An *in vivo* CRISPR base editing therapy to inactivate *ANGPTL3*: nomination of a development candidate for VERVE-201

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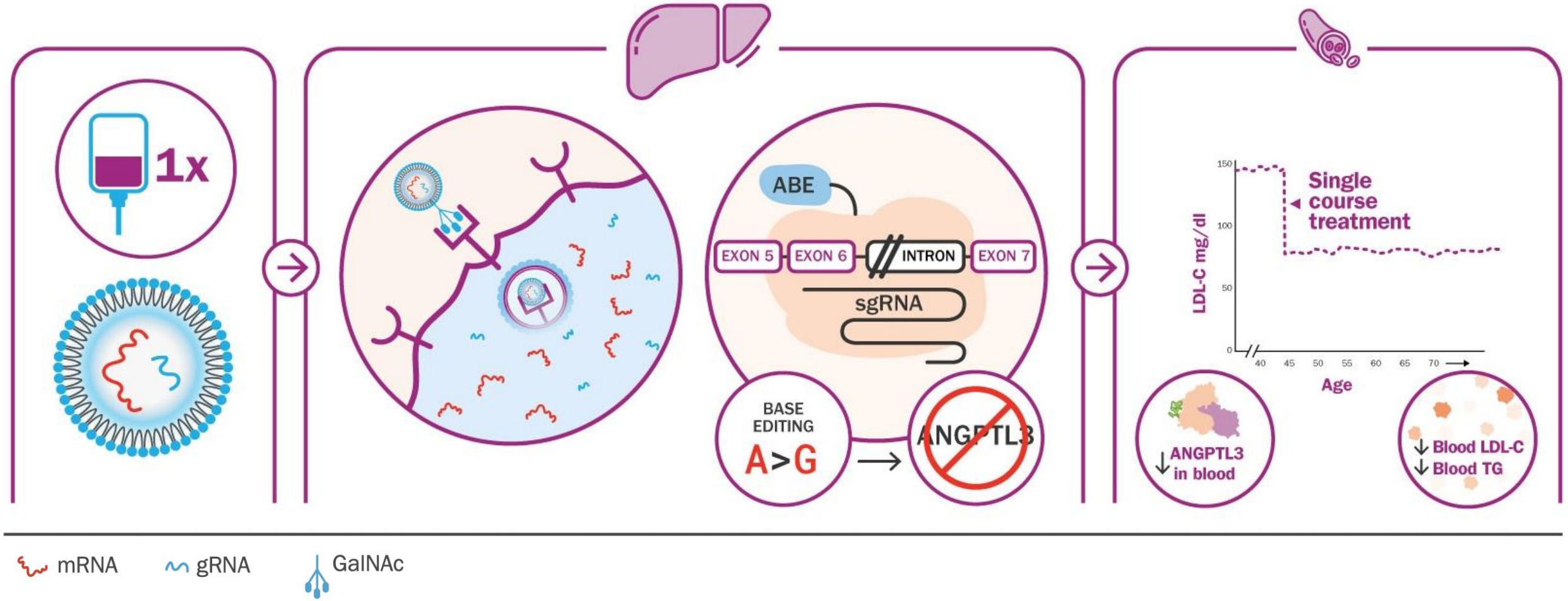
Forward looking statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the initiation, and timing, of the Company’s planned regulatory submissions, future clinical trial initiation of VERVE-201, its research and development plans and the potential advantages and therapeutic potential of the Company’s programs. All statements, other than statements of historical facts, contained in this presentation, including statements regarding the Company’s strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with the Company’s limited operating history; the timing of and the Company’s ability to submit applications for, and obtain and maintain regulatory approvals for, its product candidates; continue to advance its product candidates in clinical trials; initiate and enroll patients in clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for the Company’s product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of VERVE-101 and VERVE-201; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date hereof and should not be relied upon as representing the Company’s views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company’s views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

Goal of ANGPTL3 program: turn off gene (permanently) in liver with base editing to lower LDL-C and treat ASCVD

