Durability of CRISPR-Cas9 Gene Editing Targeting ANGPTL3 with CTX310

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C5 Research

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Late-Breaking Clinical Trials:

Rewriting Cardiovascular Disease on Gene and Molecular Therapies

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Disclosures: Dr. Laffin serves/served as a consultant or on steering committees for Arrowhead, AstraZeneca, Crispr Therapeutics, Diamedica, Eli Lilly, Kardigan, Madrigal, Medtronic, Mineralys, Novo Nordisk, Novartis, Recor, Retension, Ripple, Viking. He receives royalties from Belvoir Media Group, Elsevier, and Springer Nature.

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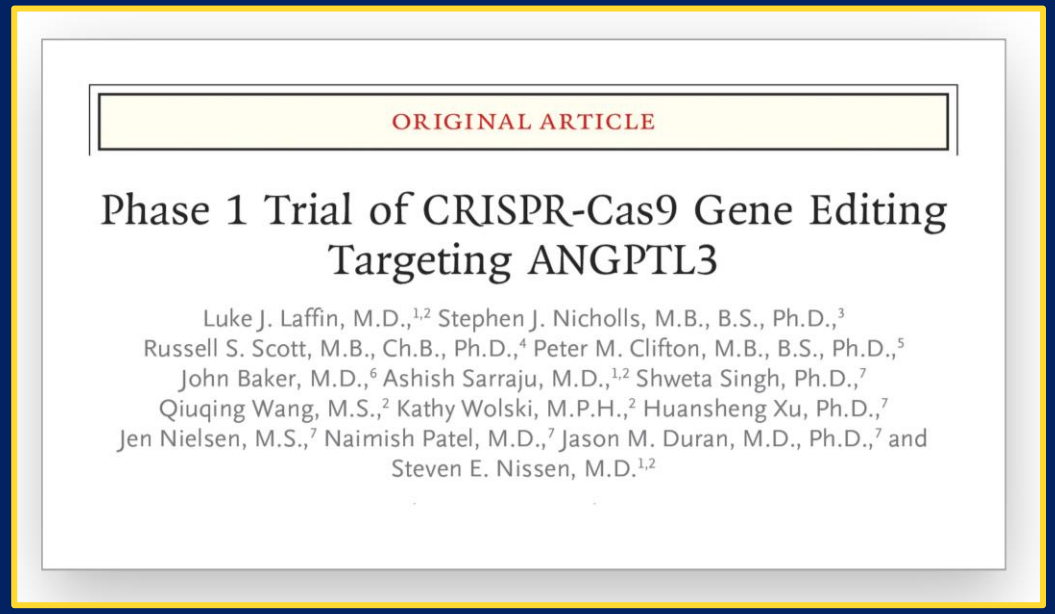
Background

- Diminishing adherence to lipid-lowering agents is a major limitation of currently available medications
- **ANGPTL3** (angiopoietin-like protein 3) is an important regulator of lipid metabolism through inhibition of lipoprotein and endothelial lipase
- A **one-time treatment** producing a loss-of-function mutation in hepatocytes that mimics natural variants associated with a reduced risk of ASCVD represents a unique therapeutic opportunity
- The **CRISPR-Cas9** system enables precise genome editing to introduce targeted loss-of-function mutations

Background



ORIGINAL ARTICLE

Phase 1 Trial of CRISPR-Cas9 Gene Editing Targeting ANGPTL3

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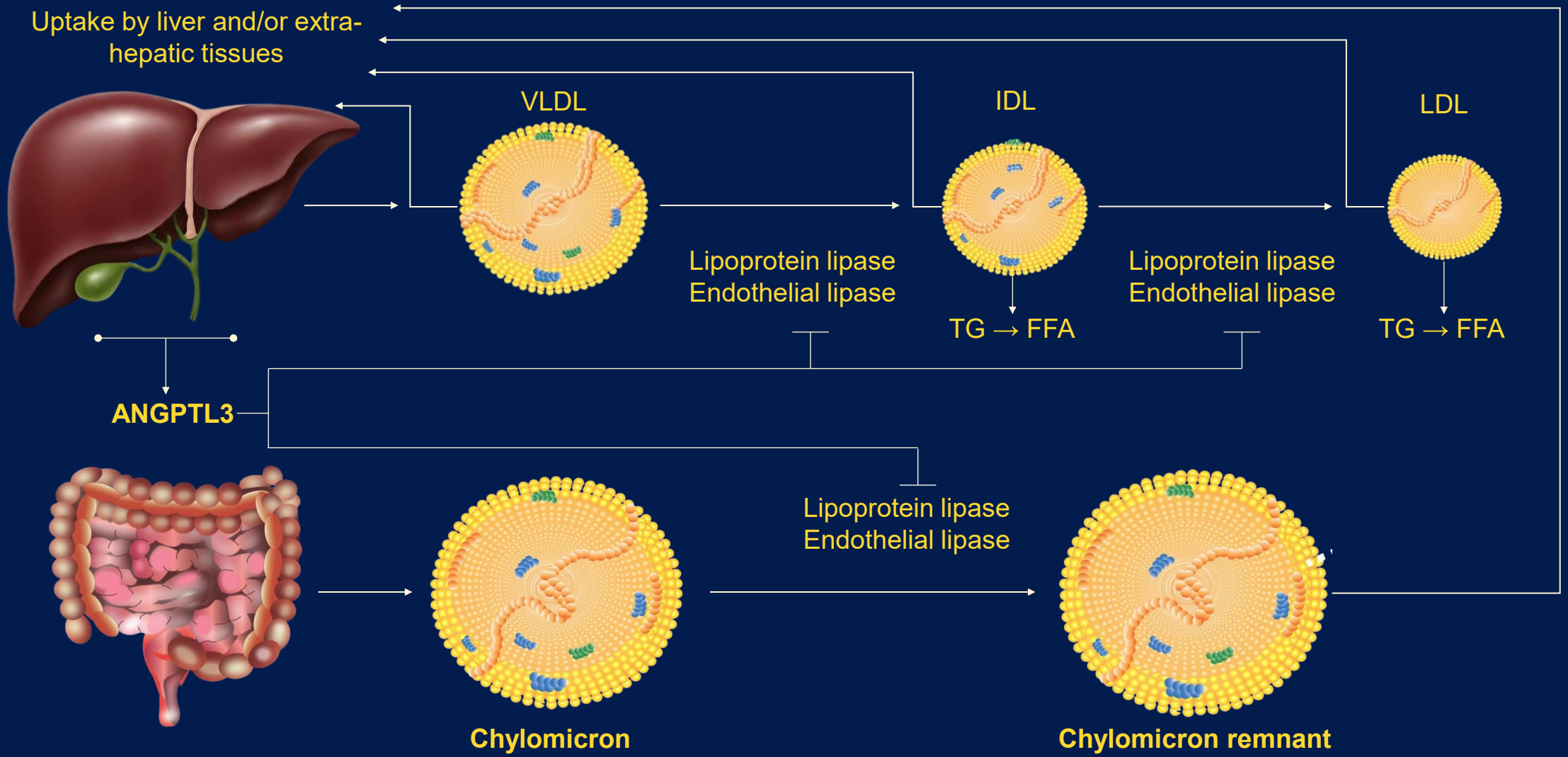
First data published in November 2025

Included 30-day data for ANGPTL3 and 60-day data lipid biomarker data for the highest dose groups:

