Preclinical Data Supporting Potential Efficacy of VERVE-201, an Investigational Base Editing Medicine Targeting *ANGPTL3*

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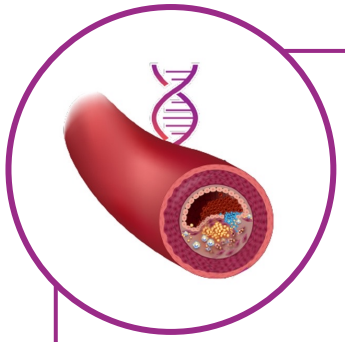
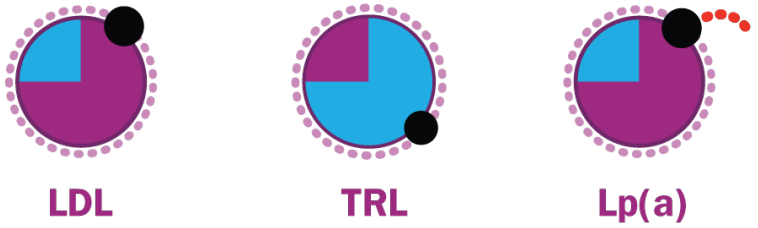
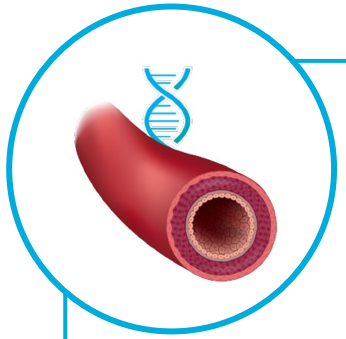
What causes ASCVD and what's a solution?
Verve developing 'once and done' medicines for 3 causal drivers



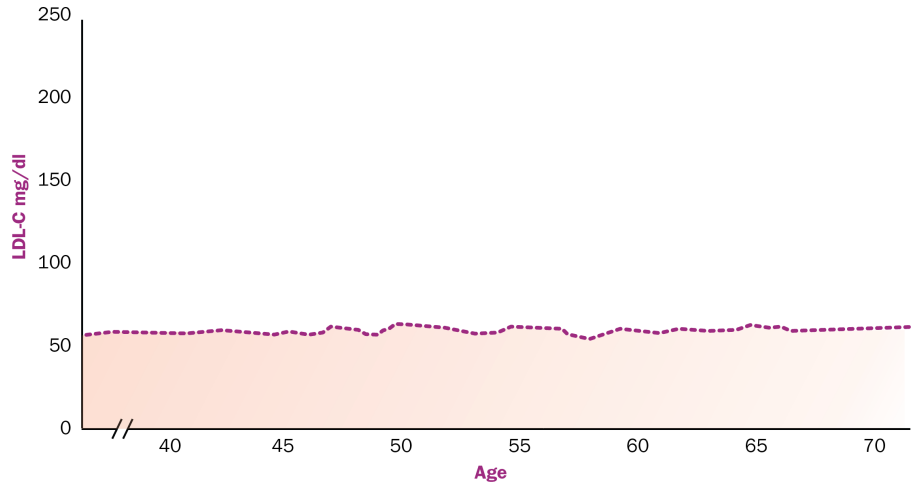
High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:





Solution: keep blood cholesterol as low as possible for as long as possible



Two ASCVD indications with unmet medical need: Homozygous FH and refractory hypercholesterolemia

Patients with homozygous familial hypercholesterolemia (HoFH)

Rare, orphan disease

LDL-C levels above 500 mg/dL

~2,800 patients in the U.S./EU

Patients with refractory hypercholesterolemia

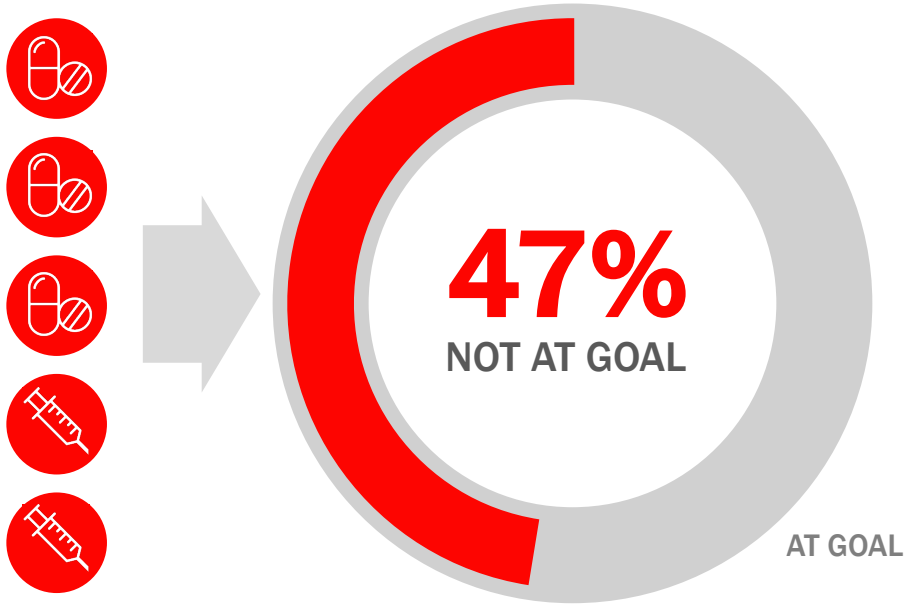
ASCVD not at LDL-C goal on oral + PCSK9i

~7M patients in the U.S.[1]/EU

1. O'Donoghue et al., *Circulation*. 2022;146:1109–1119.

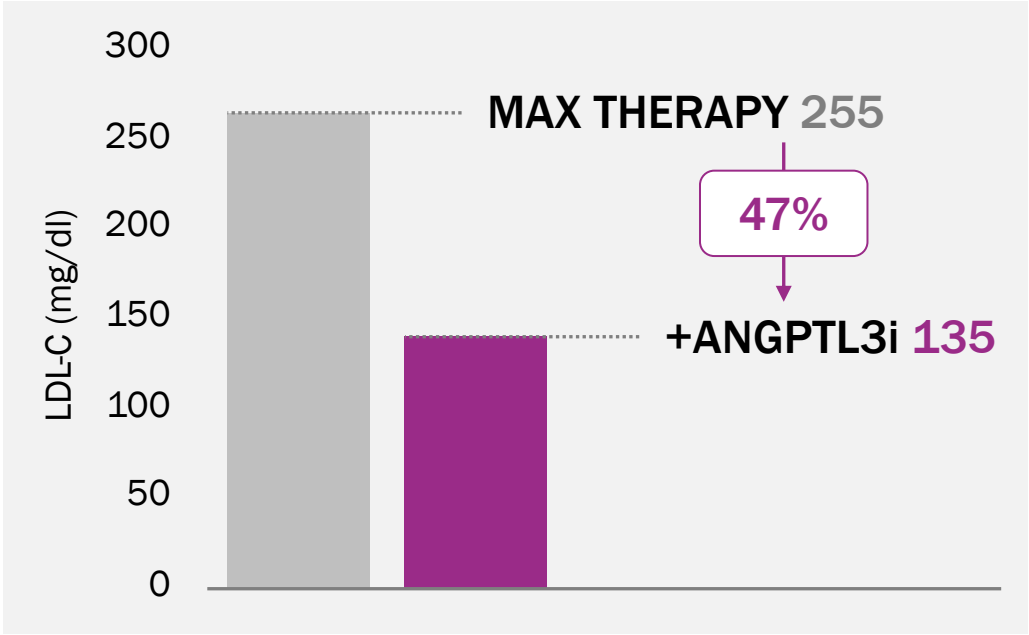
HoFH: severe orphan disease where medicine targeting ANGPTL3 is approved to lower LDL-C

Unmet Medical Need



In a global registry of HoFH patients, 47% did not attain LDL-C goal even on 5 lipid-lowering therapies[1]

Clinical Validation of ANGPTL3 Mechanism



Registration trial of evinacumab (Evkeeza) in HoFH patients on maximum lipid-lowering therapy
ANGPTL3 inhibition ↓ LDL-C by 47%[2]

1. Tromp TR et al. *Lancet*. 2022;399(10326):719-728.
2. Raal FJ et al. *N Engl J Med*. 2020;383(8):711-720.

VERVE-201 medicine candidate: adenine base editor mRNA + gRNA packaged in a GalNAc-LNP; edit designed to turn off *ANGPTL3*

