CRISPR-Cas9 Gene Editing Therapy Targeting *ANGPTL3* for Severe Hypertriglyceridemia: *Results From a Phase 1b Trial*

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C5 Research





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Late-Breaking Science:

New Frontiers in Cardiometabolic Risk Reduction

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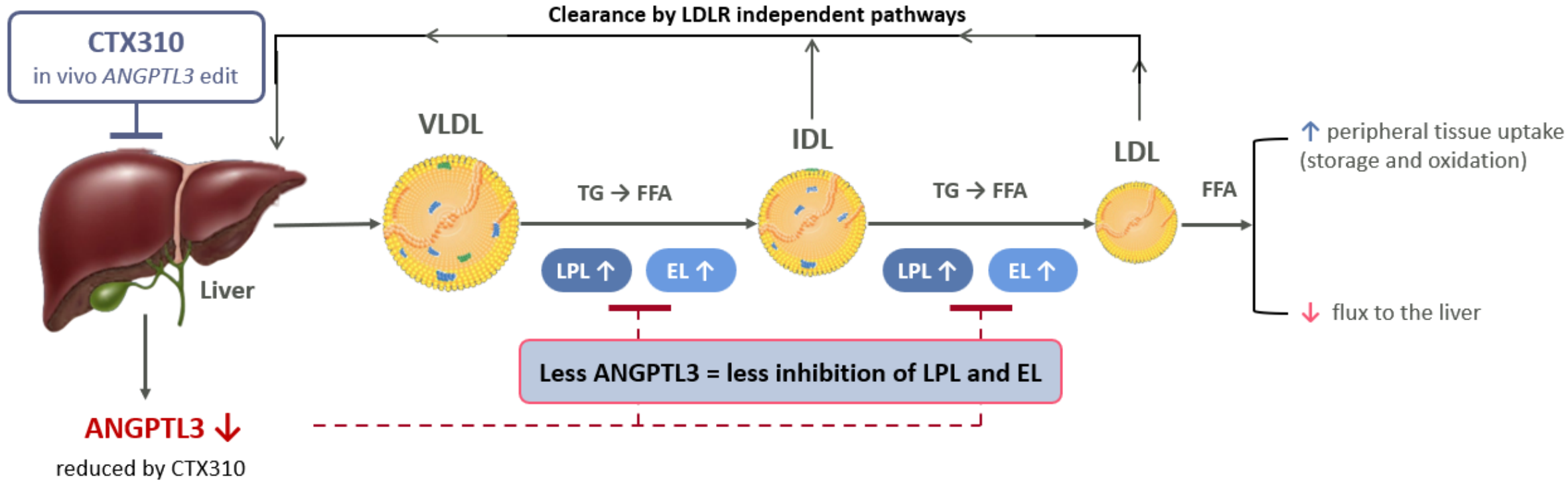
Disclosures: Dr. Sarraju serves/has served as a consultant or on steering committees or trial leadership activities for Astrazeneca, Arrowhead, CRISPR Therapeutics, Kardigan, Kylonova, Kalexo, Ionis, New Amsterdam Pharma, Mineralys, Novartis, vTv Therapeutics. .

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Background

- Severe hypertriglyceridemia, a condition of fasting serum triglycerides exceeding 500 mg/dL, is associated with greater risk for acute pancreatitis and cardiovascular disease
- **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 hypertriglyceridemia represents a unique therapeutic opportunity
- The **CRISPR-Cas9** system enables precise genome editing to introduce targeted loss-of-function mutations

Mechanism of Triglyceride Lowering with CTX310



↓ Triglycerides

LPL de-repression speeds TG hydrolysis to reduce serum TG

↓ LDL-C and ApoB

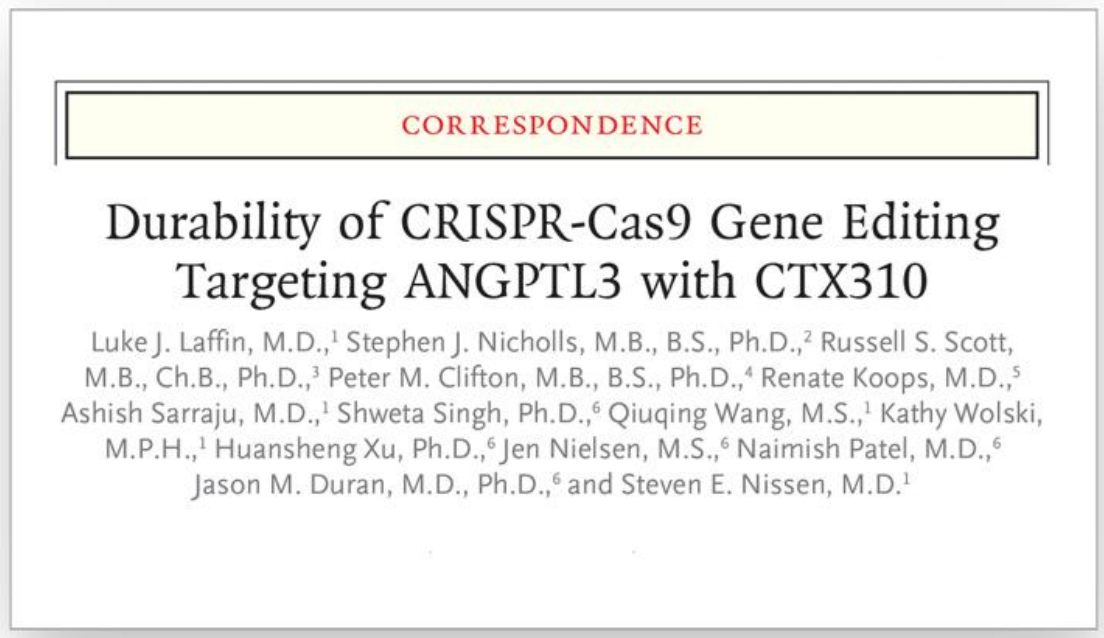
LPL and EL de-repression enhances TRL clearance and reduce LDL

FFA flux shift

Away from the liver and toward adipose/muscle tissue storage and oxidation

LPL, lipoprotein lipase; EL, endothelial lipase; TG, triglyceride; FFA, free fatty acid; IDL, intermediate-density lipoprotein; LDL-C, LDL cholesterol, TRL , triglyceride rich lipoproteins. ↑/↓ = expected direction of change after ANGPTL3 knockdown by CTX310.