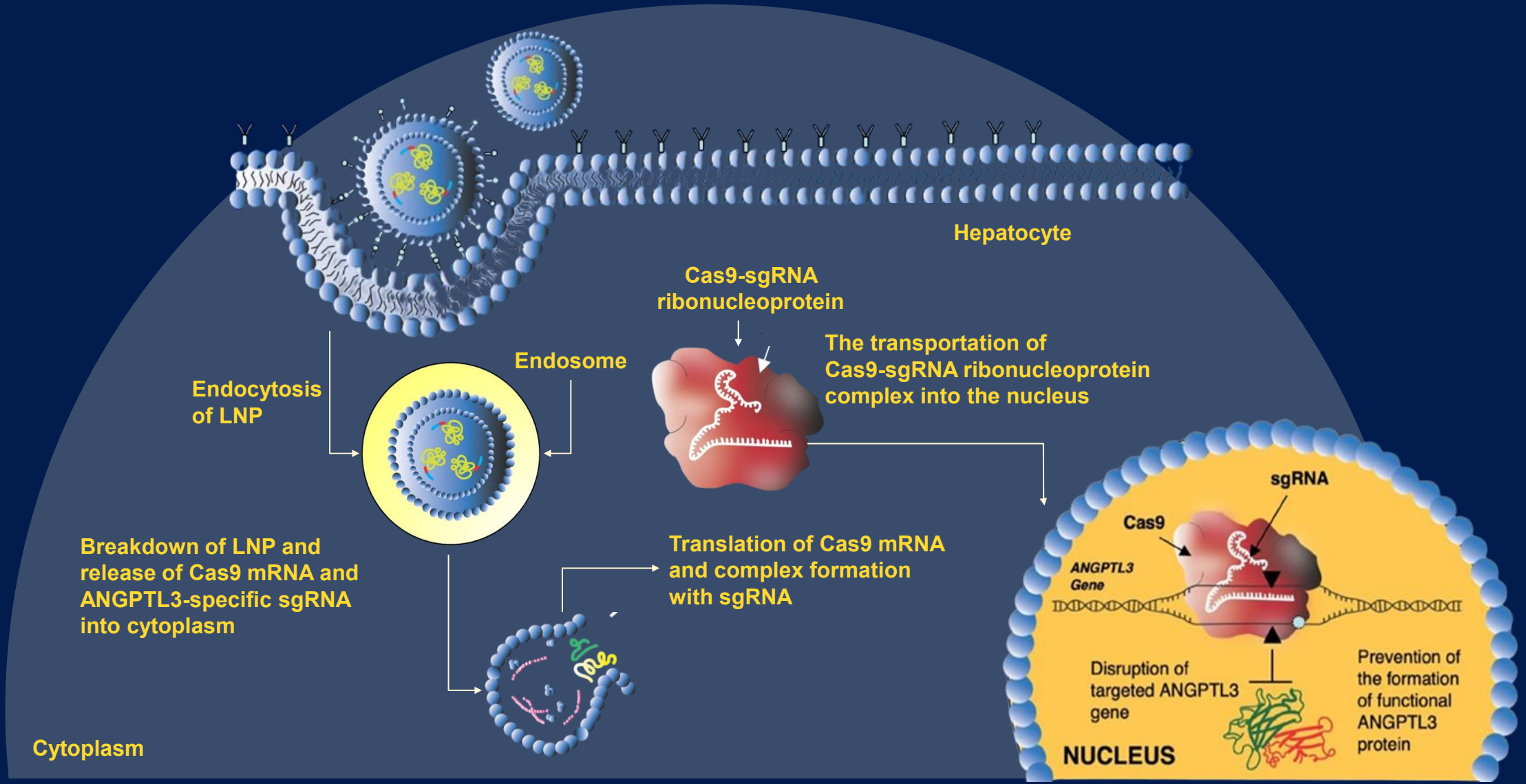
- 48.9% in LDL-C

- 55.2% in Triglycerides

Role of ANGPTL3 in Lipid Metabolism



CTX310: CRISPR-Cas9 Editing of ANGPTL3



Objective

Describe the safety and durability of ANGPTL3 and lipid biomarkers changes 12-months following treatment for all participants

Study Design

- Multicenter, Open-Label, Single-Ascending Dose, Phase 1a
- CTX310 administered intravenously to 15 participants with HoFH, HeFH, elevated triglycerides or mixed dyslipidemia on maximally tolerated medical therapy
- Participants assigned to 0.1, 0.3, 0.6, 0.7 or 0.8 mg/kg of CTX310 infused over 1 to 4.5 hours
- Safety and tolerability assessed during follow up with biomarkers collected to assess lipid effects and liver safety

Primary Safety and Efficacy Endpoints

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

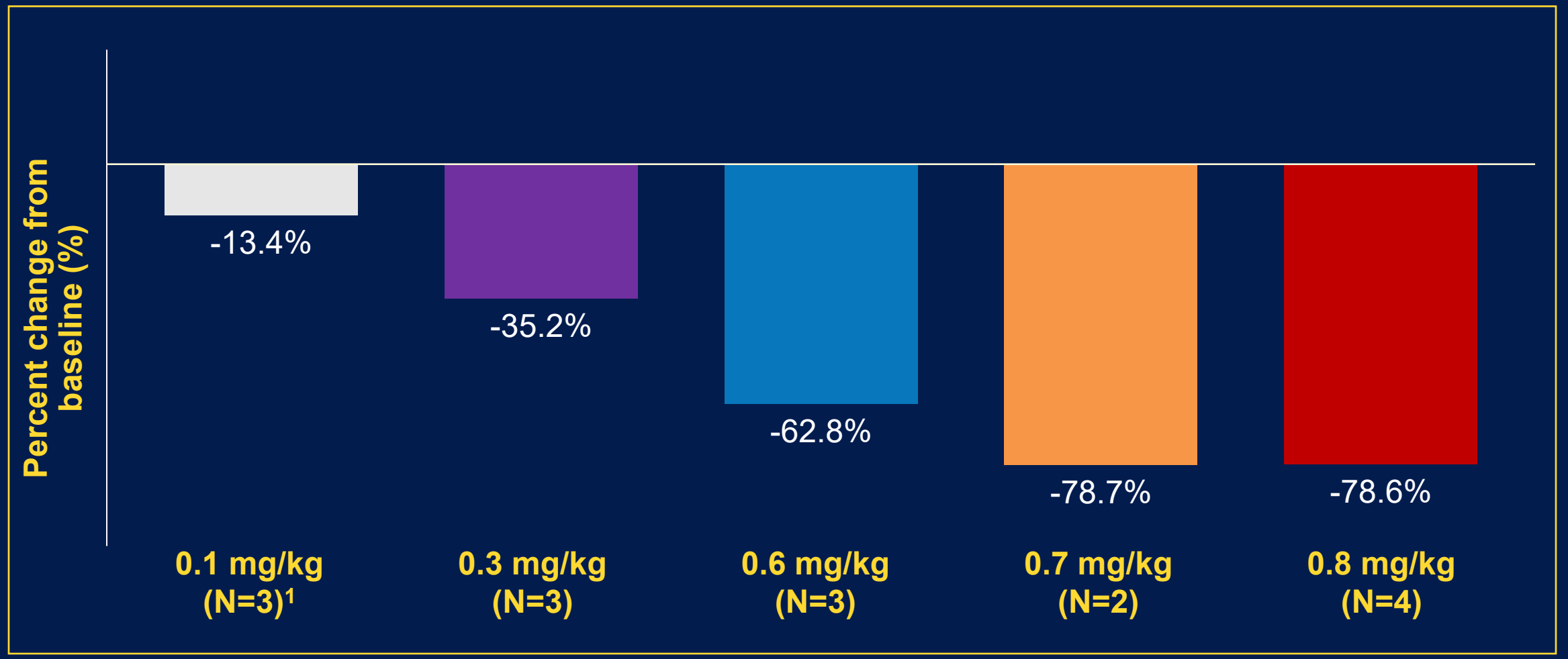
Efficacy endpoints included percent changes over time for

- ANGPTL3
- LDL cholesterol
- Triglycerides
- Apolipoprotein B
- Non-HDL cholesterol
- Triglyceride-rich lipoprotein cholesterol

