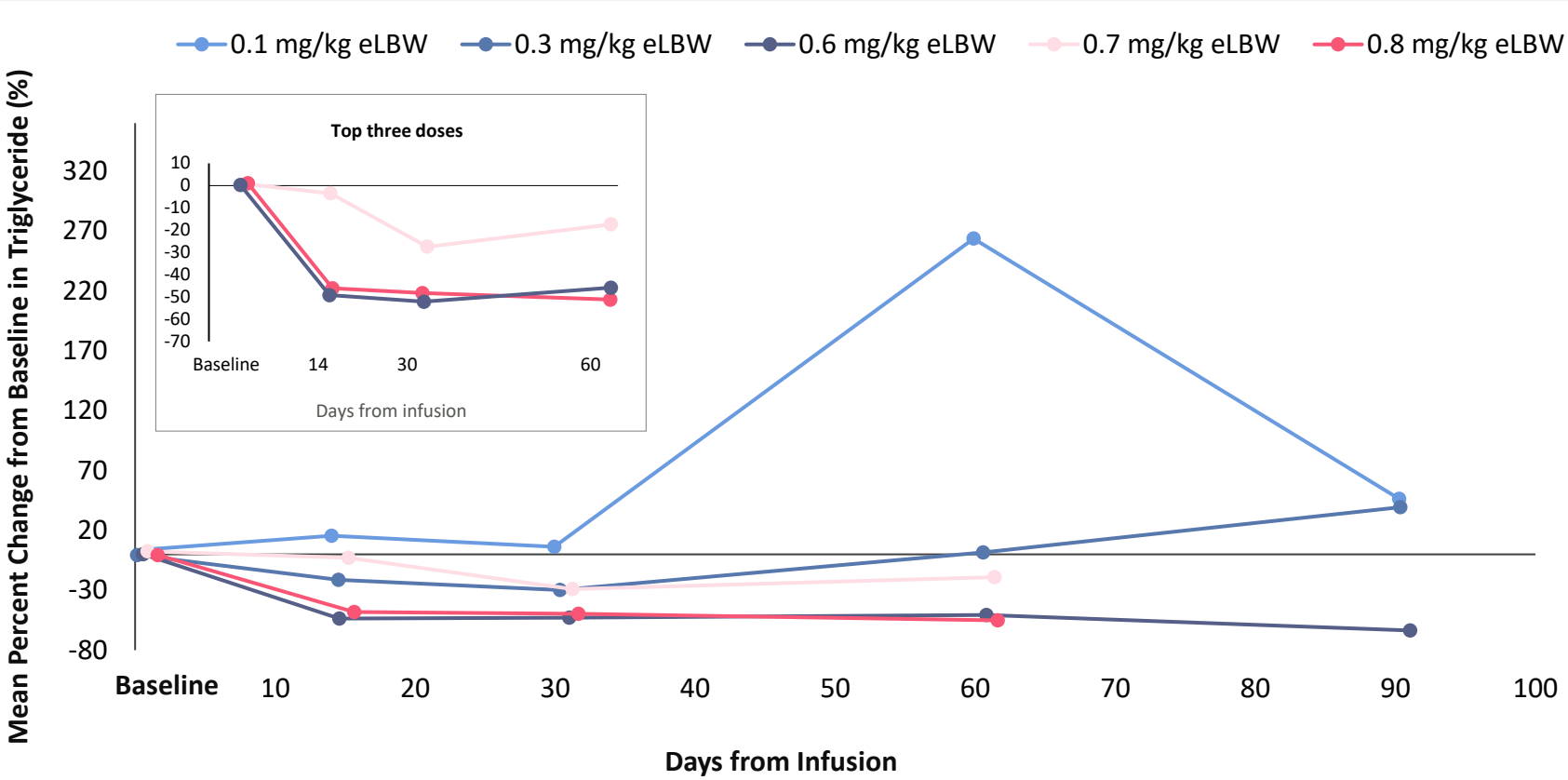
Mean Percent Change in ANGPTL3 During First 30 Days