Phase 1a Results



CORRESPONDENCE

Durability of CRISPR-Cas9 Gene Editing Targeting ANGPTL3 with CTX310

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Data published in August 2026

Included 12-month follow-up data:

-79% in ANGPTL3

-48% in Triglycerides

-53% in LDL-C

Objective

To describe the safety and efficacy of CRISPR-Cas9 gene-editing targeting hepatic *ANGPTL3* in participants with severe hypertriglyceridemia

Study Design

- Multicenter, Open-Label, Phase 1b
- CTX310 administered intravenously to 10 participants with severe hypertriglyceridemia (serum triglycerides ≥ 500 mg/dL)
- Participants received a one-time infusion of CTX310 at a fixed dose of 40 mg (weight ≤85 kg) or 50 mg (weight >85 kg)*
- Safety and tolerability assessed during follow up with biomarkers collected to assess lipid effects and liver safety

*One participant from phase 1a who received a dose of 56.5 mg is included in this cohort

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

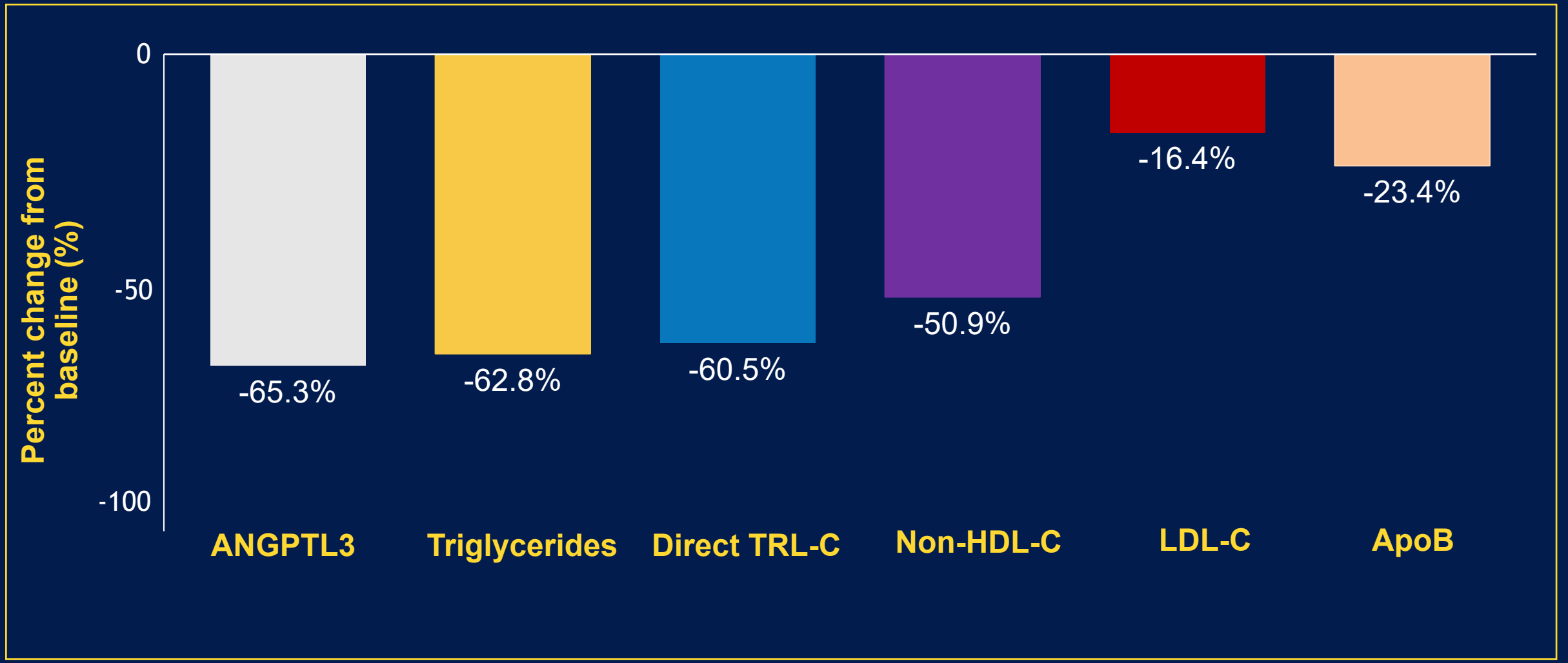
- ANGPTL3
- Triglycerides
- Triglyceride-rich lipoprotein cholesterol (TRL-C)
- Non-HDL cholesterol (non-HDL-C)
- LDL cholesterol (LDL-C)
- Apolipoprotein B