DRUG SUBSTANCES

RNA components encode base editor and a guide targeting ANGPTL3 gene

- mRNA for adenine base editor
- gRNA localizes editor to *ANGPTL3* gene

+

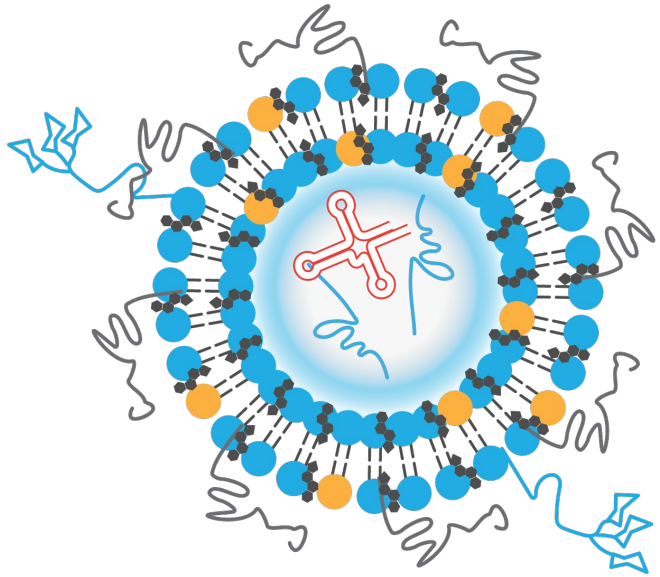
DELIVERY VEHICLE

Lipid nanoparticle for delivery to liver cell includes 5 components

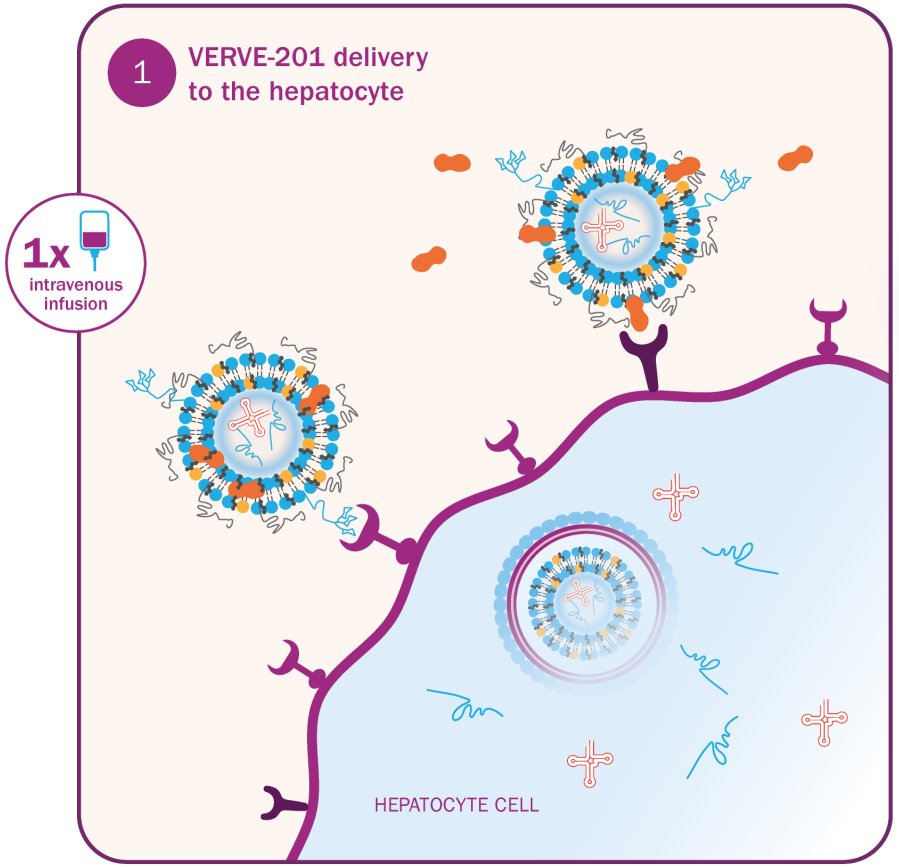
- Ionizable amino lipid
- DSPC
- Cholesterol
- GalNAc
- PEG

=

VERVE-201



VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG



GalNAc lipid nanoparticle:

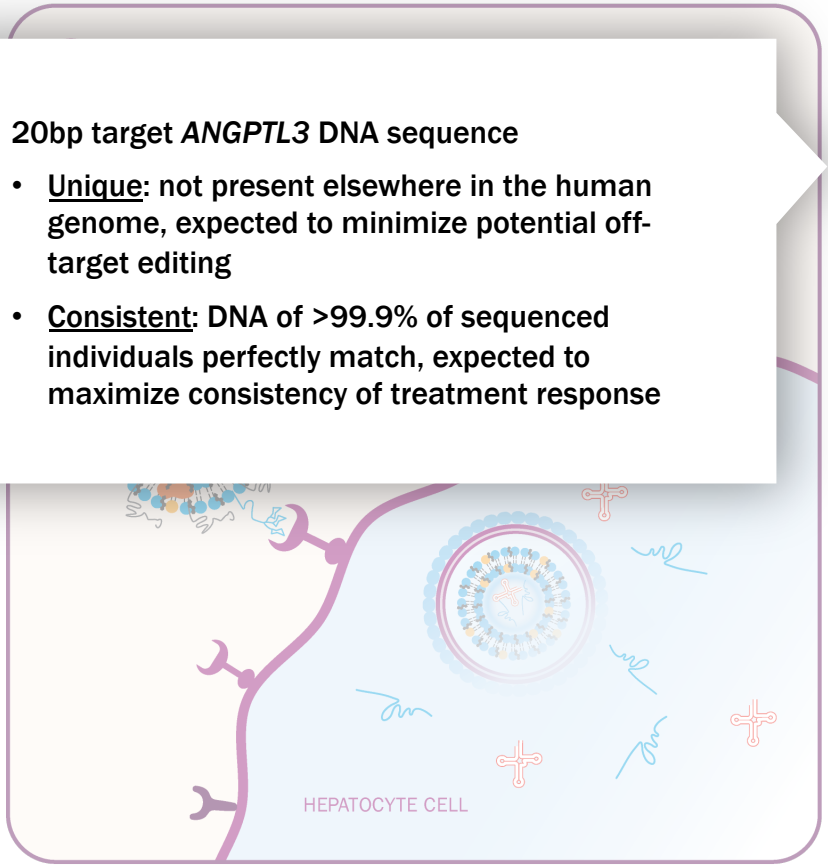
- **Enables delivery into hepatocyte via either of two receptors: LDLR or ASGPR**
- **Potential for potent editing in target liver tissue with minimal editing elsewhere**
- **No potential for exogenous DNA to integrate into patient DNA (as can occur with viral vectors)**

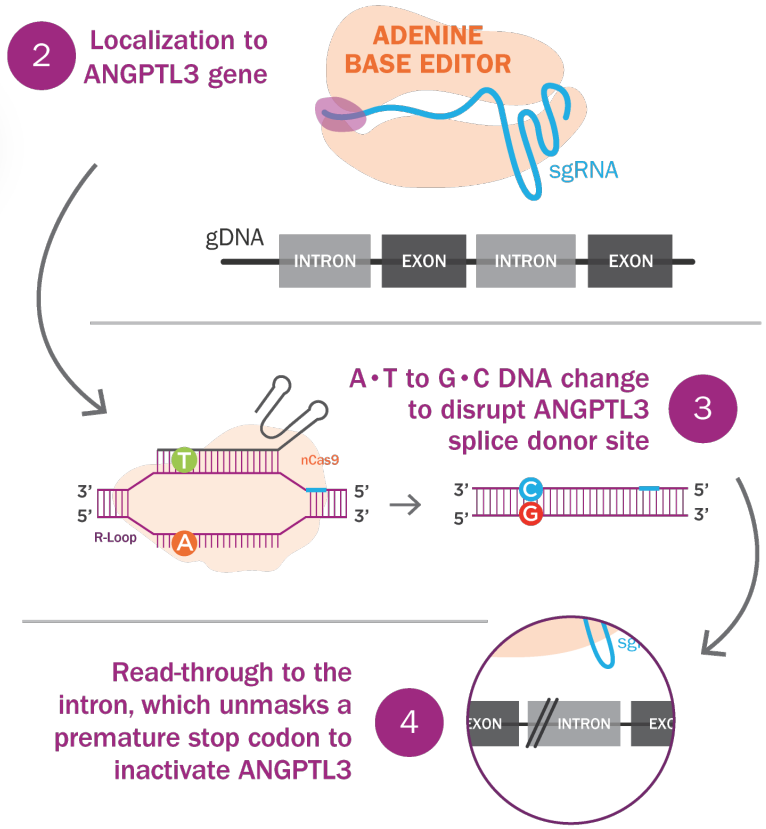
Lipid nanoparticle | Ionizable amino lipid | DSPC | Asialoglycoprotein receptor (ASGPR) | LDL receptor (LDLR) | GalNAc | apoE | mRNA | gRNA | PEG Lipid | Cholesterol

VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG

20bp target *ANGPTL3* DNA sequence

- Unique: not present elsewhere in the human genome, expected to minimize potential off-target editing
- Consistent: DNA of >99.9% of sequenced individuals perfectly match, expected to maximize consistency of treatment response