Patients

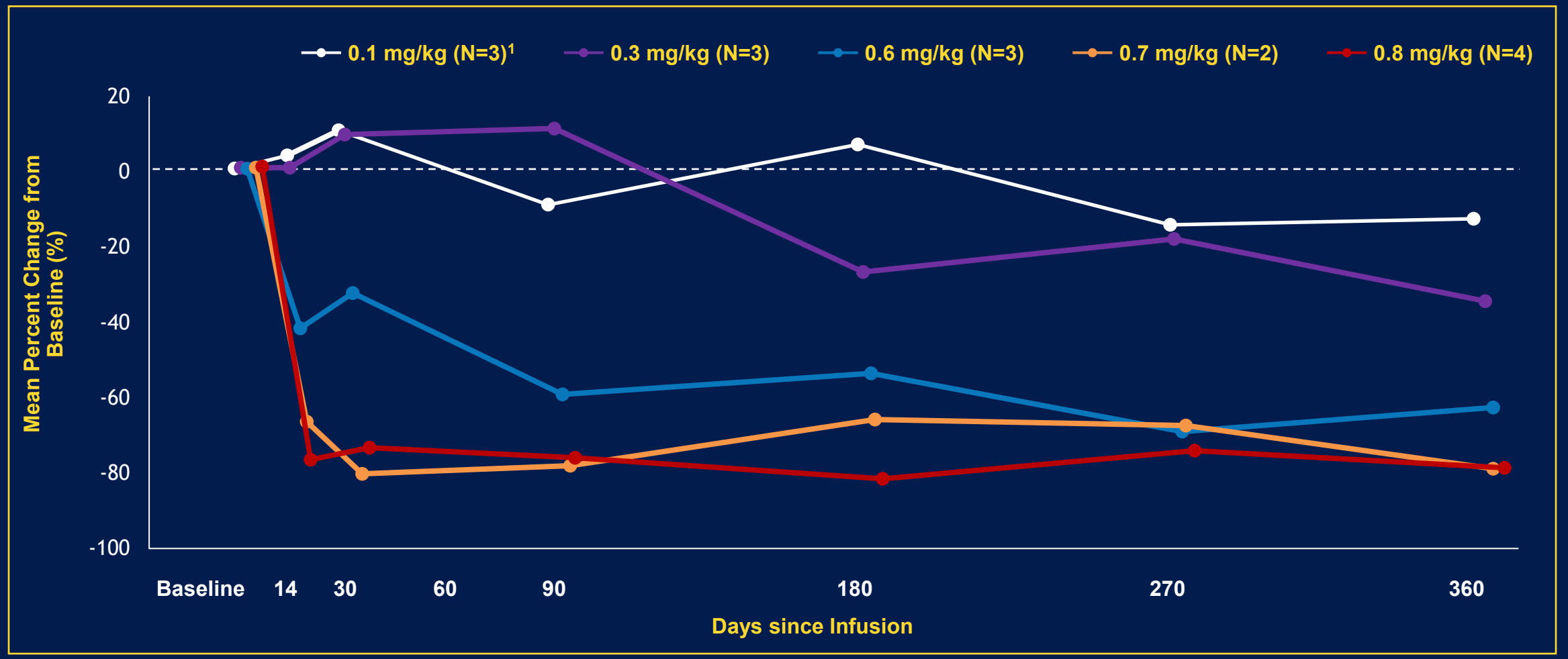
Baseline Characteristics	All participants (n=15)
Median Age	53 years
Male	87%
Clinical ASCVD	40%
Familial Hypercholesterolemia	40%
Severe Hypertriglyceridemia	13%
Mixed Dyslipidemia	40%
Mean LDL cholesterol	4.01 mmol/L (155 mg/dL)
Median Triglycerides	2.17 mmol/L (192 mg/dL)

Mean Percent Change from Baseline in ANGPTL3 at 12 Months



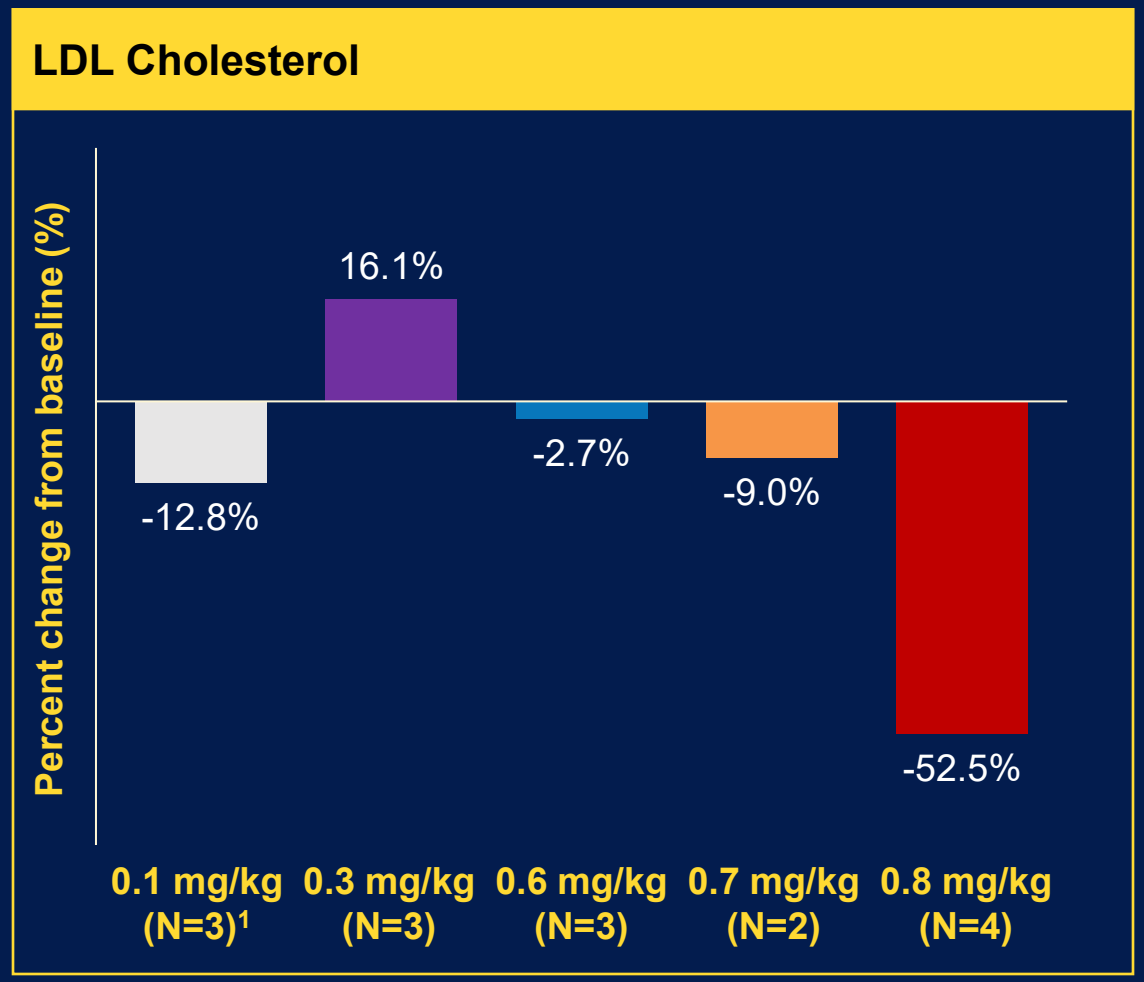
1. One participant died 179 days following drug administration; thus 2 participants are included in the 12 month mean percent change