Participants

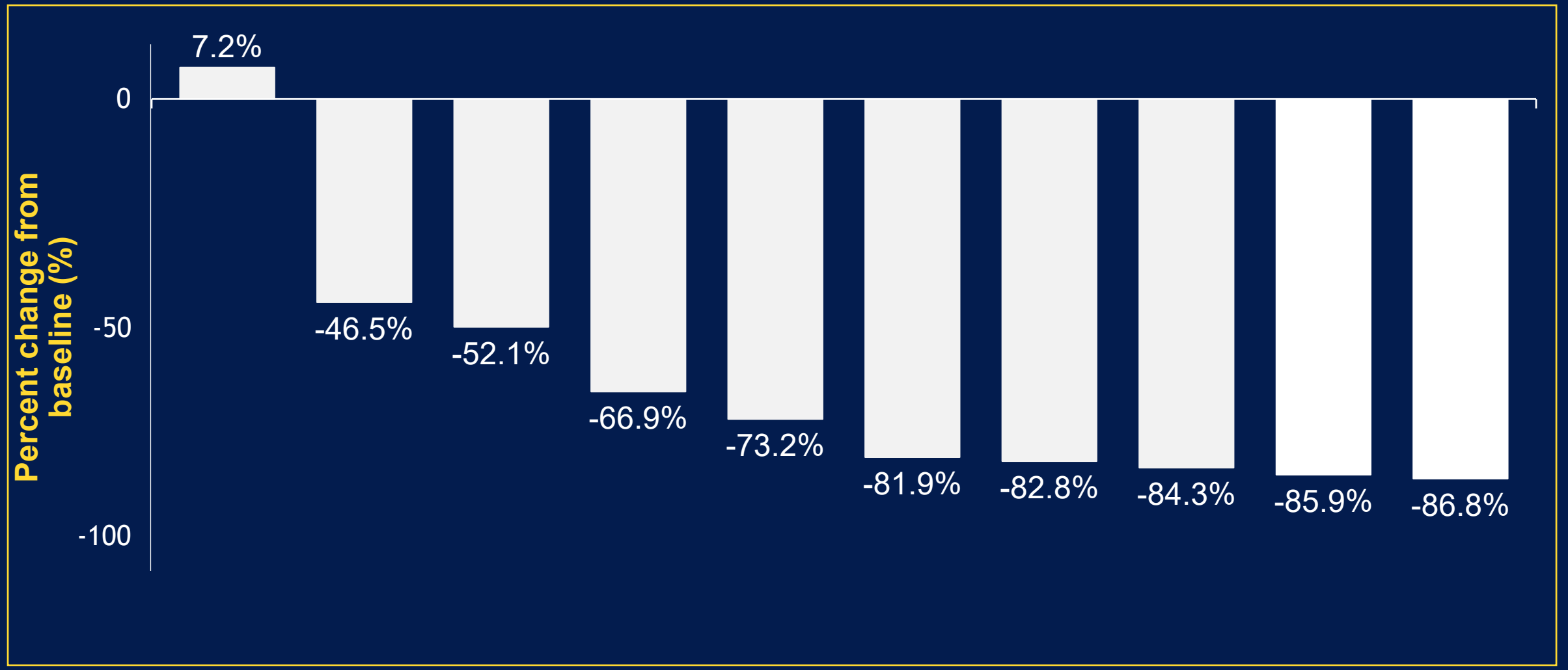
Baseline Characteristics	Participants (n=10)
Median Age	56.5 (53.0, 66.0)*
Male	6 (60%)
[a]Clinical ASCVD	2 (20%)
Pancreatitis	3 (30%)
Diabetes	10 (100%)
[b]Mean LDL cholesterol, mg/dL	59.9 ± 34.0
Median Triglycerides, mg/dL	1067.7 (740.4, 2269.2)*
[c]Hepatic fat fraction (%)	20.2 ± 7.7
Statin	7 (70%)
Fibrate	8 (80%)
Fish oil/omega-3 fatty acid	2 (20%)

*Median (Q1, Q3), [a]prior myocardial infarction, [b]n=1 with LDL-C > 100 mg/dL, [c]n=9 for %HFF

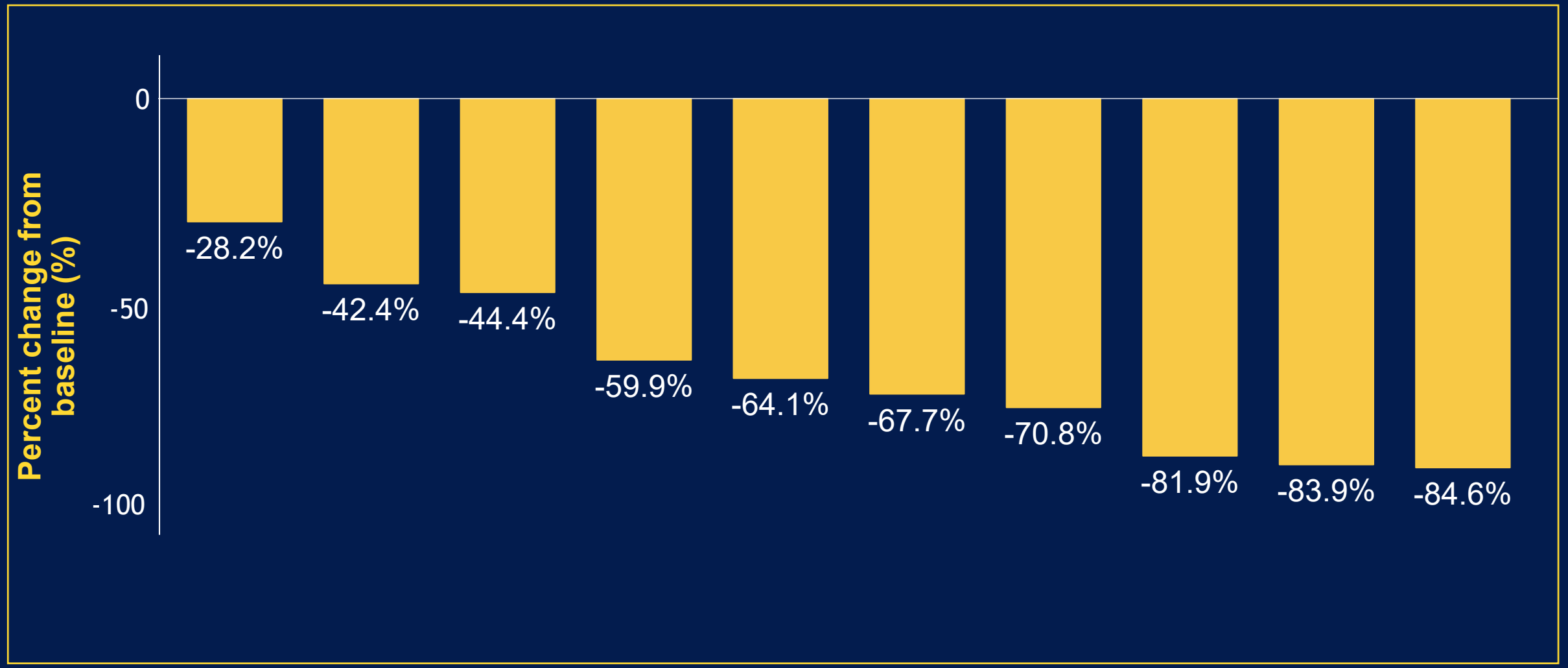
Mean Percent Change from Baseline in ANGPTL3 and Lipids at 30 Days