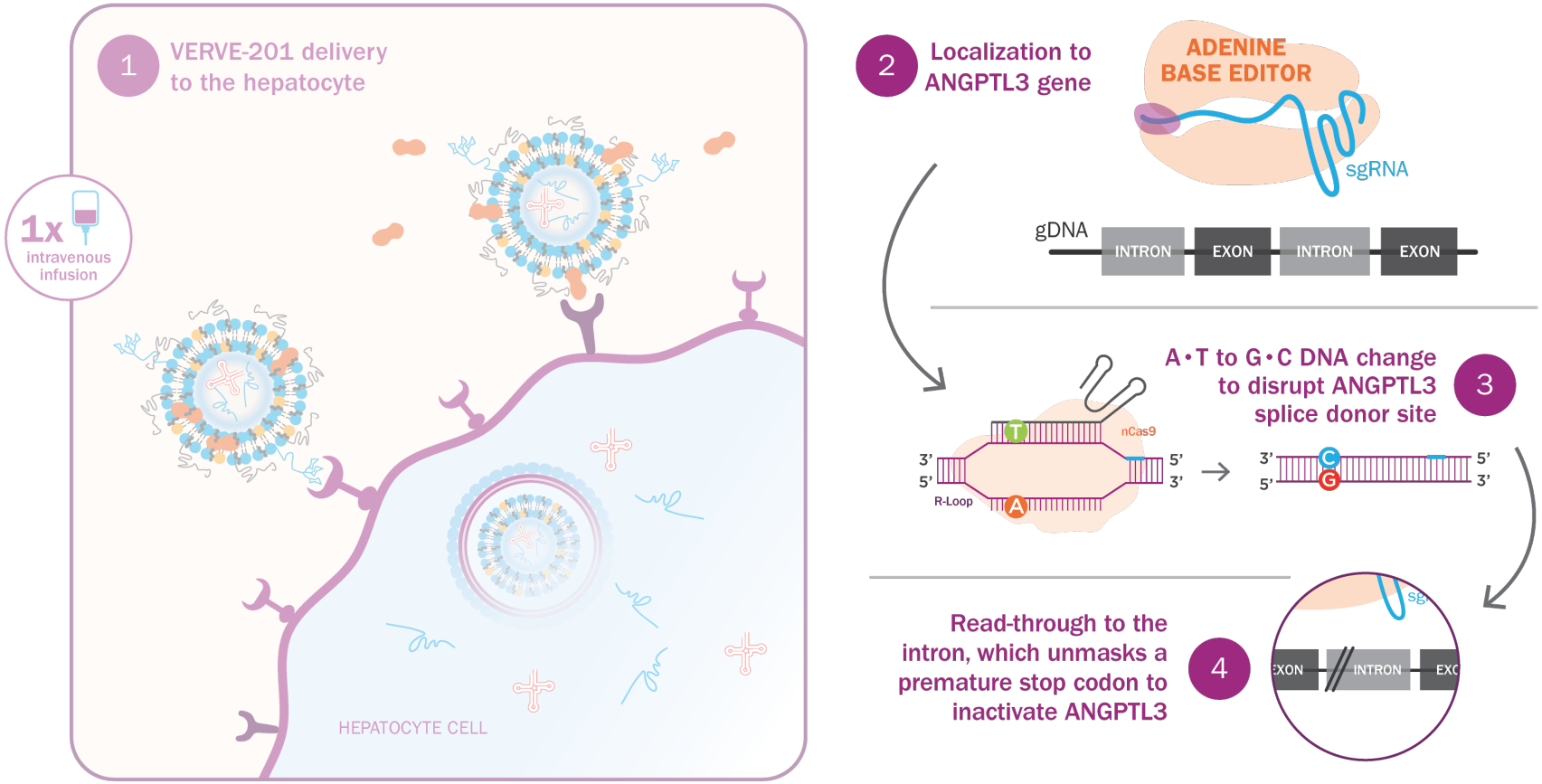




Adenine Base Editor:

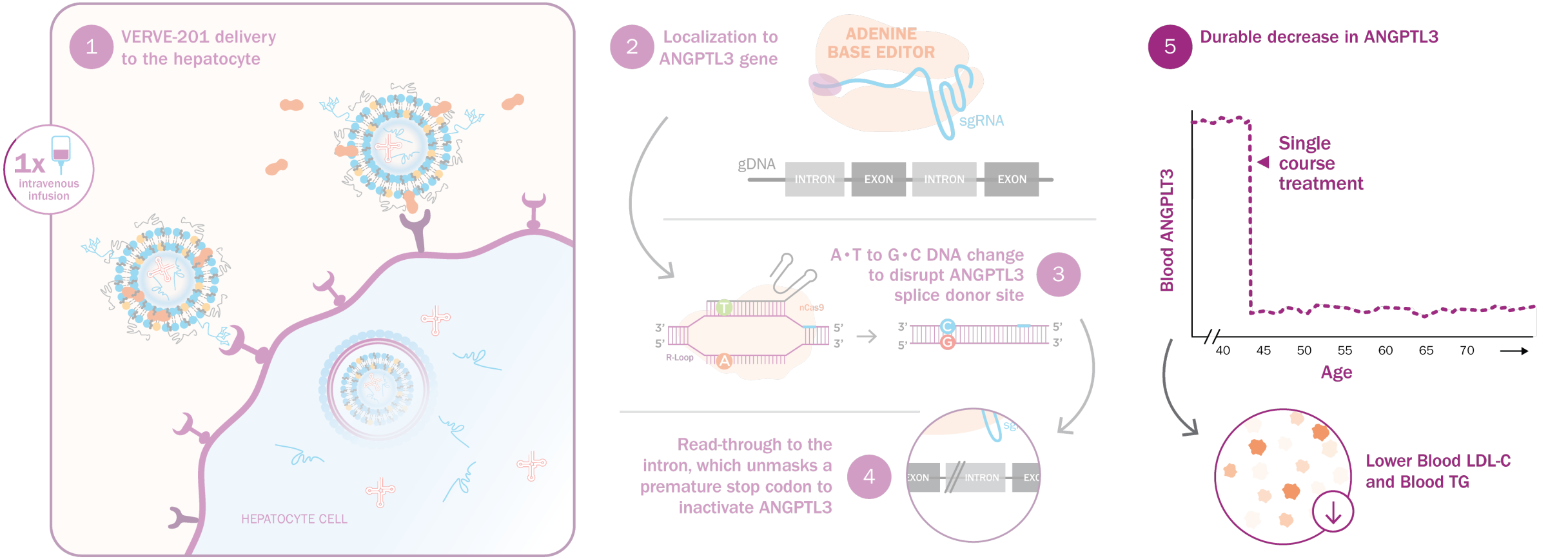
- Precise and predictable DNA change to inactivate gene
- No requirement for a double-strand DNA break, as needed for Cas9 nuclease
- Elimination from body within days minimizes potential for delayed adverse effects

VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG



Lipid nanoparticle · Ionizable amino lipid · DSPC · Asialoglycoprotein receptor (ASGPR) · LDL receptor (LDLR) · GalNAc · apoE · mRNA · gRNA · PEG Lipid · Cholesterol

VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG

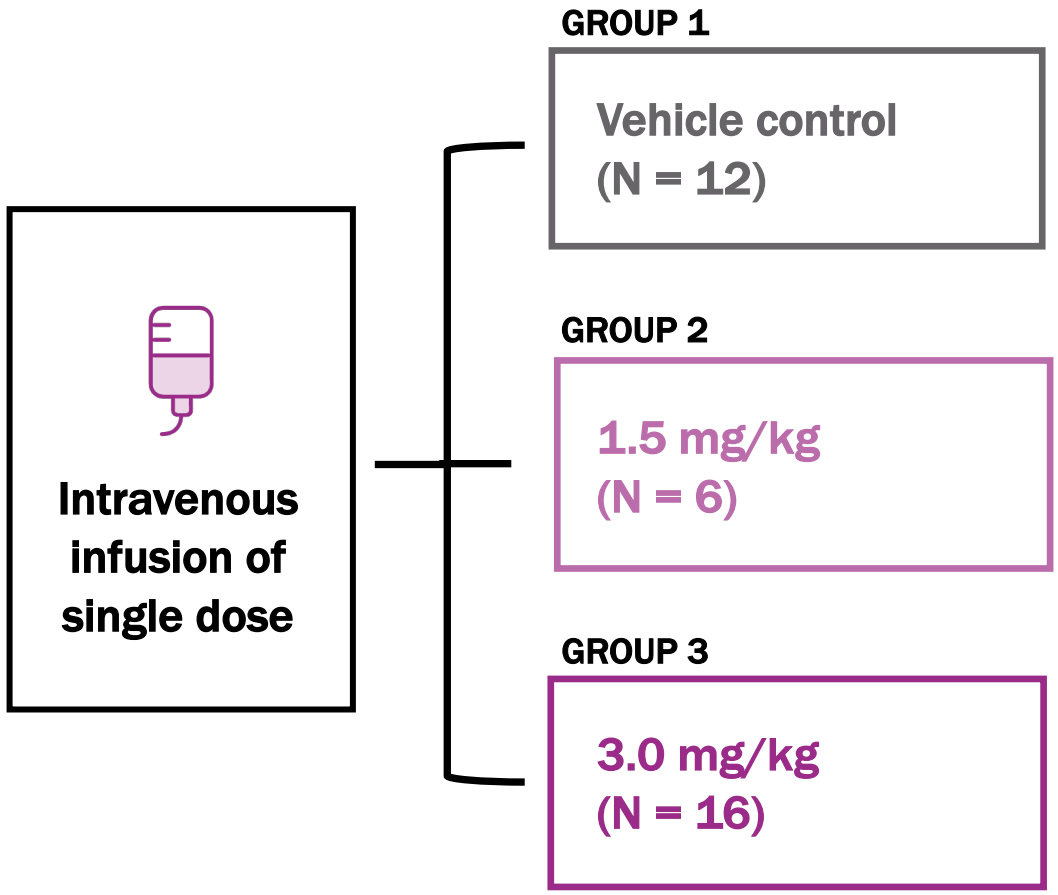


Lipid nanoparticle | Ionizable amino lipid | DSPC | Asialoglycoprotein receptor (ASGPR) | LDL receptor (LDLR) | GalNAc | apoE | mRNA | gRNA | PEG Lipid | Cholesterol