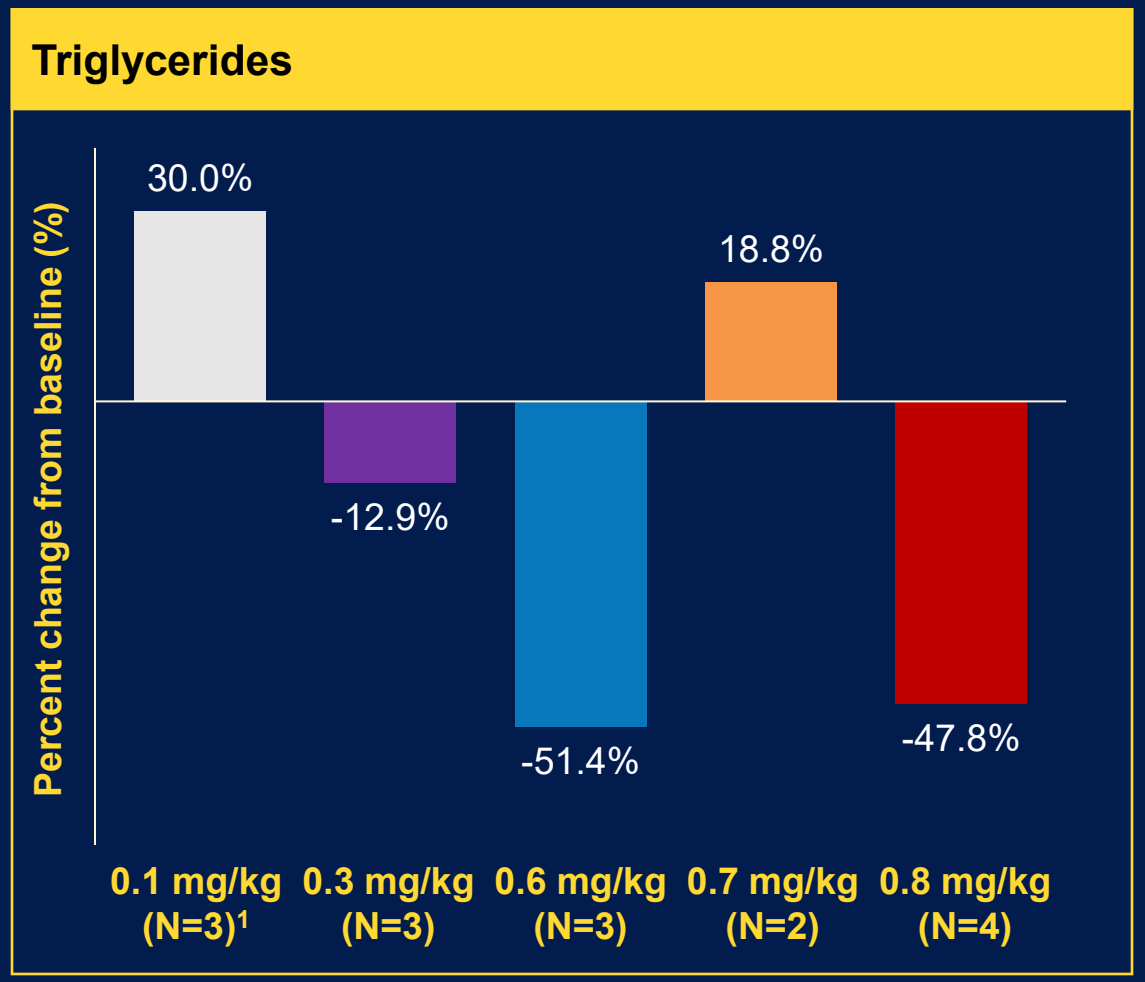
Mean Percent Change in ANGPTL3 Over 12 Months



1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

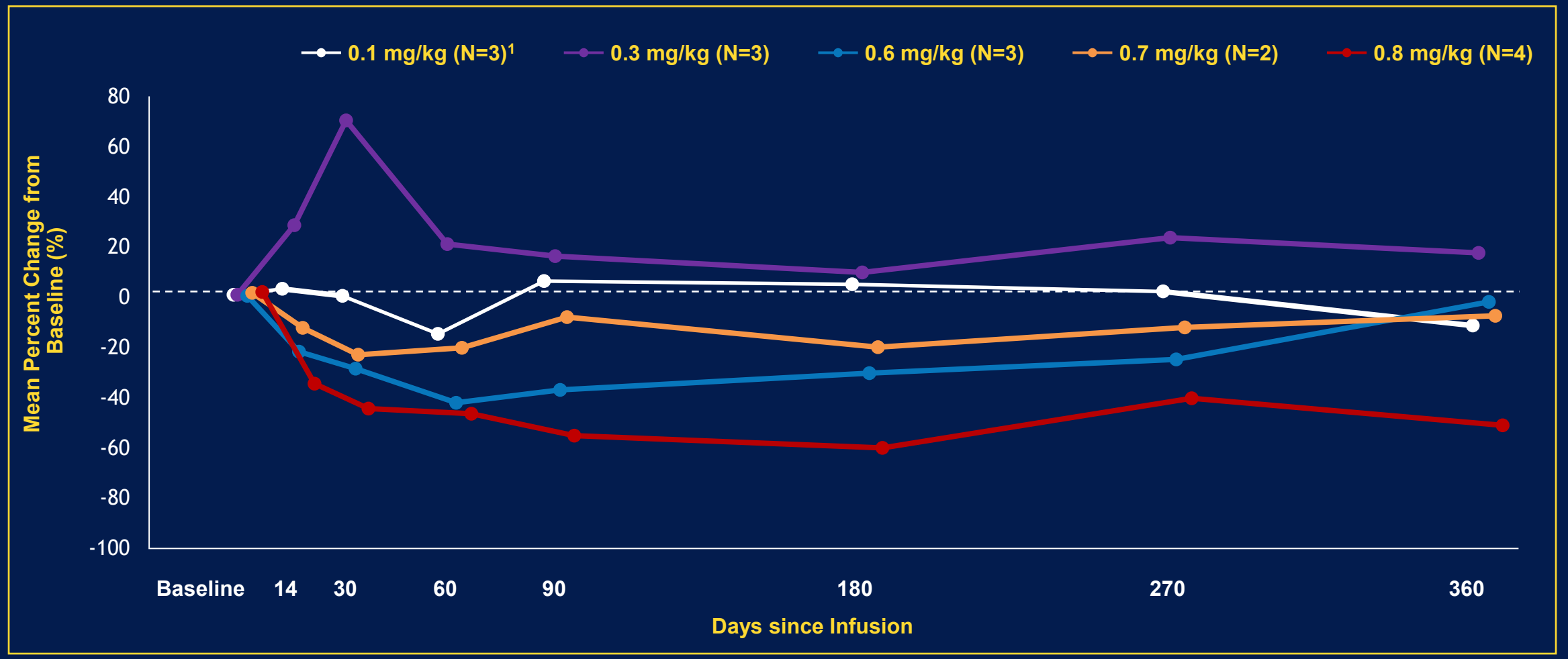
Mean Percent Change from Baseline in LDL-C and Triglycerides at 12 Months





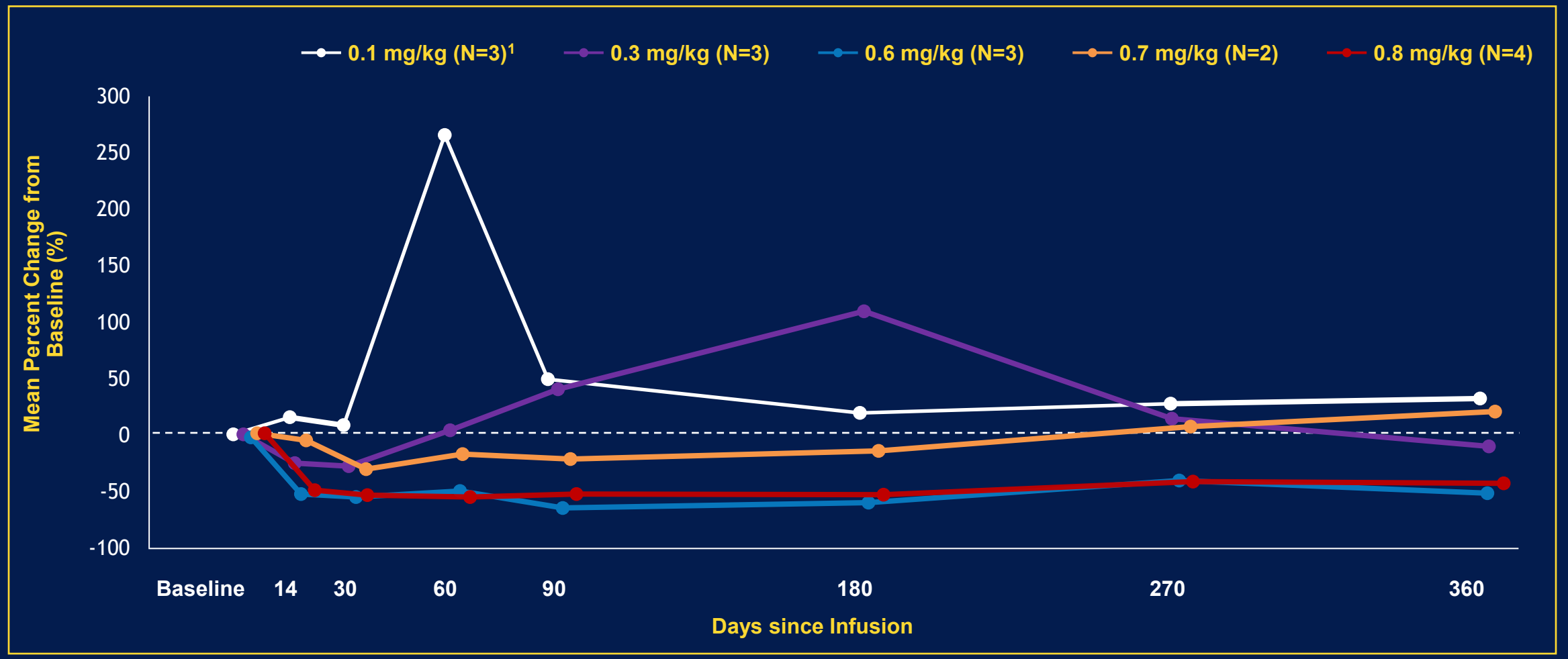
1. One participant died 179 days following drug administration; thus 2 participants are included in 12 month mean percent change