Percent Change from Baseline in ANGPTL3 at 30 Days by Individual Participant



Percent Change from Baseline in Triglycerides at 30 Days by Individual Participant

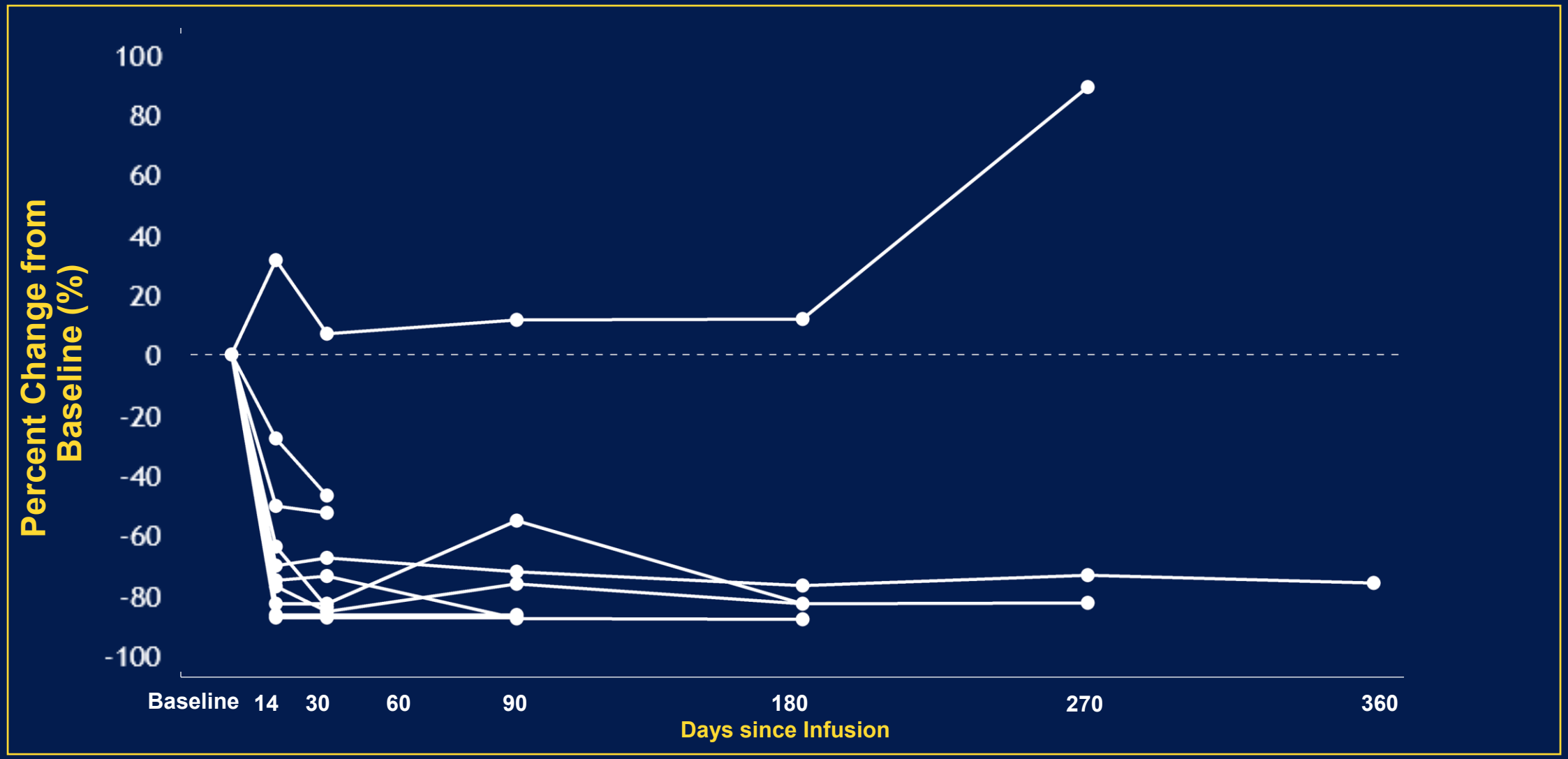


Absolute Change from Baseline in Triglycerides at 30 Days by Individual Participant