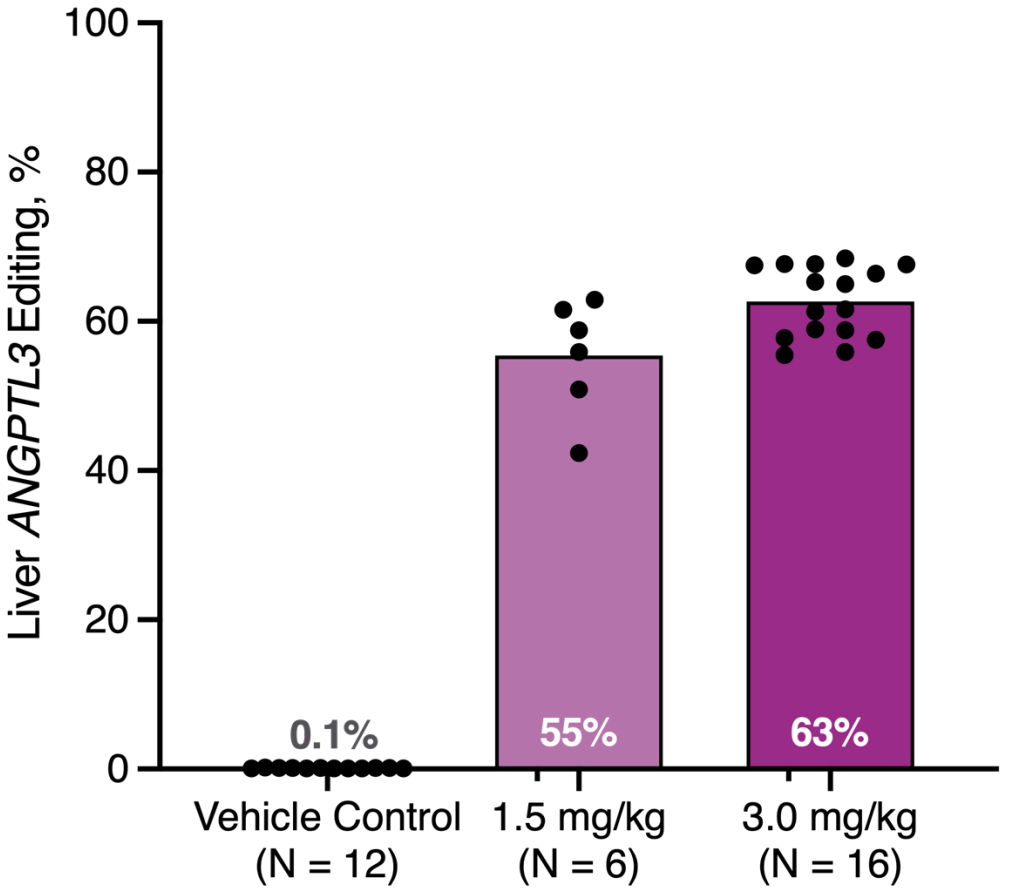
Pharmacology study of VERVE-201cyn in non-human primates

In non-human primates, VERVE-201cyn achieved mean liver *ANGPTL3* editing of 63% at higher dose