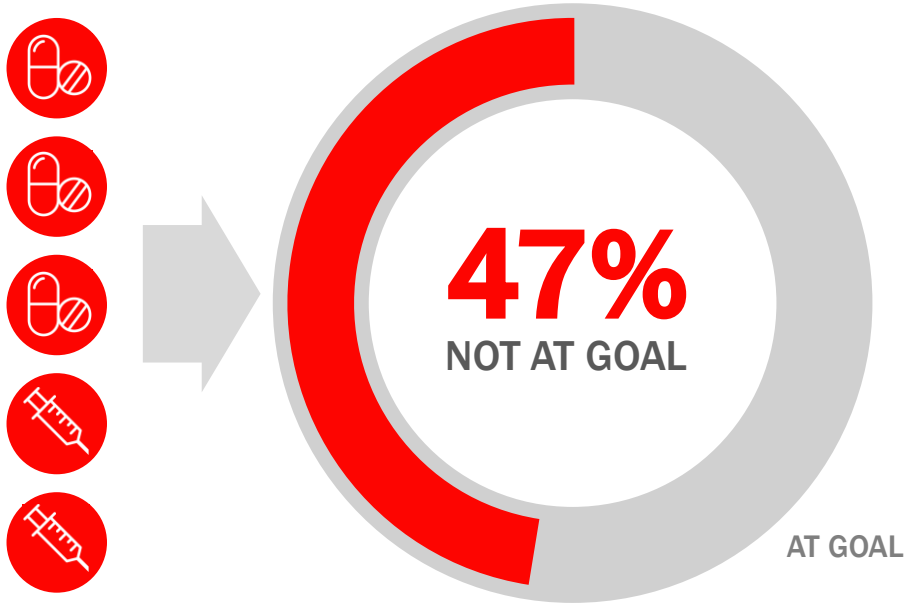


Advancing a pipeline of single-course *in vivo* gene editing programs to safely and durably lower LDL-C and treat ASCVD

PROGRAM	INDICATIONS	DEVELOPMENT STATUS				
		Research/ Lead optimization	IND-Enabling	Phase 1	Phase 2	Phase 3
Low-density lipoprotein cholesterol (LDL-C)						
VERVE-101 PCSK9	Heterozygous familial hypercholesterolemia					
	ASCVD not at LDL-C goal on oral therapy					
LDL-C & Triglyceride-rich lipoprotein (TRL)						
VERVE-201 ANGPTL3	Homozygous familial hypercholesterolemia					
	ASCVD not at LDL-C goal on oral + PCSK9i					