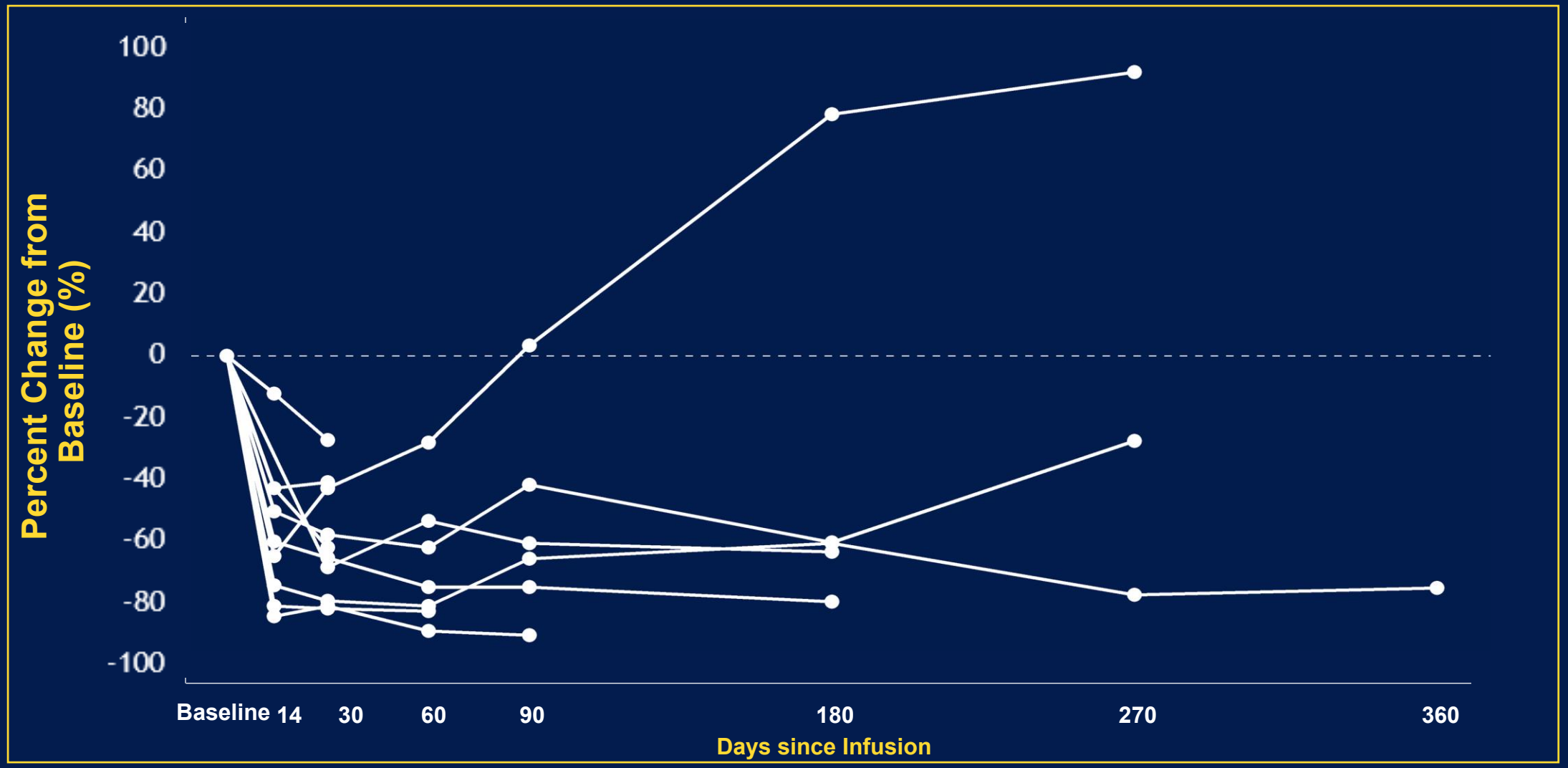
Participant	Baseline TG	TG at 30 days	Absolute change at 30 days	Percent change at 30 days
1	2349.8	378.2	-1971.6	-83.9
2	3944.0	2830.7	-1113.3	-28.2
3	2269.2	1261.2	-1007.9	-44.4
4	1062.0	163.9	-898.1	-84.6
5	1073.5	194.0	-879.5	-81.9
6	1095.6	354.3	-741.3	-67.7
7	875.1	314.4	-560.6	-64.1
8	740.4	216.1	-524.3	-70.8
9	600.5	240.9	-359.6	-59.9
10	705.9	406.5	-299.4	-42.4