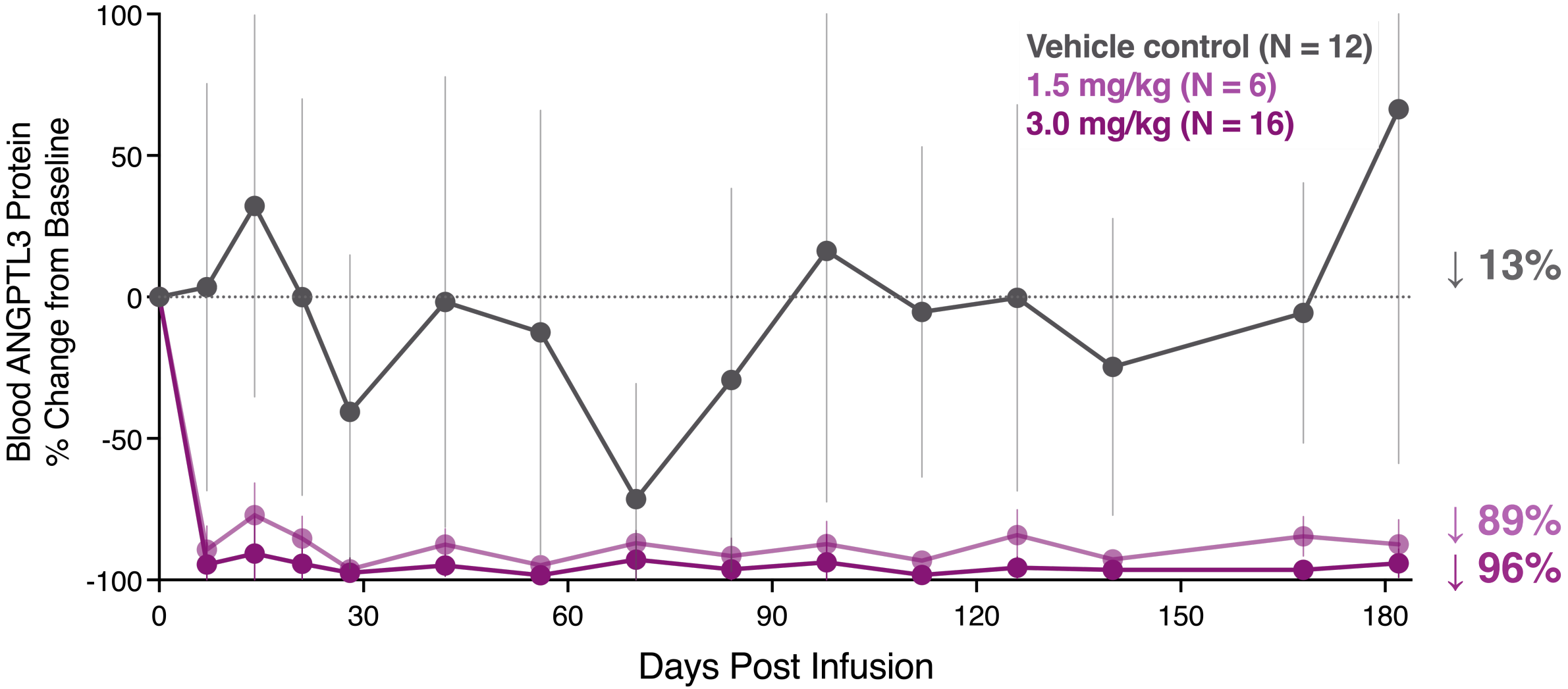
Study of 34 Non-human Primates



Liver *ANGPTL3* editing

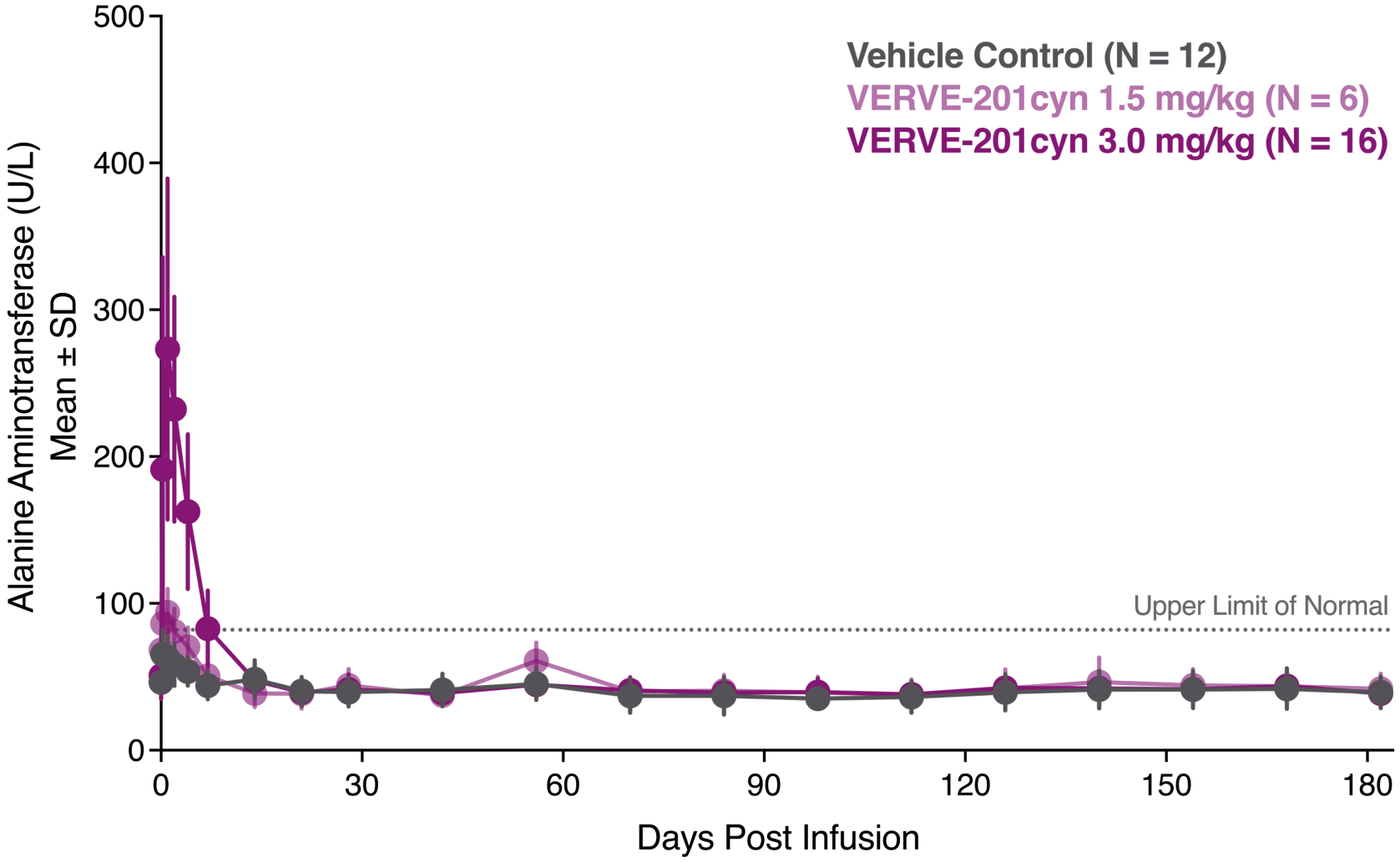


In non-human primates, VERVE-201cyn achieved mean 96% reduction* in blood ANGPTL3 protein at higher dose



* Measured as time-weighted average % change from baseline from days 28 to 182 following dosing.

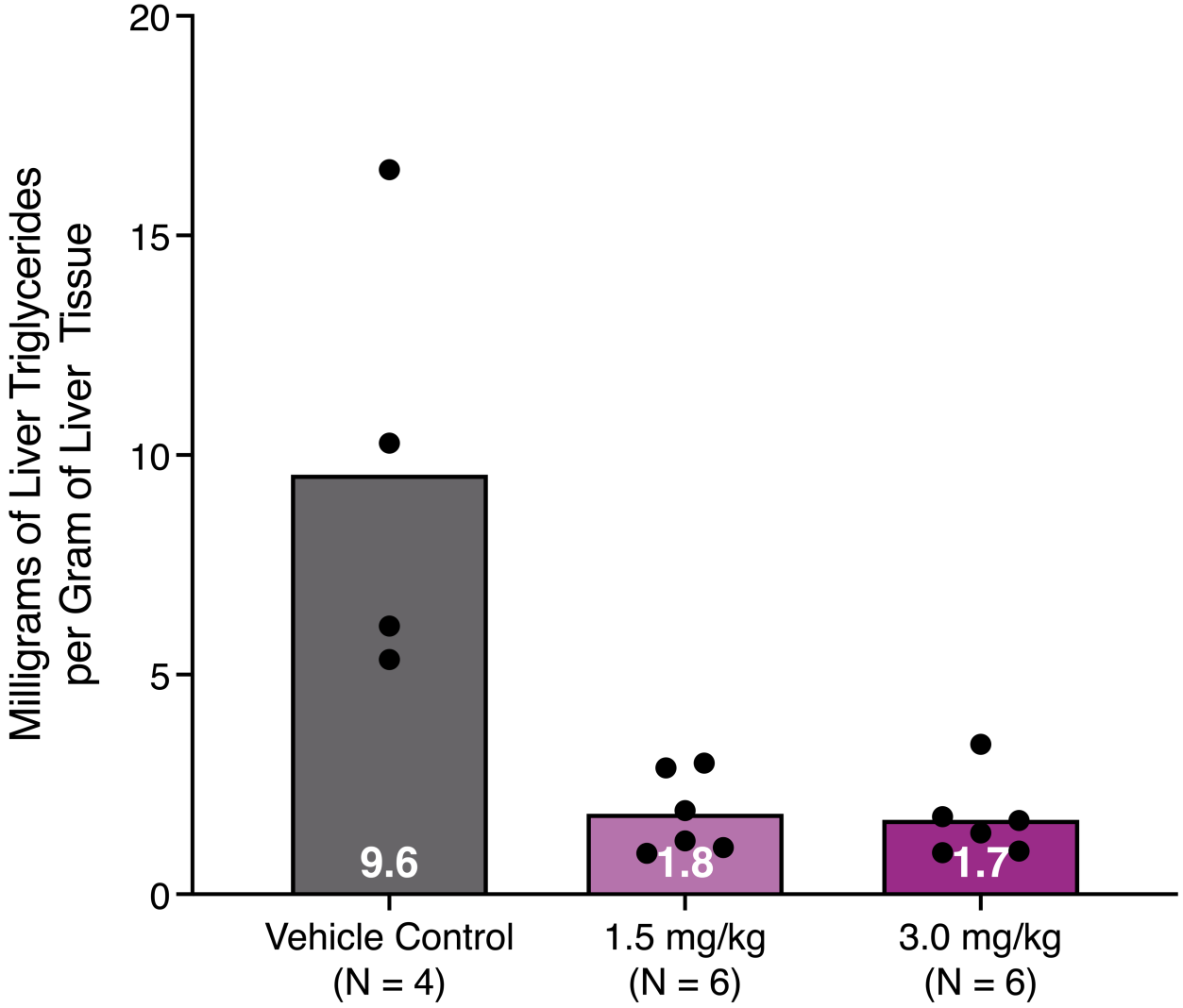
In non-human primates, VERVE-201cyn was well-tolerated with only transient impact on ALT



Liver safety monitoring

- Maximal ALT and AST concentrations noted 24 hours after dosing, normalized by day 14
- Normal total bilirubin observed with no change from baseline

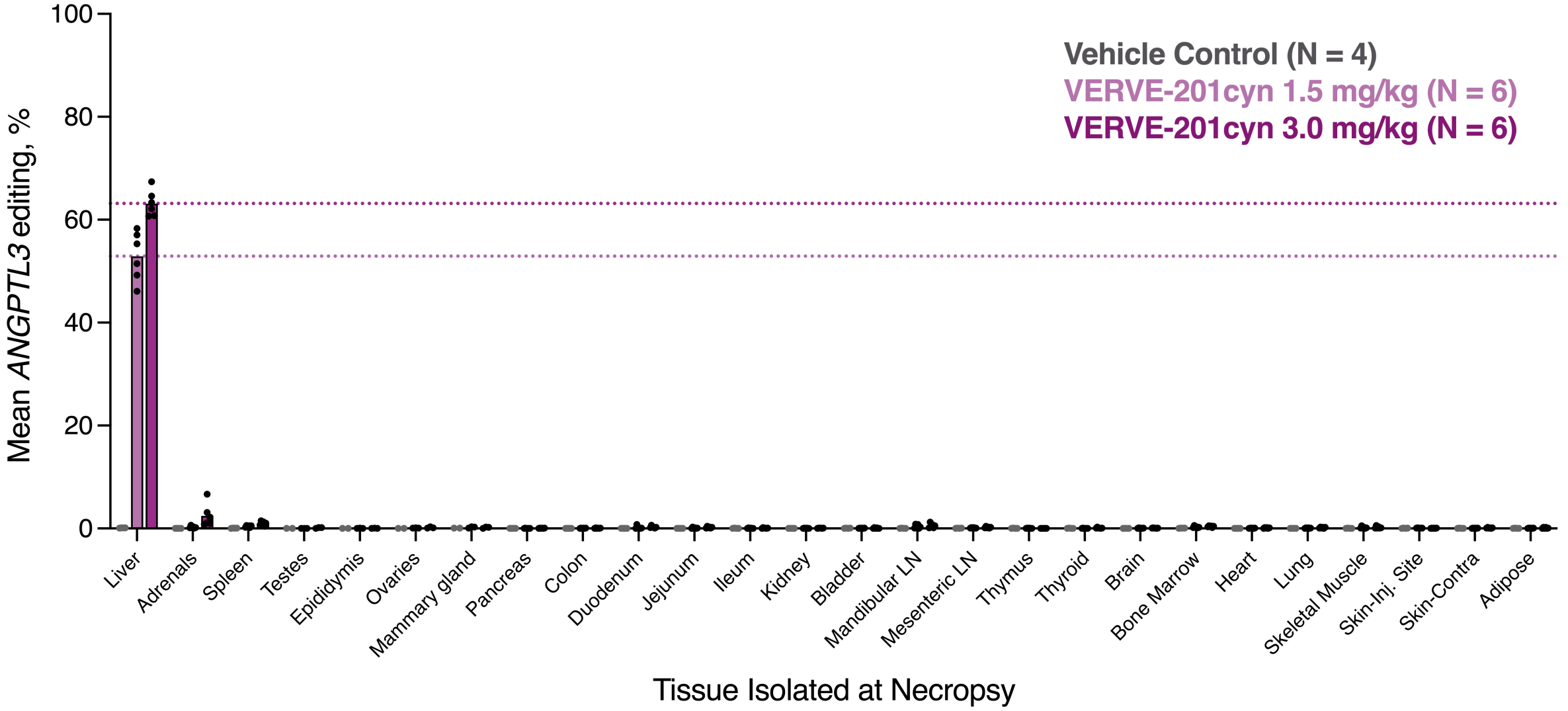
In non-human primates, VERVE-201cyn was associated with lower liver triglycerides 6 months after dosing versus control