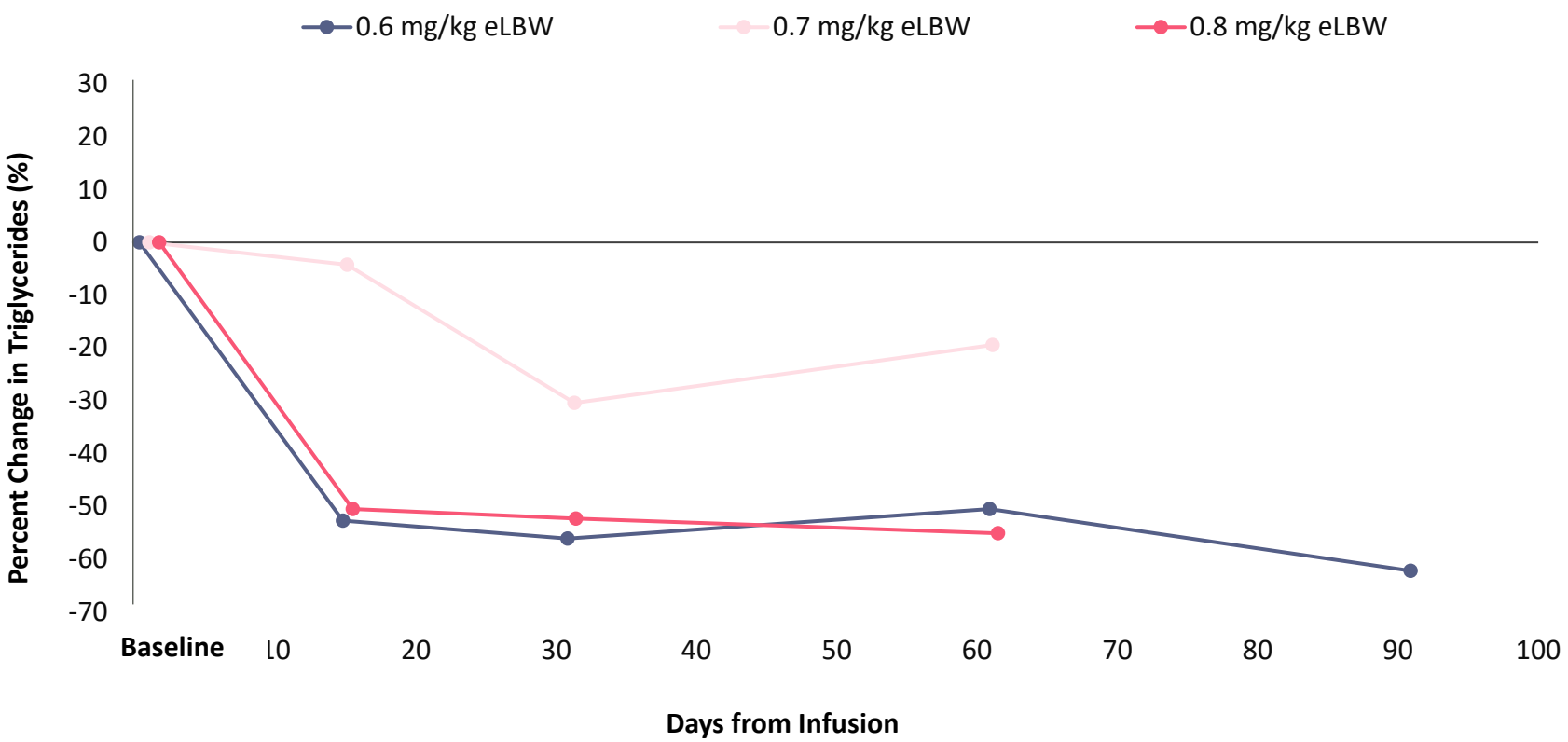
Mean Percent Change in LDL Cholesterol During First 90 Days