TG = serum triglyceride concentration, mg/dL

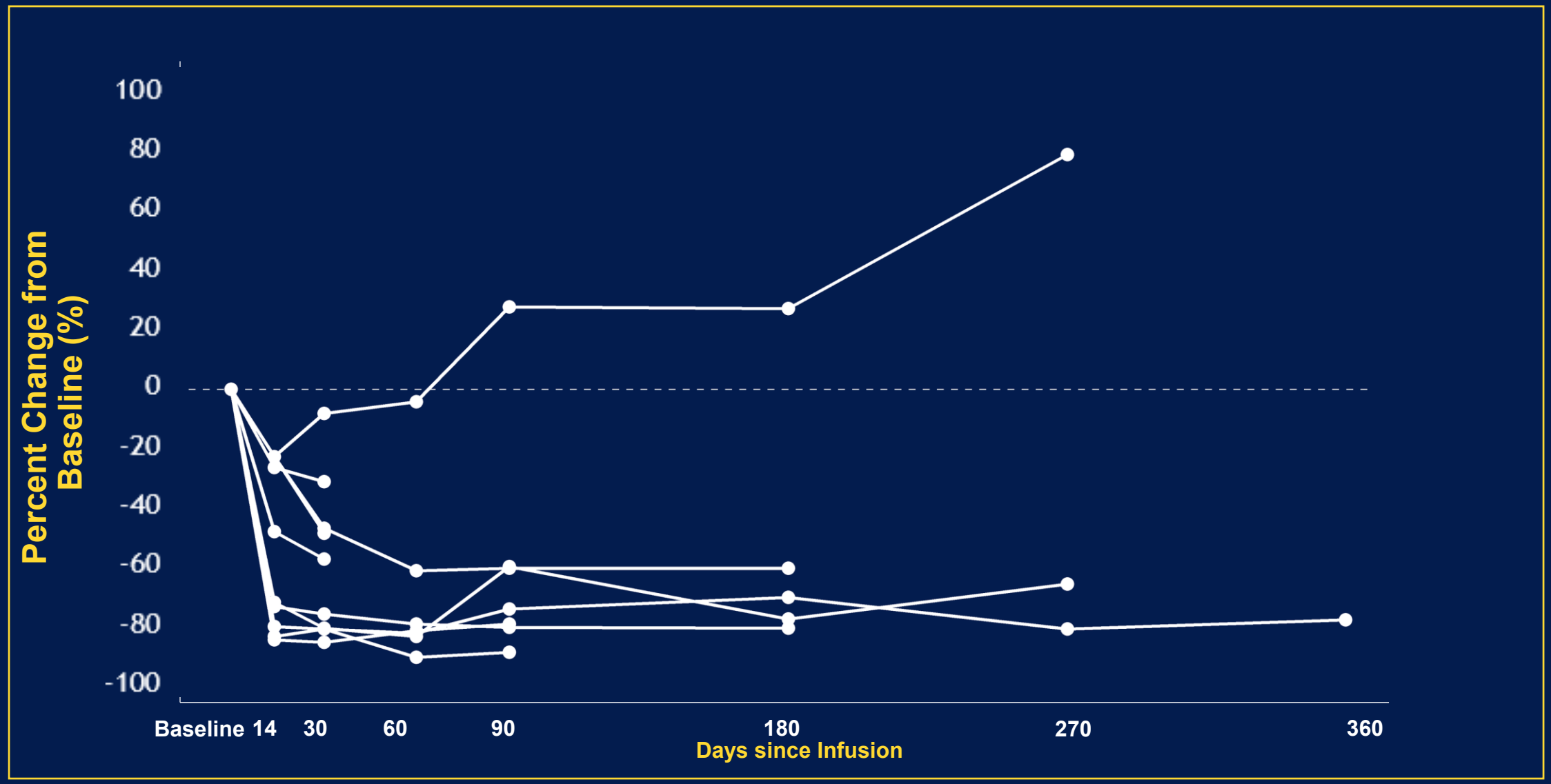
Percent Change in ANGPTL3 over time by Individual Participant