Mean Percent Change in LDL Cholesterol Over 12 Months



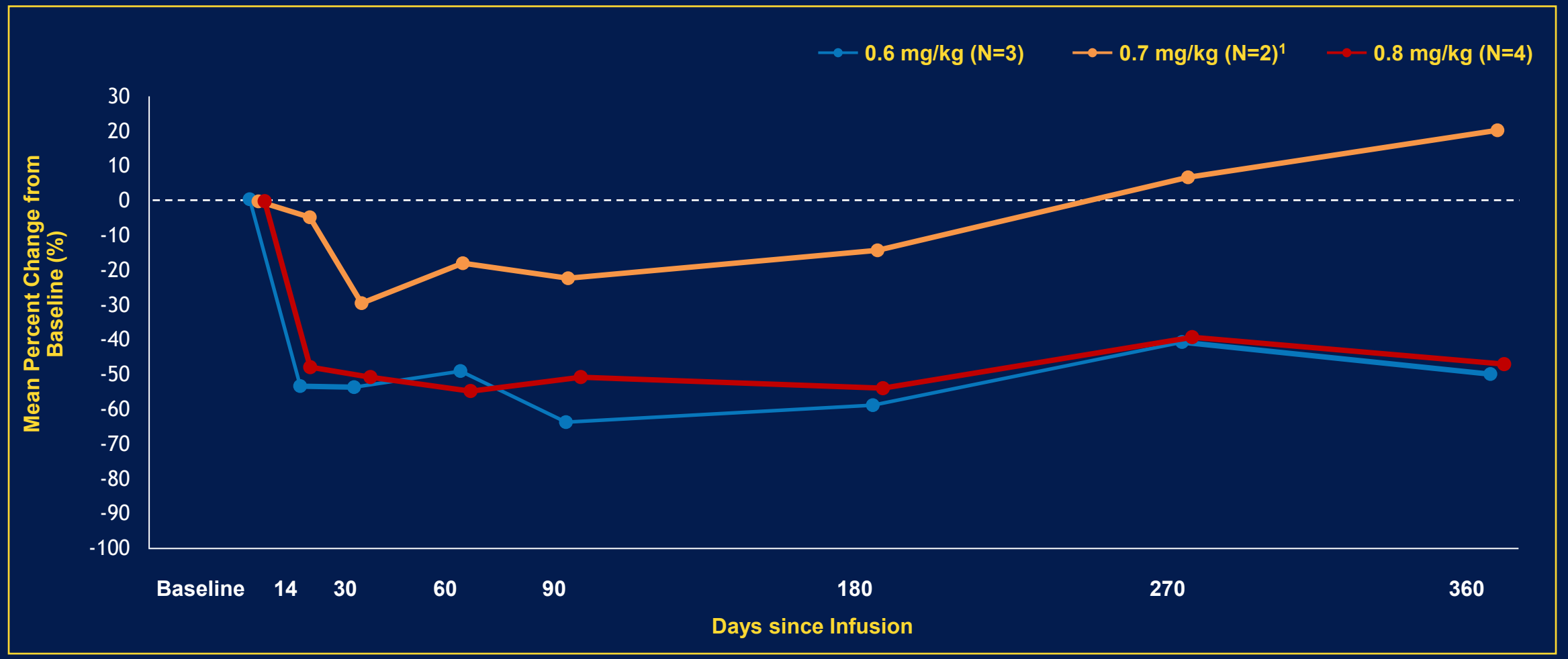
1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

Mean Percent Change in Triglycerides Over 12 Months



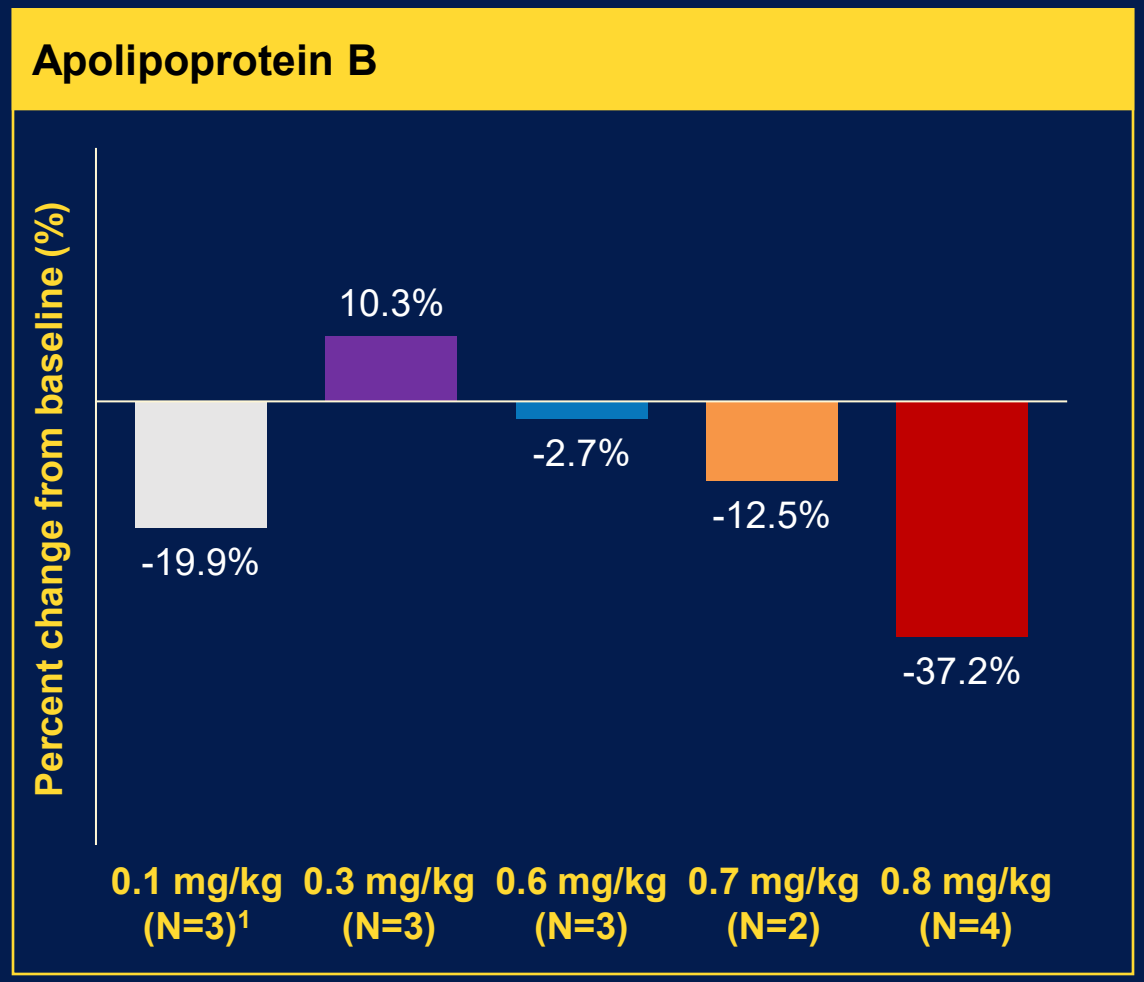
1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