Liver Triglyceride Assessment

- Liver triglyceride mass — a nonclinical surrogate of hepatic steatosis — quantified in 16 NHPs at time of scheduled necropsy six months after dosing.
- Liver triglyceride mass was significantly lower in NHPs treated with VERVE-201cyn at a dose of 1.5 or 3.0 mg/kg as compared to control ($P < 0.01$ for each)

In non-human primates dosed with VERVE-201cyn, on-target *ANGPTL3* editing occurred mostly in the liver*

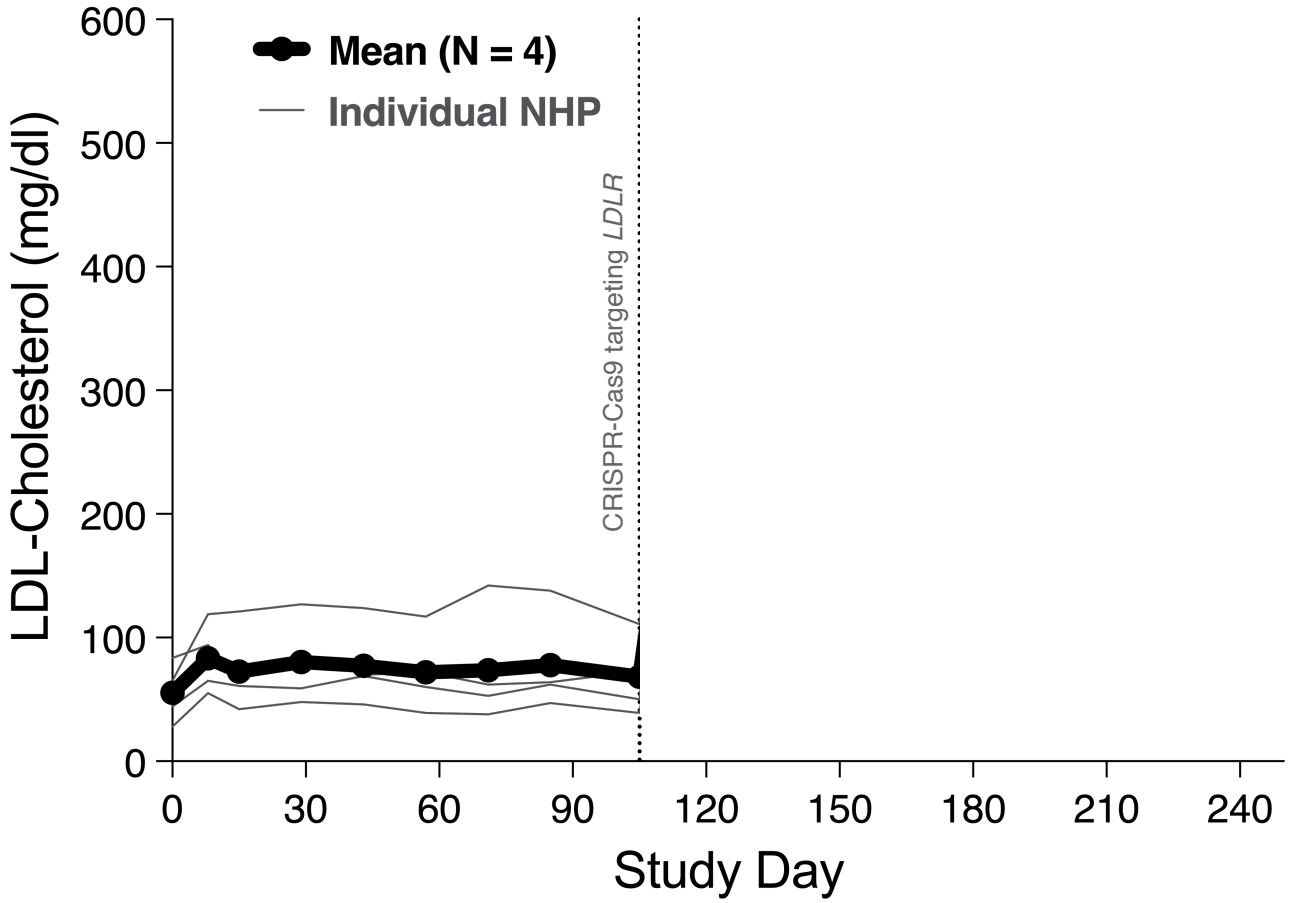


* *ANGPTL3* editing assessed using targeted amplicon sequencing in tissues isolated at scheduled necropsy 6 months after dosing

Non-human primate model of homozygous FH physiology

Study of VERVE-201cyn

To model homozygous FH physiology, Verve developed LDLR-deficient non-human primates

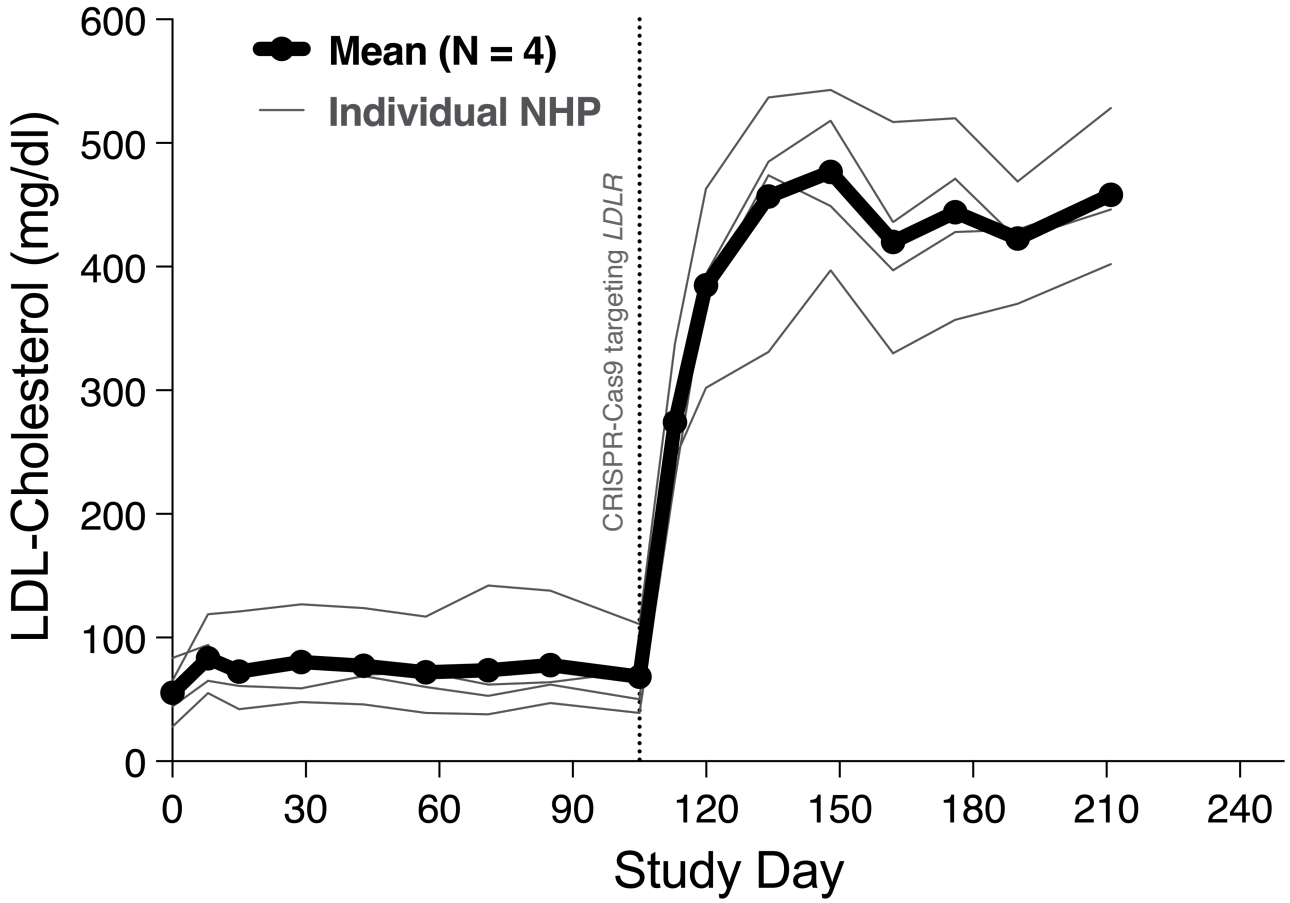


Step #1: Develop LDLR-deficient NHPs

- NHP model of LDLR-deficiency not readily available
- Treated 4 NHPs with CRISPR-Cas9 to inactivate *LDLR* in the liver.[1]