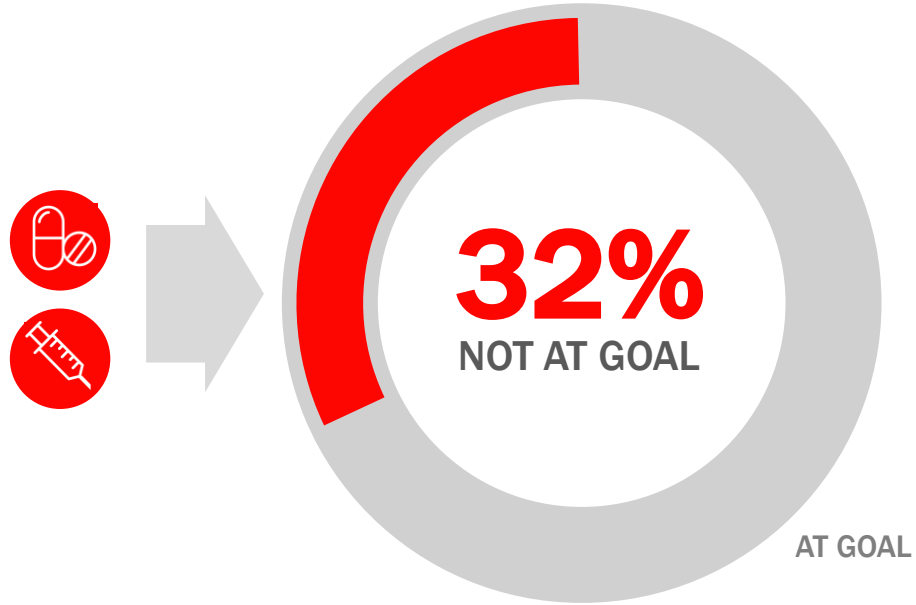
Two indications with high unmet need

Homozygous familial hypercholesterolemia



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

Atherosclerotic CVD not at LDL-C goal on oral SOC + PCSK9i

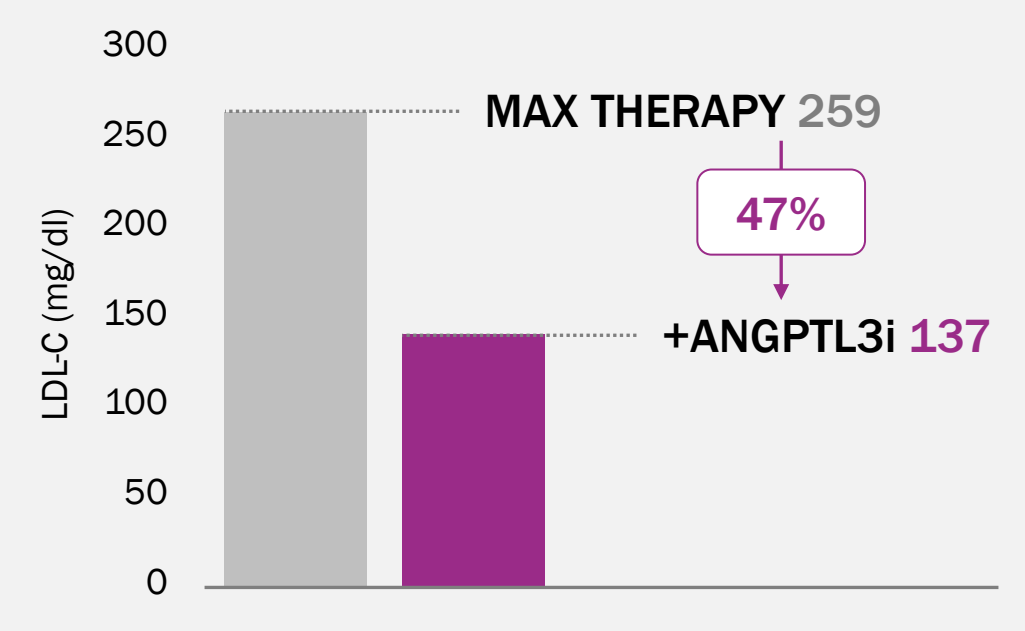


In the ORION-9, -10, and -11 clinical trials of inclisiran,
32% did not attain LDL-C < 70 mg/dl
even on oral (statin) + PCSK9i (inclisiran) therapy