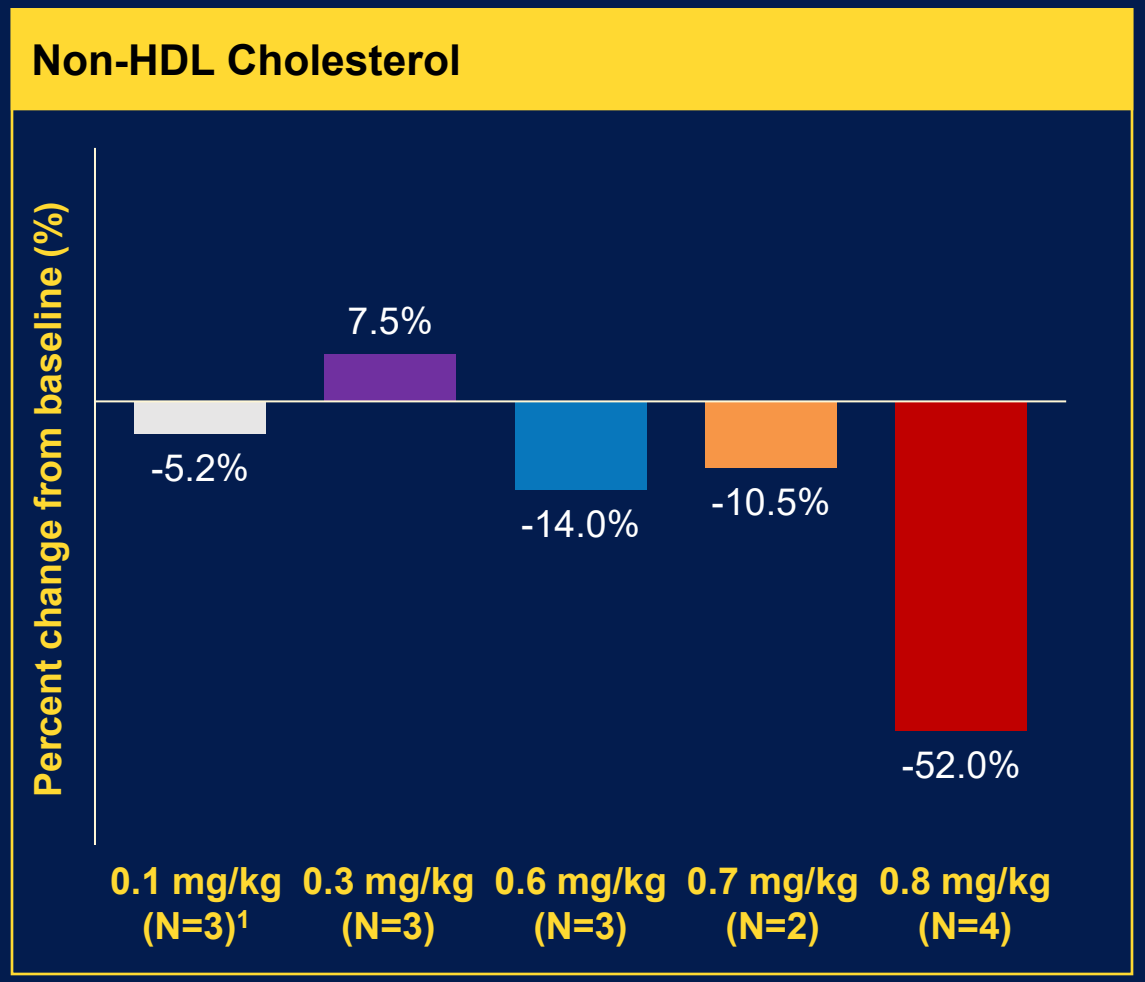
Mean Percent Change in Triglycerides Over 12 Months (Top 3 Doses)



1. One participant was enrolled with a diagnosis of mixed dyslipidemia; however, laboratory values were consistent with hypercholesterolemia alone