Mean Percent Change from Baseline in Triglycerides



Mean Percent Change in Triglycerides for Top Three Doses

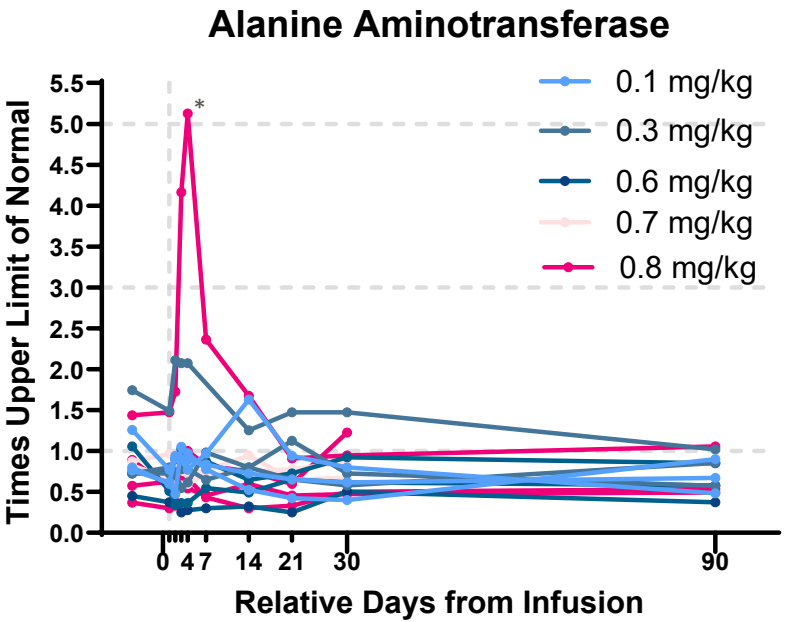


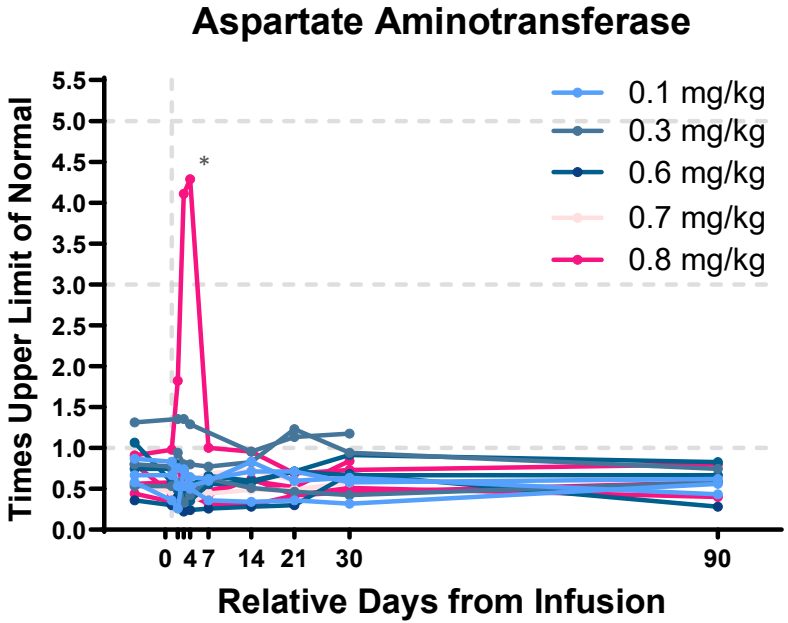
Adverse Events and Laboratory-Related Safety Findings

	N (%)
Any serious adverse events	2 (13)
Serious adverse events related to CTX310	0 (0)
Participants with any investigator-reported adverse event	14 (93)
Adverse event deemed related to CTX310	7 (47)
Adverse event of special interest	4 (27)
▪ Allergic or localized reaction	1 (7)
▪ Infusion-related reaction	3 (20)
▪ Elevation in AST or ALT	1 (7)
Death[1]	1 (7)

[1]Occurred in a participant 179 days after treatment with the 0.1 mg/kg dose, deemed unrelated to CTX310