Slide previously presented at 2022 ACC Scientific Sessions

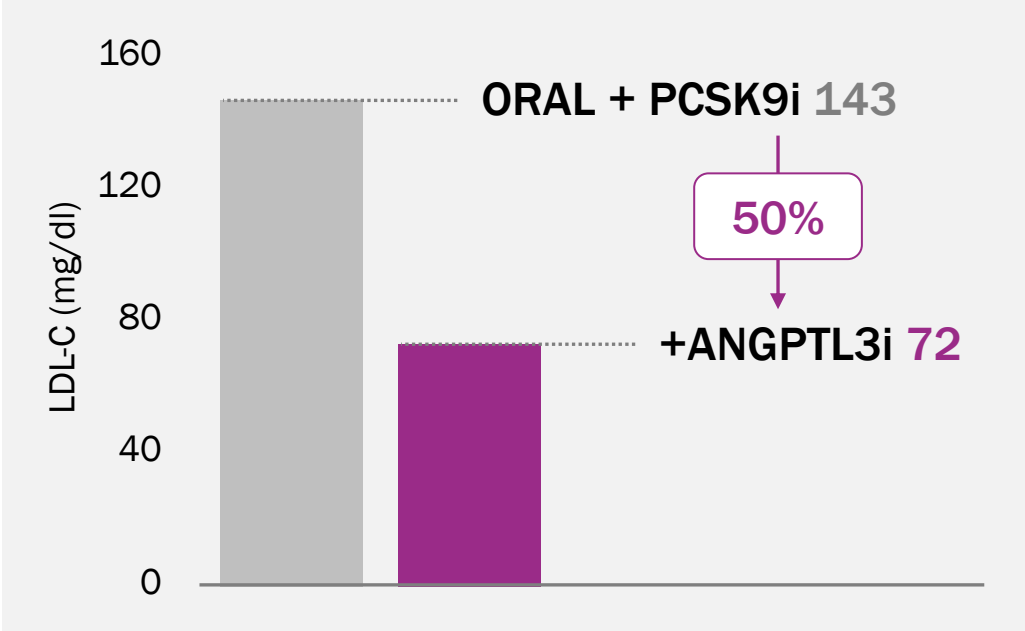
In these two indications, inhibition of the ANGPTL3 protein by a monoclonal antibody has been proven to work

Homozygous familial hypercholesterolemia



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

Atherosclerotic CVD not at LDL-C goal on oral SOC + PCSK9i



trial of evinacumab (Evkeeza)
in ASCVD patients with LDL-C ≥ 70
on oral + PCSK9i therapy
ANGPTL3 inhibition ↓ LDL-C by 50%

Slide previously presented at 2022 ACC Scientific Sessions

Inactivation of ANGPTL3 is a compelling target to lower LDL-C: validated by human genetics of ANGPTL3 deficiency

Lower LDL-C and ASCVD

Heterozygous deficiency
lower lipids in population
resistant to ASCVD

Homozygous deficiency
'Human knockout'
LDL-C: 37 mg/dL

Rare Gene Mutations Inspire New Heart Drugs

By Gina Kolata

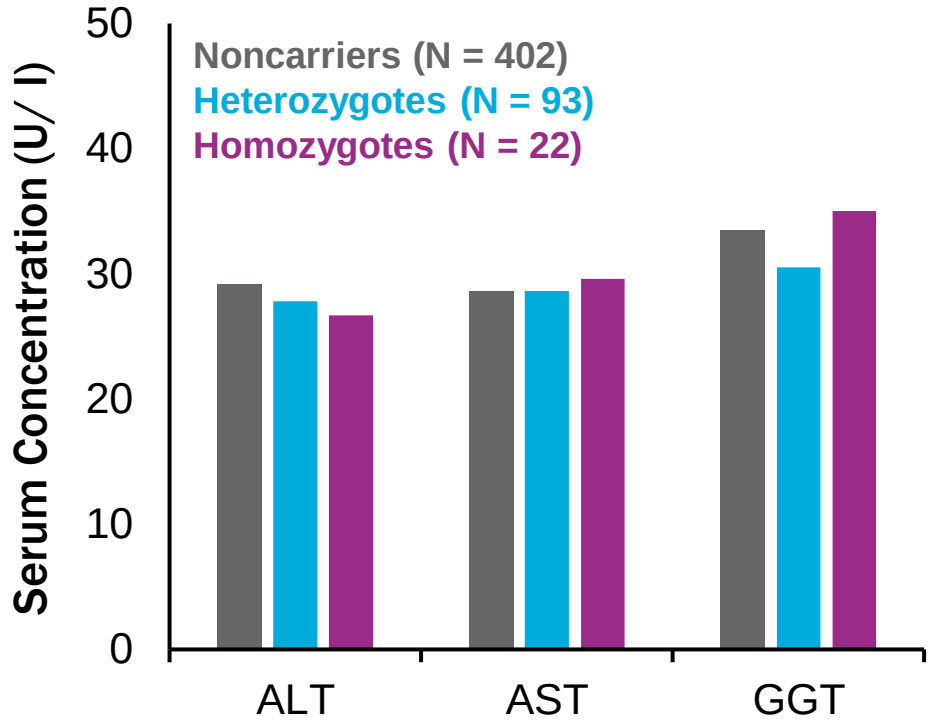
May 24, 2017

Anna Feurer learned she had unusually low triglyceride levels after having bloodwork at a corporate health fair. The discovery prompted researchers to recruit her and her family for a research study of their genetic makeup.