Percent Change in Triglycerides over time by Individual Participant

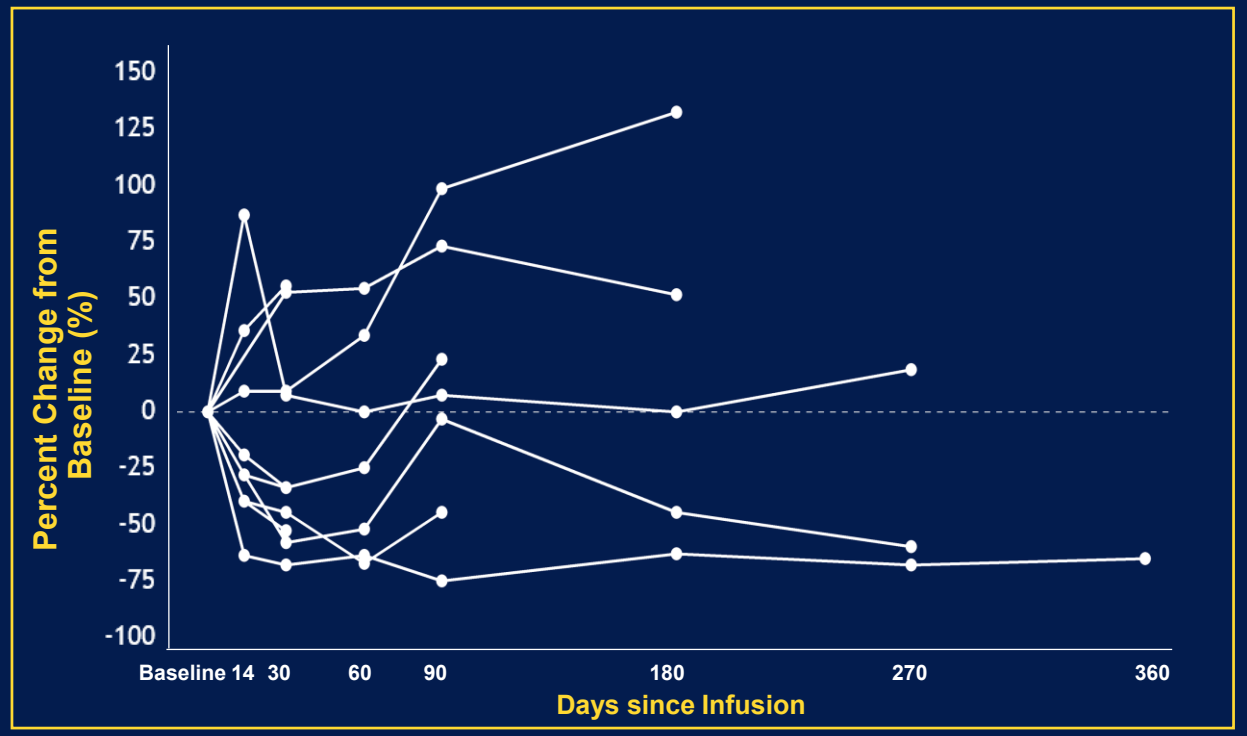


Percent Change in Direct TRL-C over time by Individual Participant

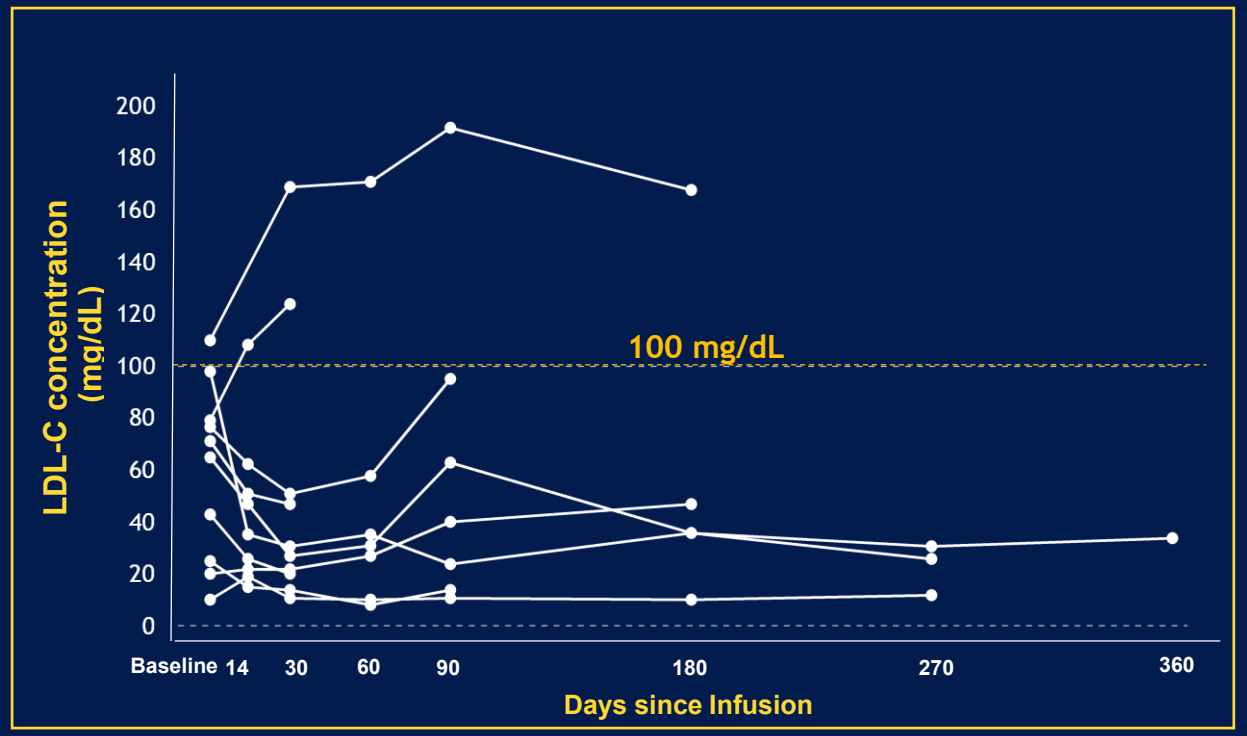


Changes in LDL Cholesterol over time by Individual Participant

Percent change over time

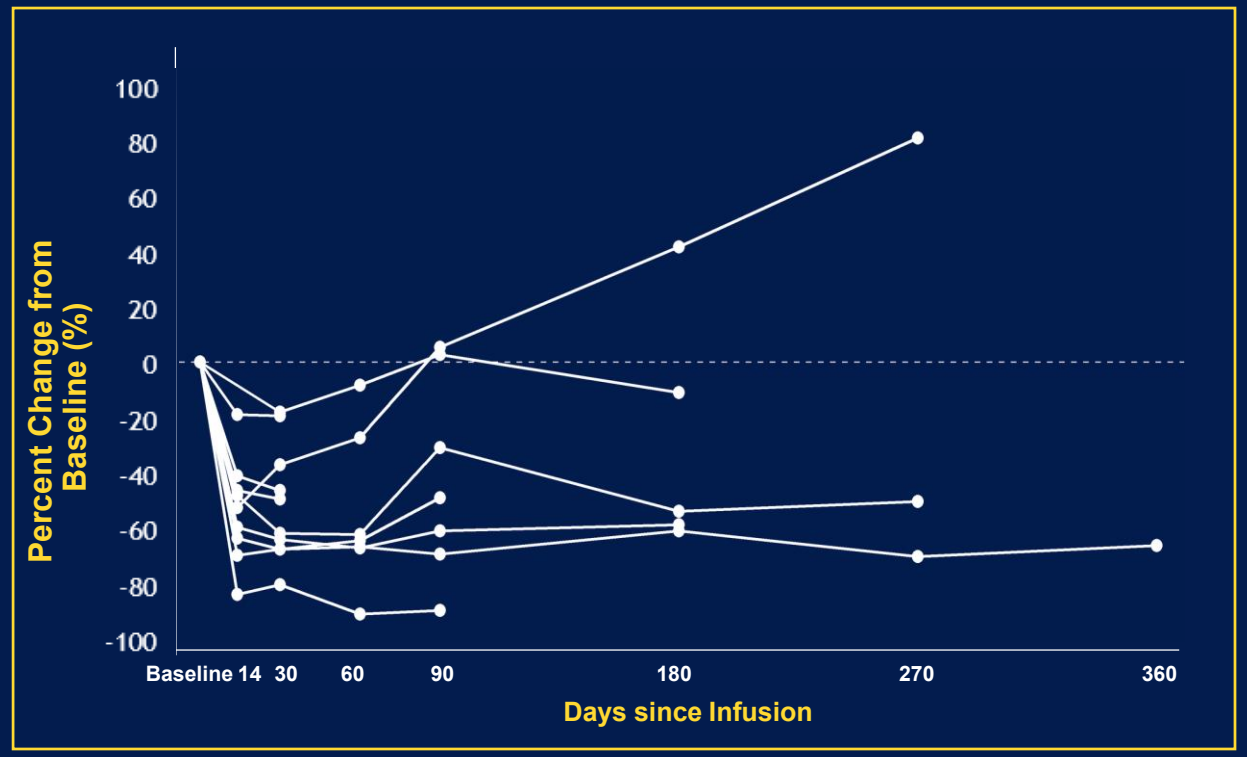


Absolute change over time

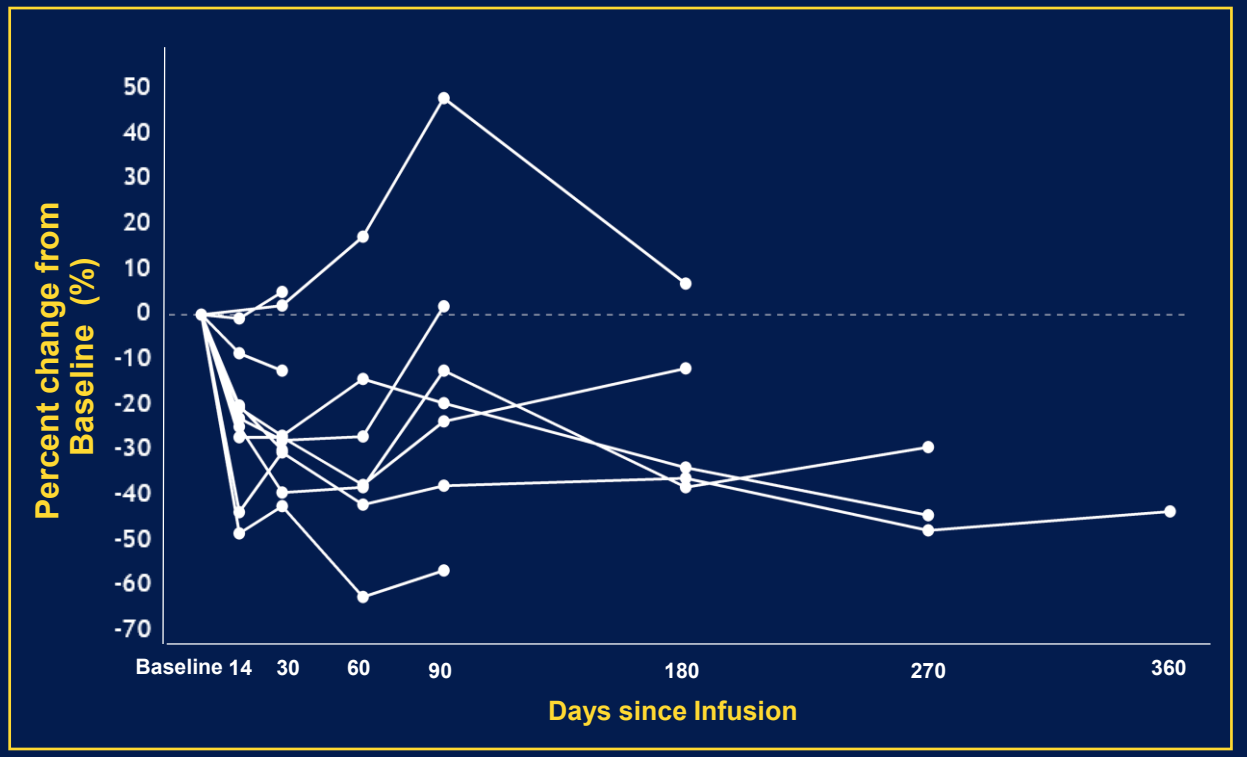


Percent changes in non-HDL cholesterol and Apolipoprotein B over time by Individual Participant

Non-HDL Cholesterol



Apolipoprotein B



Safety

Adverse Events and Laboratory-Related Safety Findings	N (%)
Any serious adverse events	1 (10%)[a]
Serious adverse events related to CTX310	0
Participants with any investigator-reported AE	8 (80%)
Adverse event deemed related to CTX310	4 (40%)
Grade 1	3
Grade 2	1*
Grade 3 or higher	0
Adverse event of special interest	1 (10%)*
▪ Allergic or localized reaction	0
▪ Infusion-related reaction	1 (10%)*
▪ Elevation in AST or ALT	0

[a] Hospitalization due to acute-on-chronic left shoulder pain and full thickness supraspinatus tendon tear (rotator cuff syndrome), occurred >6 months from infusion date.
*Grade 2 infusion related reaction characterized by mild low back pain occurring within 30 minutes of infusion, receiving IV paracetamol 500 mg (the patient was on paracetamol at baseline for low back pain). No acute pancreatitis events were reported.

Conclusions

First-in-human Phase 1b CRISPR Cas9 gene editing study for severe hypertriglyceridemia (median baseline triglycerides exceeding **1000 mg/dL**)