1. Method previously described in Kasiewicz et al. biorXiv, 2021

LDL-C goes up > 8-fold in the LDLR-deficient NHPs

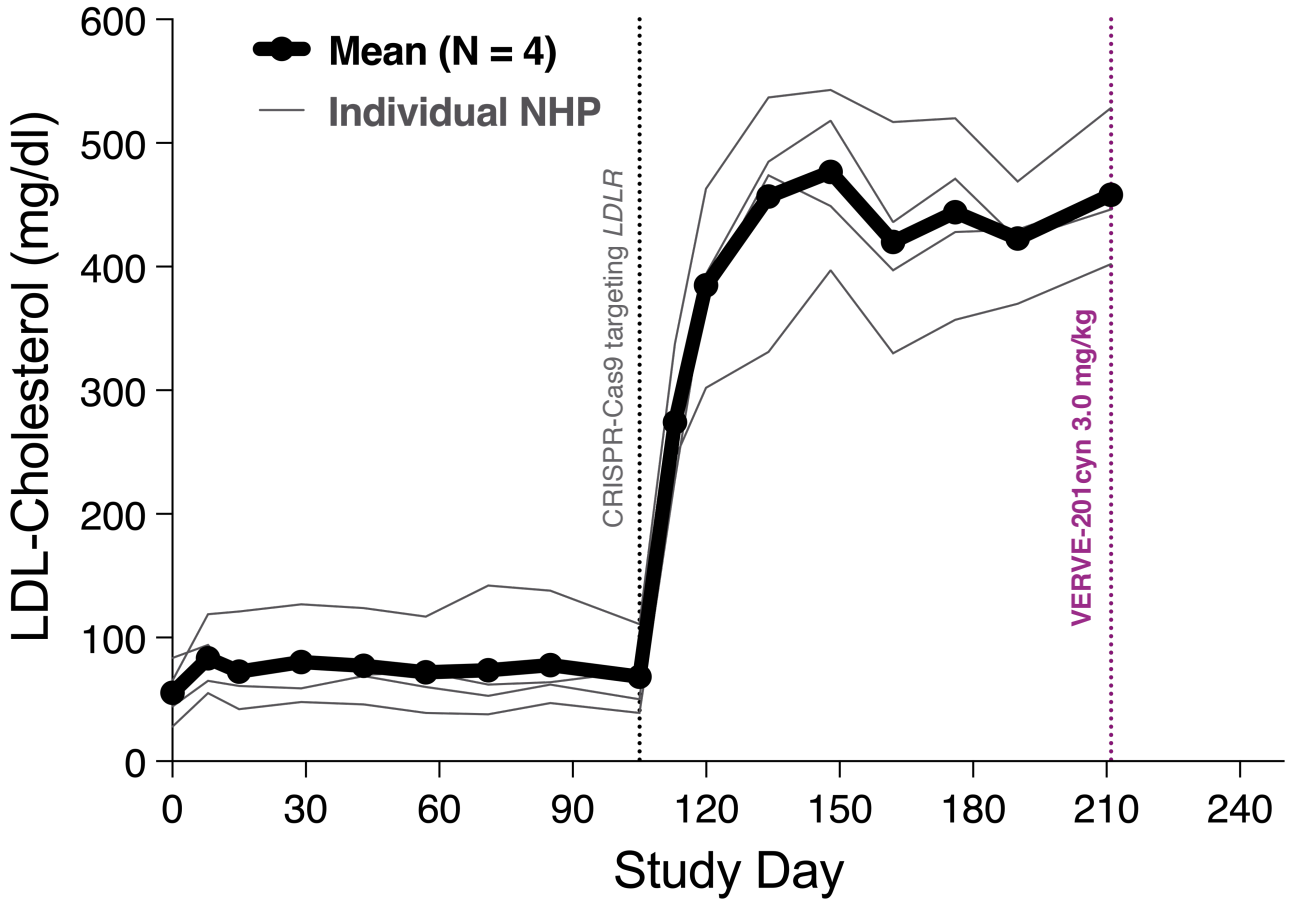


Step #1: Develop LDLR-deficient NHPs

- NHP model of LDLR-deficiency not readily available
- Treated 4 NHPs with CRISPR-Cas9 to inactivate *LDLR* in the liver:[1]
  - 64% mean *LDLR* editing
  - >80% lower hepatic LDLR protein versus control NHPs
  - Mean LDL-C increased from baseline of 55 to 458 mg/dL

1. Method previously described in Kasiewicz et al. biorXiv, 2021

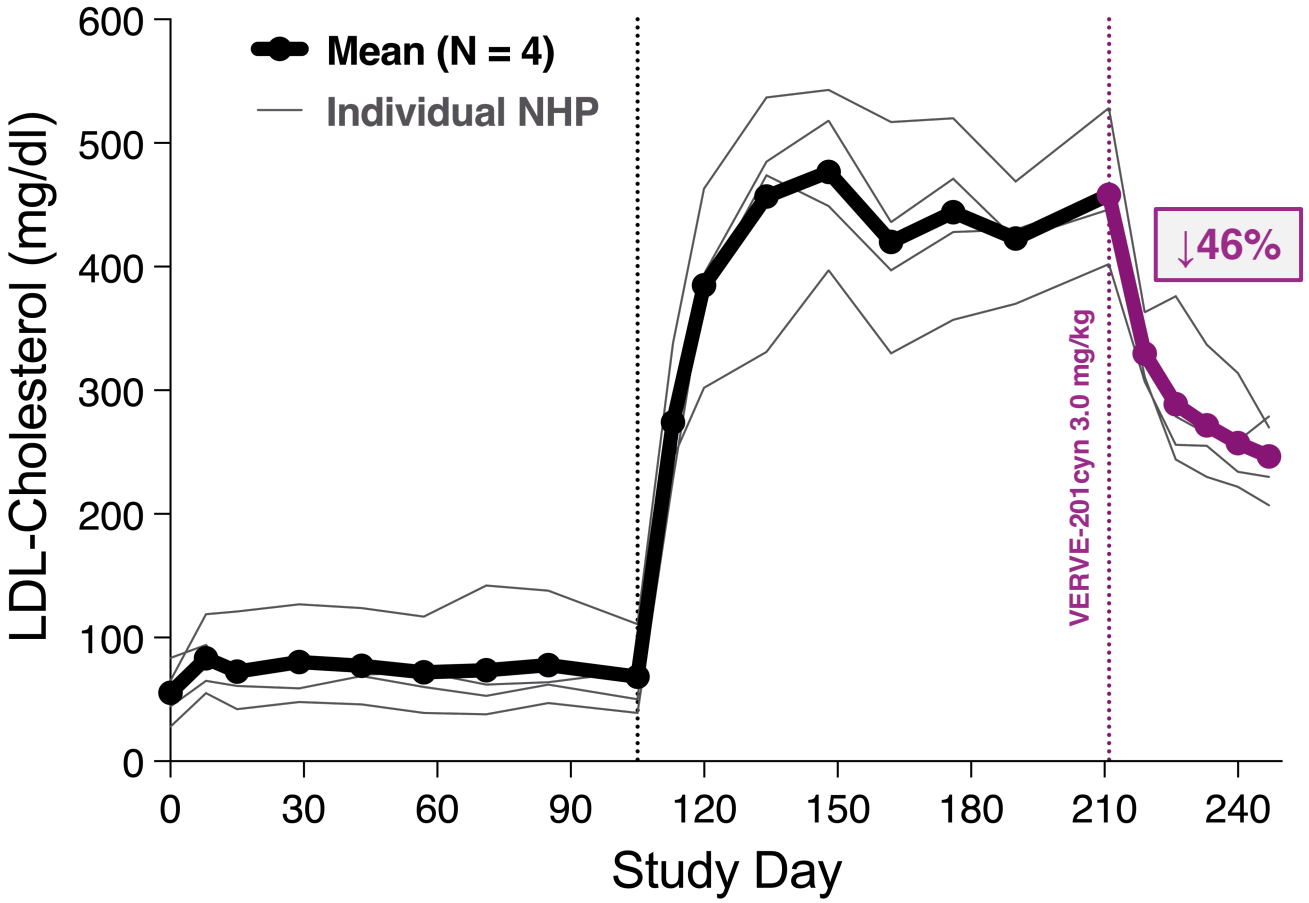
Treat with VERVE-201cyn – 84% reduction in blood ANGPTL3



Step #2: Treat with VERVE-201cyn

- Treated 4 NHPs with VERVE-201cyn at a dose of 3.0 mg/kg.
- At time of necropsy 5 weeks following dosing:
  - 60% mean *ANGPTL3* liver editing
  - 84% mean reduction from baseline in blood ANGPTL3