Credit. Jess T. Dugan for The New York Times

No adverse effects

No increase in markers of liver injury or prevalence of liver steatosis in heterozygous or homozygous deficiency

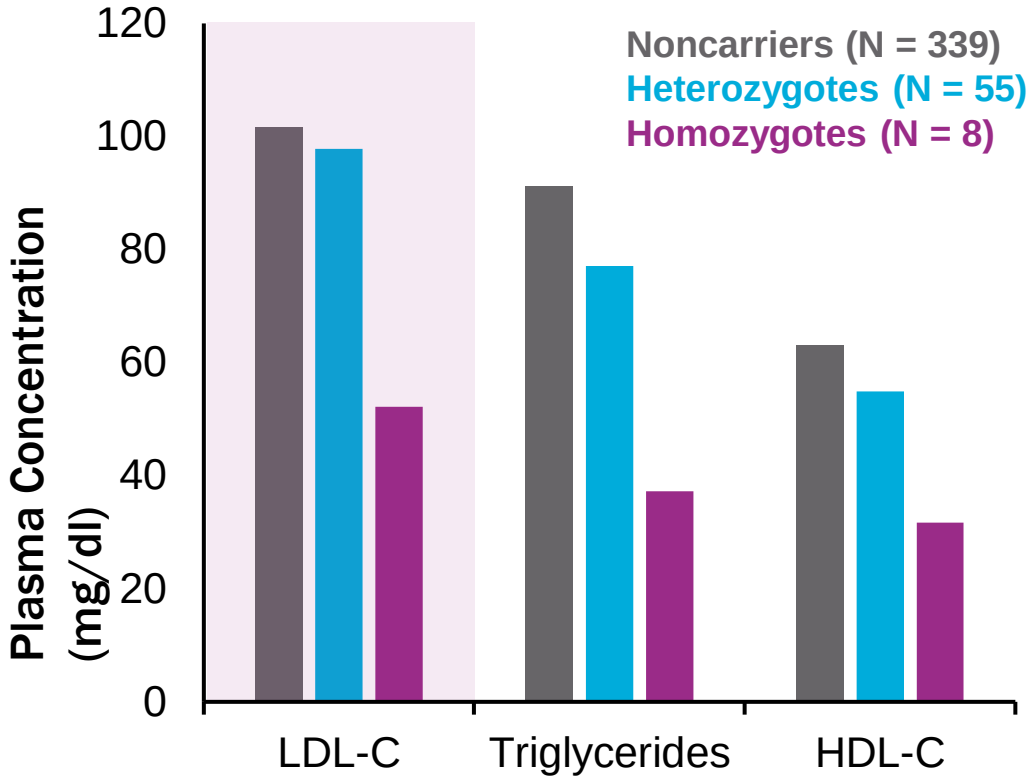


Slide previously presented at 2022 ACC Scientific Sessions

Human genetic and pharmacologic data indicate >90% blood ANGPTL3 reduction required to lower LDL-C