Mean Percent Change in ApoB and Non-HDL-C at 12 Months





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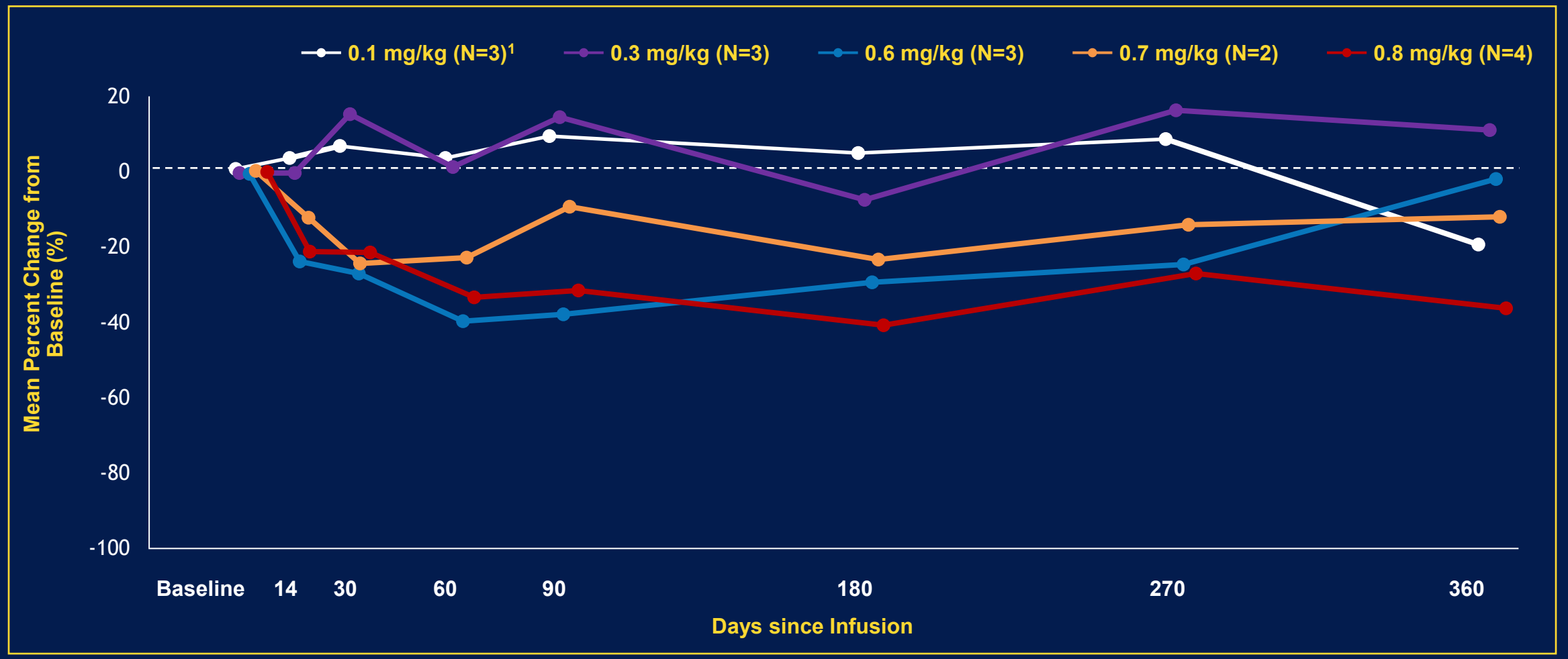
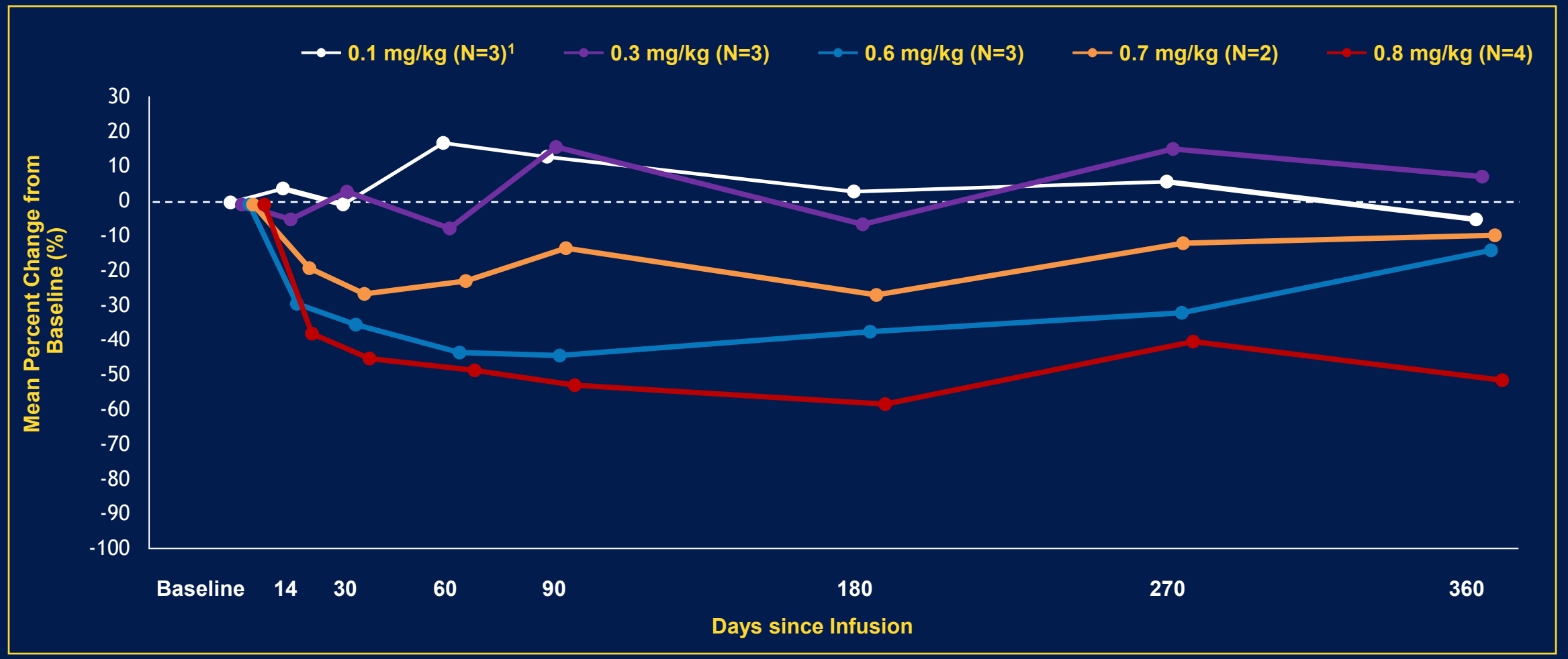
Mean Percent Change in ApoB Over 12 Months



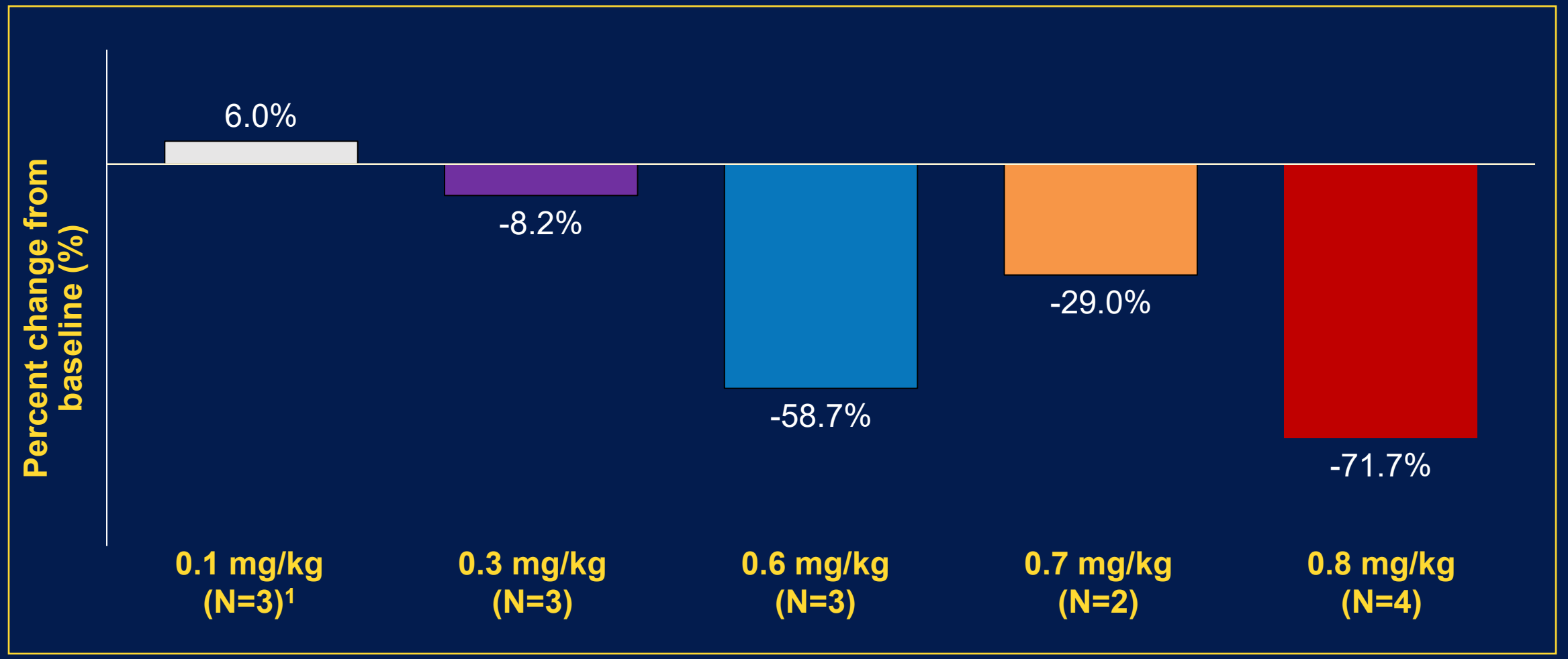
1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