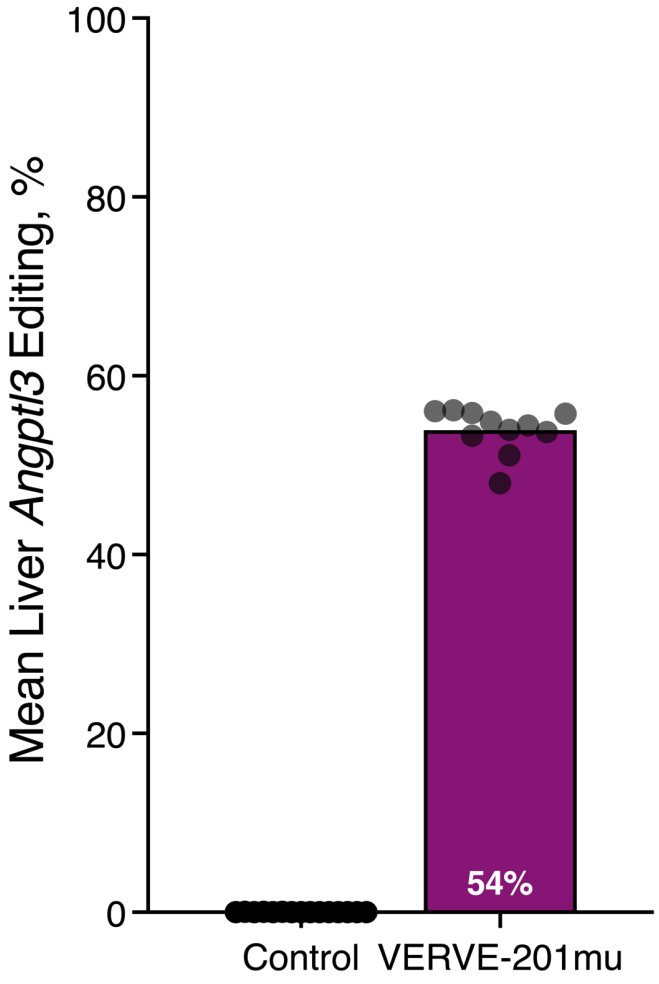
In LDLR-deficient NHPs treated with VERVE-201cyn, 46% mean decrease in LDL-C observed (458 to 247 mg/dL)

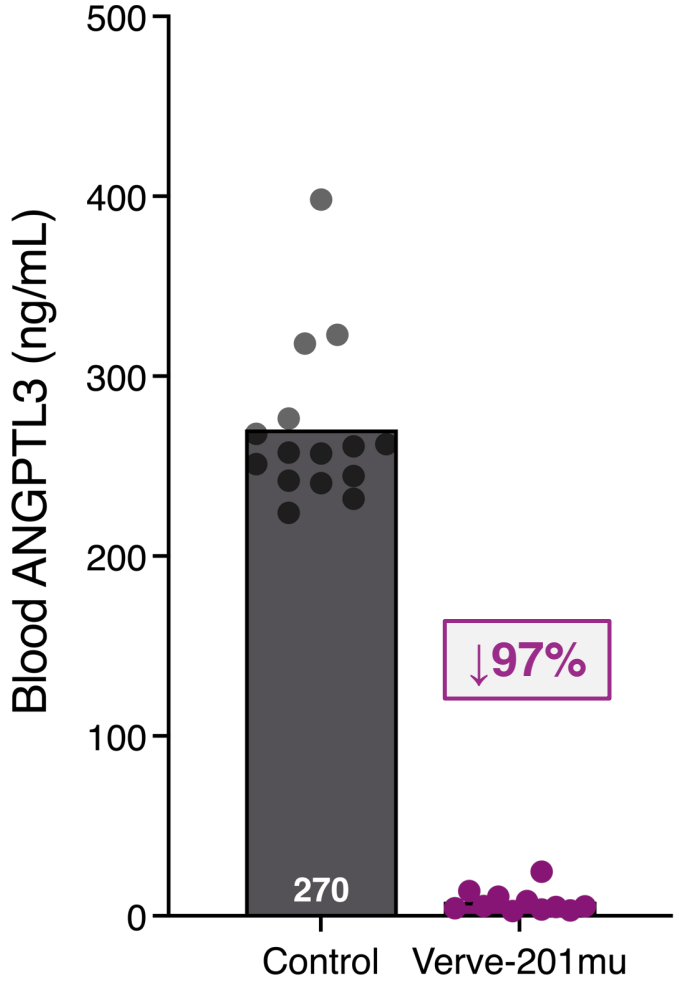


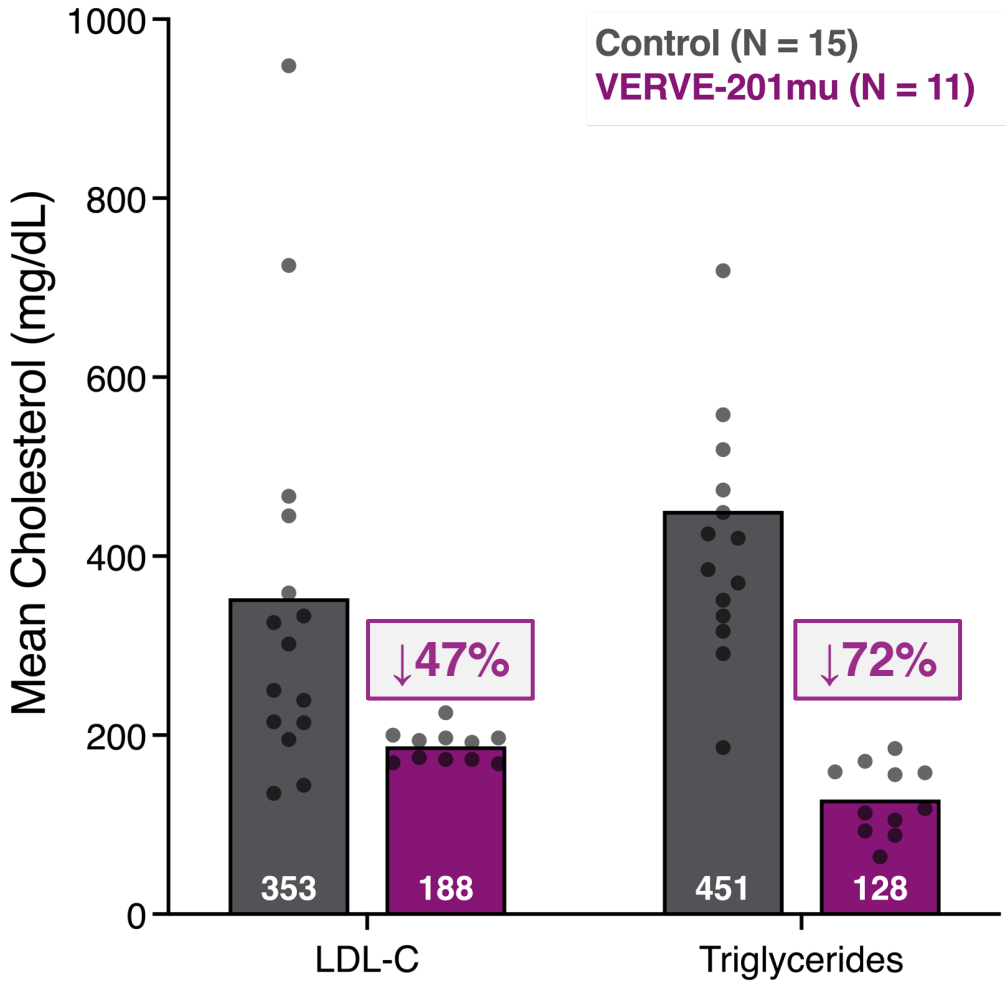
Step #2: Treat with VERVE-201cyn

- Mean LDL-C decreased from 458 to 247 mg/dL
- VERVE-201cyn in NHPs:
  - 46% decrease in LDL-C
  - 54% decrease in TG

Ldlr$^{-/-}$ mice on Western diet treated with VERVE-201mu precursor, 97% reduction in blood ANGPTL3 | 47% reduction in LDL-C







Mice placed on high-fat ('Western') diet for 14 weeks prior to dosing with either vehicle control or VERVE-201mu at a dose of 5 mg/kg.

VERVE-201: base editing medicine designed to inactivate *ANGPTL3*
Anticipate initiation of Phase 1b clinical trial in 2024

- VERVE-201 designed to address unmet need in homozygous familial hypercholesterolemia, a rare, severe disease with extremely high LDL-C and ASCVD risk
- Potential to expand to refractory hypercholesterolemia patient population
- In NHPs, VERVE-201cyn was well-tolerated and achieved a durable and potent mean reduction in blood ANGPTL3 protein up to 96%
- Reduced liver triglyceride mass was observed in NHPs treated with VERVE-201cyn compared with a vehicle control
- GalNAc LNP delivery system enabled potent *ANGPTL3* liver editing in a NHP model of HoFH physiology, achieving a 46% mean reduction in LDL-C from 458 to 257 mg/dL

Future directions: GalNAc-LNP delivery used in VERVE-201 may allow targeting a range of liver targets, including the *PCSK9* gene

- GalNAc LNP allows for delivery in setting of severe LDLR deficiency
- PCSK9 inhibitors are approved to lower LDL-C in two LDLR-deficient populations:
  - Homozygous FH (severe or complete deficiency)
  - Heterozygous FH (partial deficiency)
- Evaluating a GalNAc-LNP to deliver a base editor targeting *PCSK9*
- GalNAc-LNP PCSK9 efficiently lowers PCSK9 in NHPs in vivo

GalNAc-LNP PCSK9
in wild-type non-human primates