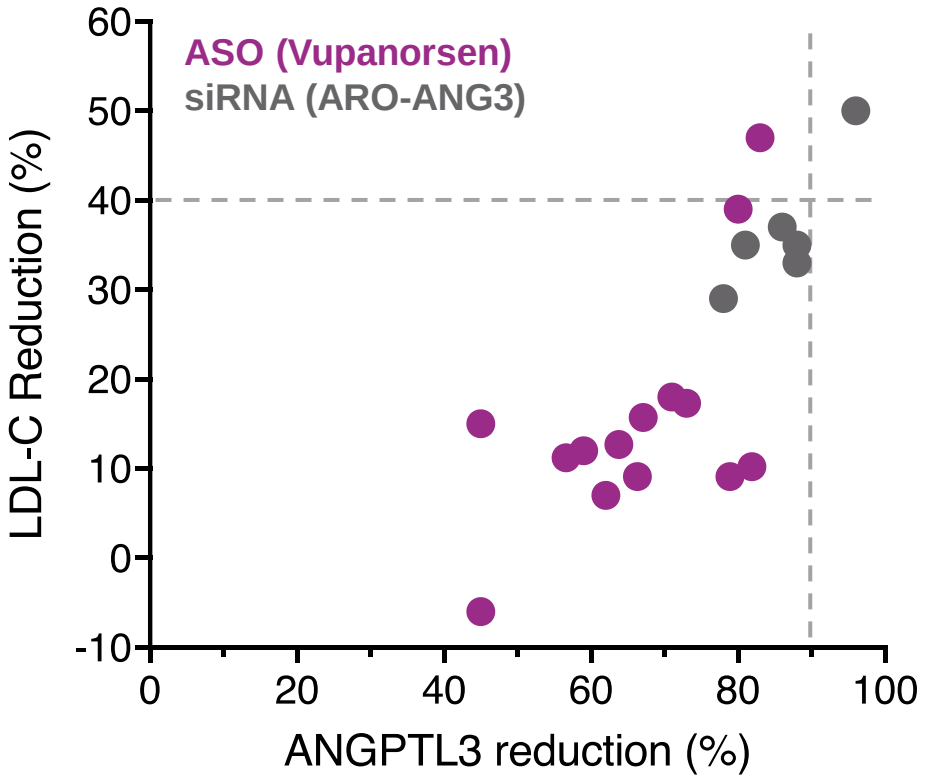
Human genetics

LDL-C ↓ by 49% in homozygote loss-of function 'human knockout' versus noncarriers



Human pharmacology

ANGPTL3 reduction of ~90% has lowered LDL-C ~40%



Slide previously presented at 2022 ACC Scientific Sessions

Nomination of a development candidate for VERVE-201
Three key questions

1. Liver safety: Is long-term and potent suppression of ANGPTL3 in non-human primates (NHPs) associated with any detectable liver toxicity?

2. Delivery: Can Verve's proprietary GalNAc lipid nanoparticle technology enable efficient delivery in both wild-type and HoFH NHP models?