- **A single dose of CTX310 was well-tolerated overall**
  - No clinically significant elevations in AST or ALT
  - No serious AEs related to CTX310 (n=7, followed for 90 days or more)
- **Reduction in triglycerides and atherogenic lipids**
- **These data support further development of CTX310 in sHTG in late phase trials**

After 30 days

ANGPTL3 reduction	Triglyceride reduction
−65.3%	**−62.8%**
Non-HDL-C reduction	ApoB reduction
−50.9%	**−23.4%**

Additional Phase 1b cohorts are ongoing with the same dosing regimen in separate specific lipid disorder cohorts

Acknowledgements

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Co-Authors	P. Clifton, L.J. Laffin, J. Taubel, R. Koops, N.P. Shah, A. Masri, M.J. Koren, S. Nicholls, P. Ochuba, D. Healy, S. Singh, A. Gattu, H. Xu, Z. Mai, H. Nierle, K.E. Wolski, Q. Wang, J. Nielsen, N. Patel, J.M. Duran, S.E. Nissen
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C5 Research Team	**CRISPR Therapeutics**

A Final Thought



In participants with severe hypertriglyceridemia, one-time in vivo CRISPR-Cas9 mediated editing of the hepatic *ANGPTL3* gene was safe and lowered serum TG levels.



Gene-editing is early in its human trials, but the safety and efficacy in the current trial is promising and **represents a new frontier for drug development** for severe hypertriglyceridemia

Additional Slide: Backup Only

Median Percent Change from Baseline in ANGPTL3 and Lipids at 30 Days