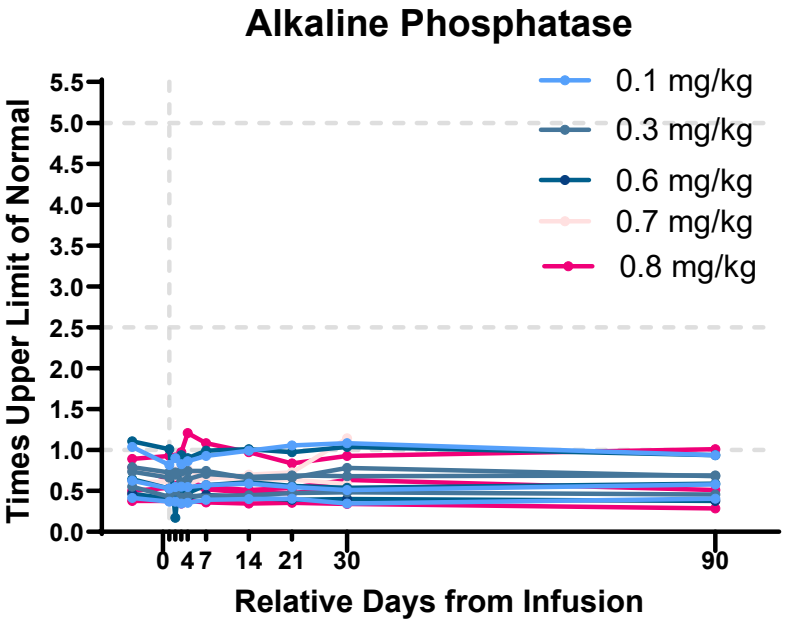
Change in Liver Enzymes Over Time

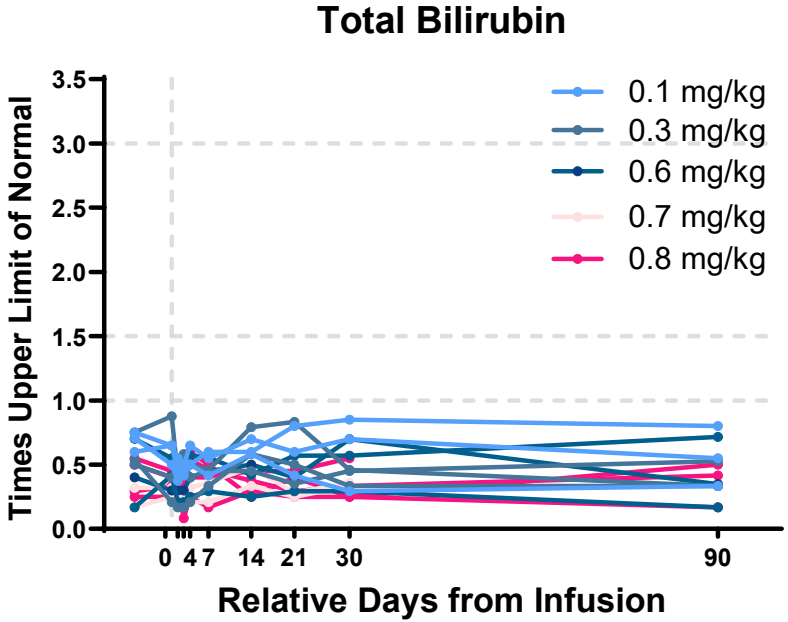




*1 participant with elevated baseline aminotransferases experienced a transient aminotransferase elevation without concurrent bilirubin elevation between 3 and 5 times their baseline peaking on day 4 and returning to baseline by day 14

Changes Alkaline Phosphatase and Total Bilirubin over Time





Limitations

- The number of participants was small (n=15) and the primary objective of this Phase 1 study was safety
- The population was heterogeneous, some with high LDL-C and others with elevated triglycerides
- The broad range of baseline values for LDL-C and triglycerides limits efficacy assessment in specific populations
- Ongoing surveillance will be essential to assess the persistence of safety and lipid-lowering efficacy of CTX310

Conclusions

CTX310, an *in vivo* CRISPR-Cas9 gene editing product targeting *ANGPTL3*, can be safely administered to patients to reduce ANGPTL3 levels

Although the study was small, reduction in LDL-C was approximately 50% and triglyceride lowering about 55%

Lifelong reductions in atherogenic lipoproteins can potentially overcome the issue of waning adherence to current therapies

Assessment of efficacy in specific populations will be feasible in further trials

Full Manuscript

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 1 Trial of CRISPR-Cas9 Gene Editing Targeting ANGPTL3

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A Final Thought

Gene-editing is now feasible via CRISPR-based therapies for a variety of targets. This approach may provide highly effective treatments for a variety of cardiovascular disorders. Although it is early in the study of gene-editing therapies, the efficacy demonstrated in the current trial is highly promising and represents a new frontier for drug development.