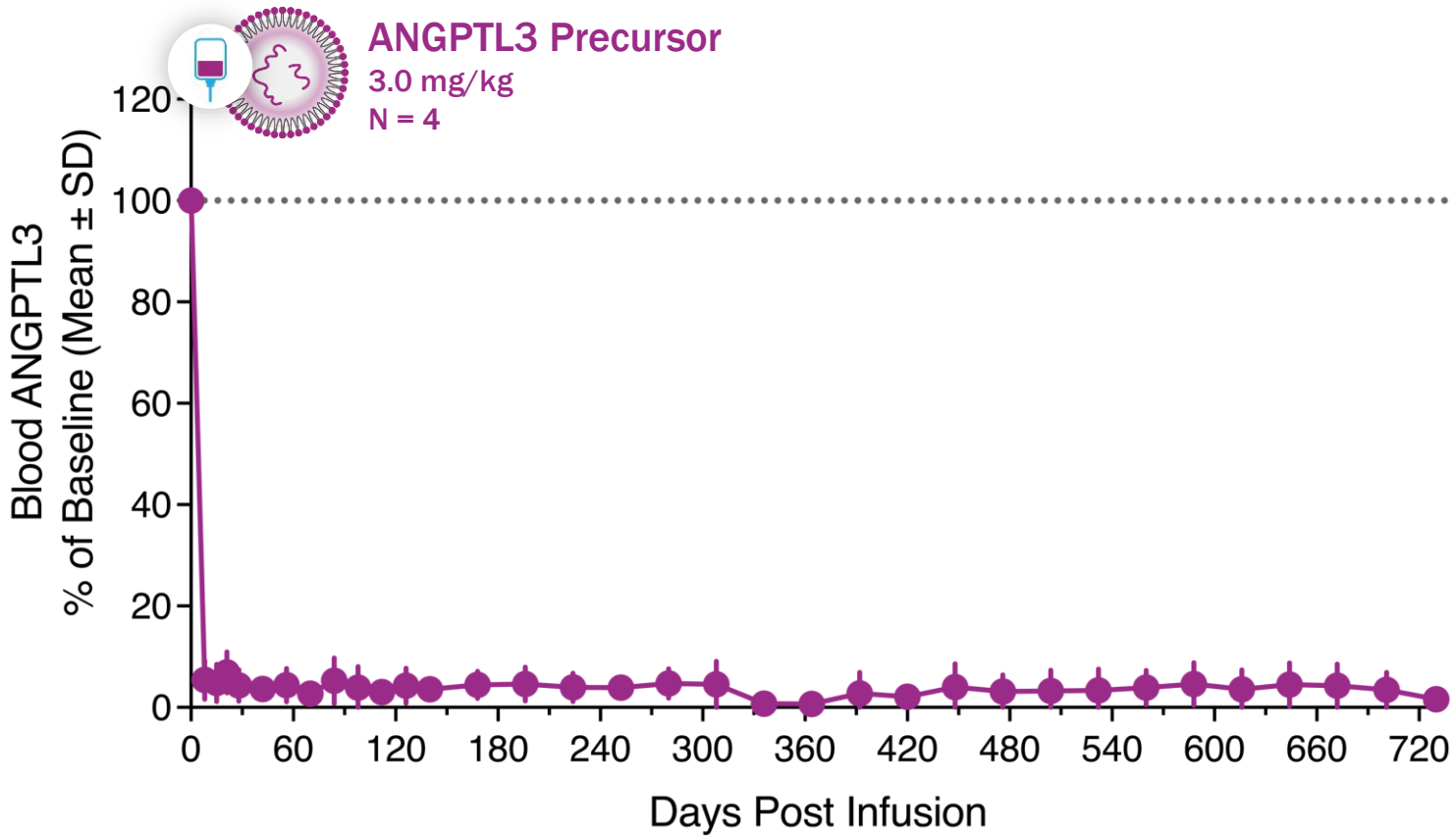
3. Off-target editing: Can chemically modified base editing / gRNA configurations preserve potency while minimizing off-target editing?

Long-term study of potent *ANGPTL3* inactivation

Data from non-human primates

ANGPTL3 precursor: potent and durable in NHPs
2-year data: >90%↓ in blood ANGPTL3, >60% liver editing

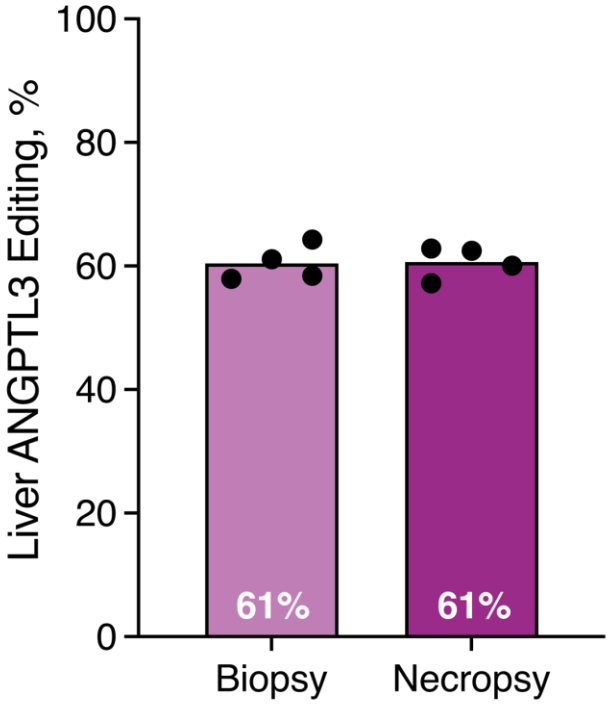
Blood ANGPTL3 protein
96% reduction* from baseline