Mean Percent Change in Non-HDL-C Over 12 Months



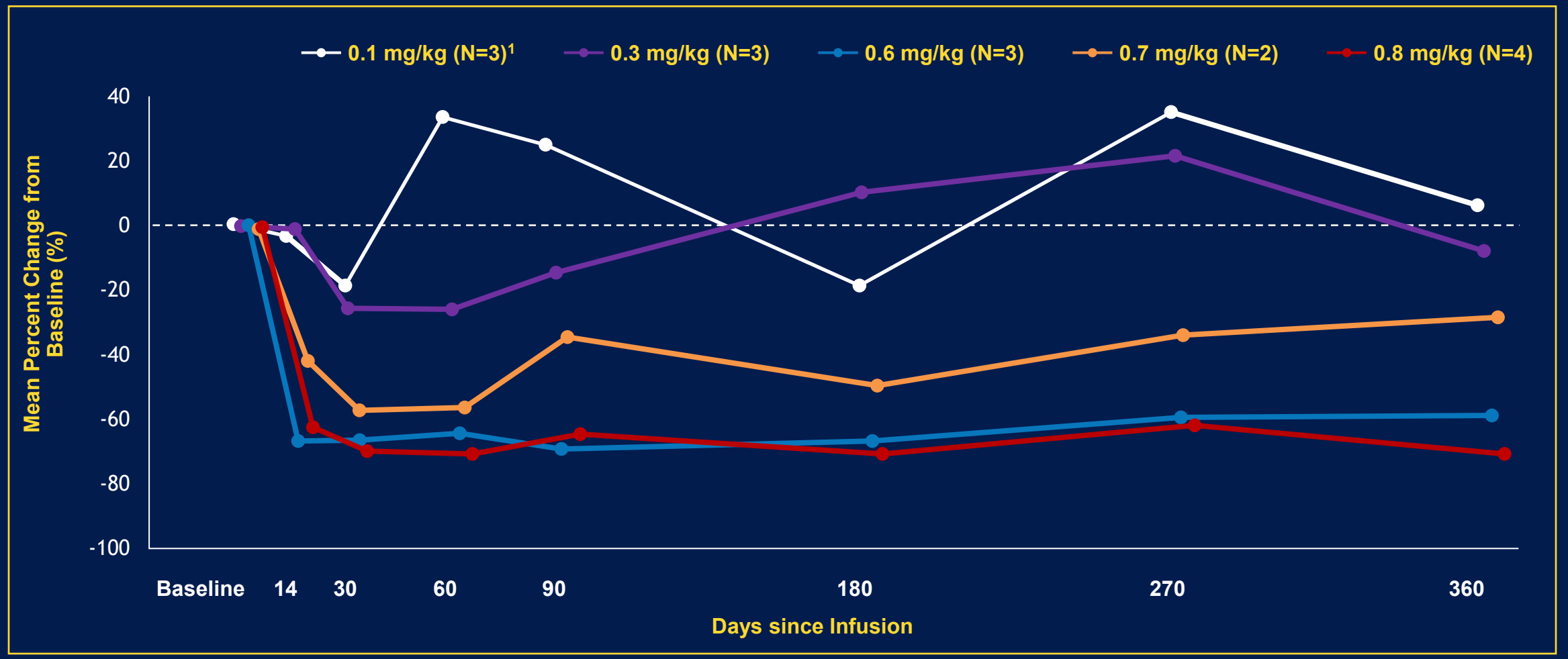
1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

Mean Percent Change in Triglyceride-Rich Lipoprotein Cholesterol at 12 Months



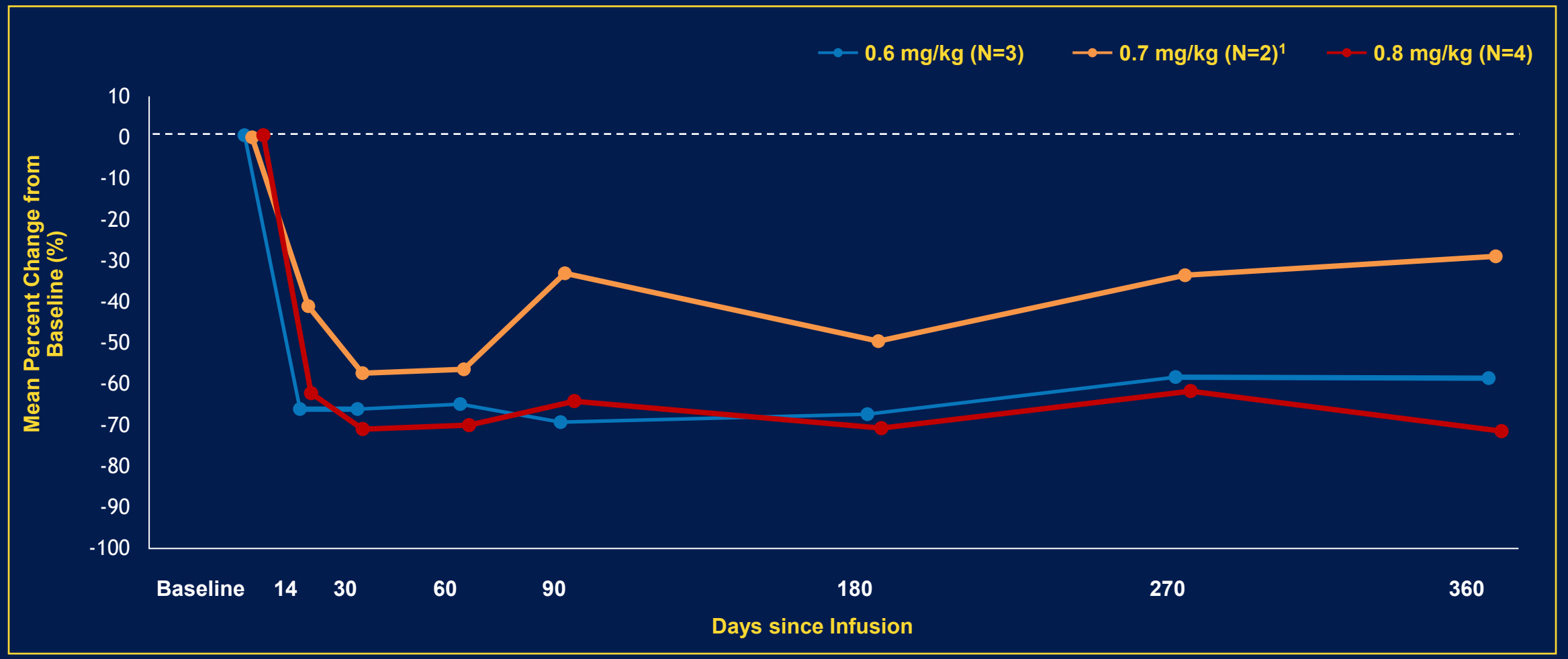
1. One participant died 179 days following drug administration; thus 2 participants are included in the 12 month mean percent change

Mean Percent Change in Triglyceride-Rich Lipoprotein Cholesterol Over 12 Months



1. One participant died 179 days following drug administration; thus 2 participants are included in the 9 and 12 month mean percent change

Mean Percent Change in Triglyceride-Rich Lipoprotein Cholesterol Over 12 Months (Top 3 Doses)



1. One participant was enrolled with a diagnosis of mixed dyslipidemia; however, laboratory values were consistent with hypercholesterolemia alone

Safety

Adverse Events and Laboratory-Related Safety Findings Through 12 months	N (%)
Any serious adverse events	1 (7)[1]
Serious adverse events related to CTX310	0 (0)
Participants with any investigator-reported AE	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)

1. 1 death deemed unrelated to CTX310, 1 reclassified as pre-existing condition

Simultaneous Publication in NEJM

Conclusions

- Longest duration of follow-up for a gene-editing approach targeting the *ANGPTL3* gene, with deep and durable efficacy
- No new safety events over course of 12-month follow-up

After 1 to 2 months	After 12 months
-73% ANGPTL3	**-79% ANGPTL3**
-49% LDL-C	**-53% LDL-C**
-55% Triglycerides	**-48% Triglycerides**

- Participants in this phase 1a trial have consented to surveillance for 15 years
- Phase 1b of this trial is ongoing and is now testing a flat dosing regimen targeting 0.8mg/kg dose exposure and efficacy in separate specific lipid disorder cohorts

Acknowledgements

Participants, Investigators and Site Staff	6 sites in New Zealand, Australia and the UK
Manuscript Co-Authors	Stephen J. Nicholls, Russell S. Scott, Peter M. Clifton, Renate Koops, Ashish Sarraju, Shweta Singh, Qiuqing Wang, Kathy Wolski, Huansheng Xu, Jen Nielsen, Naimish Patel, Jason M. Duran, and Steven E. Nissen
Independent DMC	Jeffrey Crippin (Chair), Lawrence Leiter, Adam Nelson, Gheorghe Doros, Shoa Clarke
C5 Research Team	**Crispr Therapeutics**

A Final Thought

One-time in vivo CRISPR-Cas9–mediated editing of the ANGPTL3 gene with CTX310 was safe and produced durable lowering of atherogenic lipoproteins at 1 year

Although gene-editing is early in its human trials, the safety and durable efficacy demonstrated in the current trial is highly promising and **represents a new frontier for drug development**