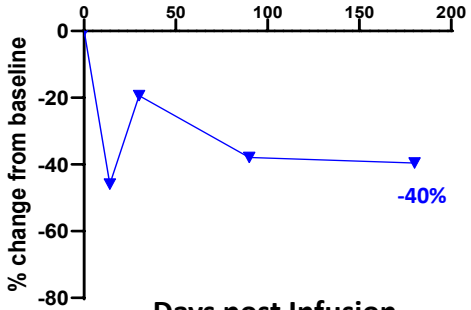
Deep Dive Slides

Case Study 1: HeFH Patient with 77%/53% Reduction in LDL/TG (DL4)

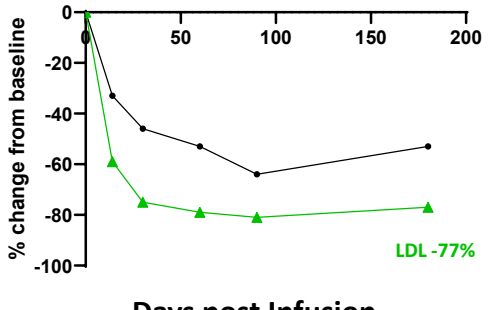
50 yo M with HeFH

- Medical History
  - s/p 3v-CABG (age 29), NSTEMI x 2 (age 49, 50), Hypertension; 78.4 kg/59.5 kg LBW
- Lipid Lowering Con Meds
  - Rosuvastatin 40mg QD (2013)
  - Ezetemibe 10mg QD (2013)
  - Evolocumab SC 420mg QM (2015)

ANGPTL3



LDL and TG



PD/Lipids	Scr	D180 (Abs, %)
ANGPTL3 (ng/mL)	190	115 (-75, -40%)
Non-HDL (mg/dL)	316	88 (-228, -72%)
ApoB (mg/dL)	211	77 (-134, -64%)
LDL (mg/dL)	256	59 (-197, -77%)
TG (mg/dL)	299	142 (-157, -53%)

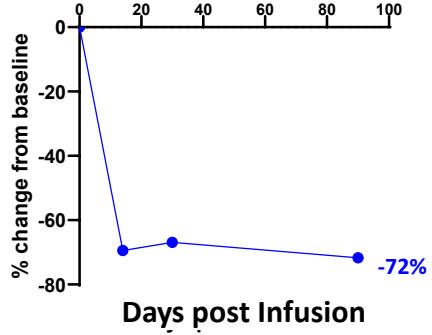
Achieved Target: TG (<150 mg/dL) and LDL (<70 mg/dL)

Case Study 2: sHTG Patient Achieved TG Reduction of 728mg/dL or 68% (DL4)

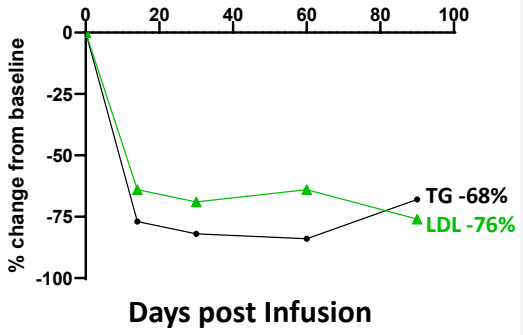
53 yo M with sHTG

- Medical History
  - s/p PCI (age 43), s/p NSTEMI (age 45), CABG (age 51); 111.4 kg/70.6 kg LBW
- Lipid Lowering Con Meds
  - Fenofibrate 145mg oral QD (2015)
  - Rosuzet 10/40 mg oral QD (2015)
  - Icosapent Ethyl 998mg oral BID (2024)

ANGPTL3



LDL and TG



PD/Lipids	Scr	D90 (Abs, %)
ANGPTL3 (ng/mL)	154	43 (-111, -72%)
Non-HDL (mg/dL)	200	62 (-138, -69%)
ApoB (mg/dL)	119	73 (-46, -39%)
LDL (mg/dL)	98	24 (-74, -76%)
TG (mg/dL)	1073	345 (-728, -68%)

Achieved Target: LDL (<70 mg/dL)