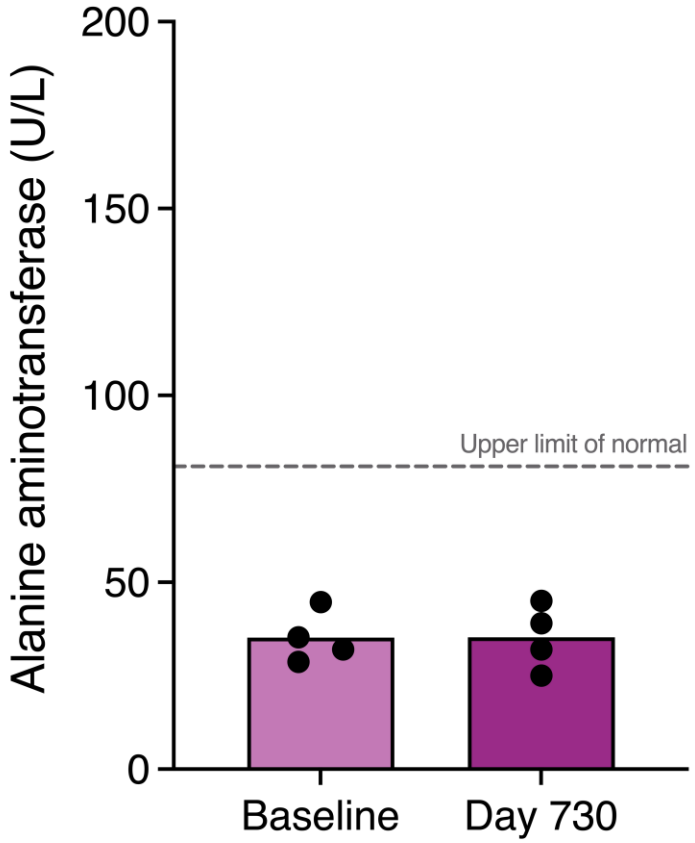
* Measured as time-weighted average % change from baseline from days 28 to 730

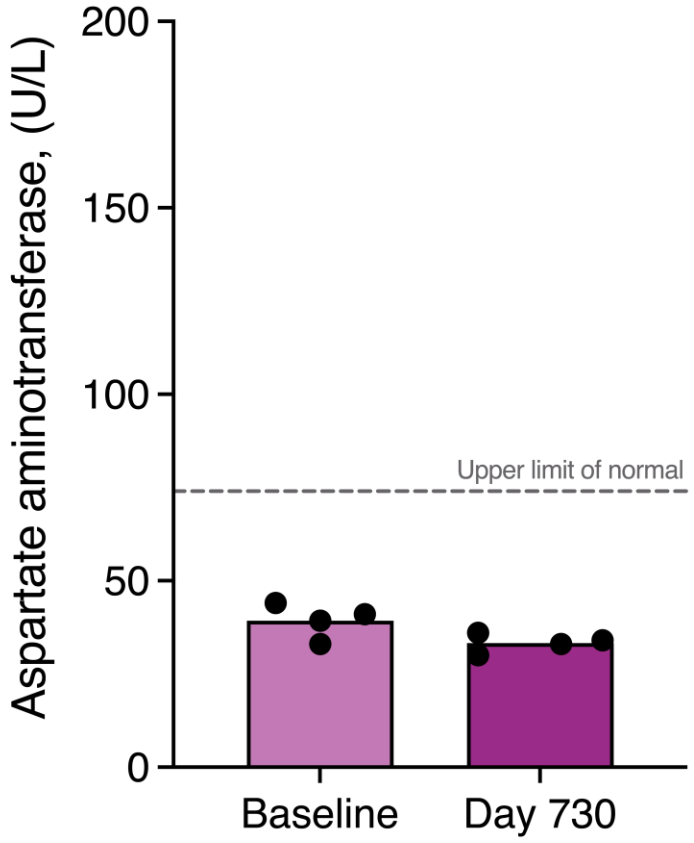
Liver *ANGPTL3* editing

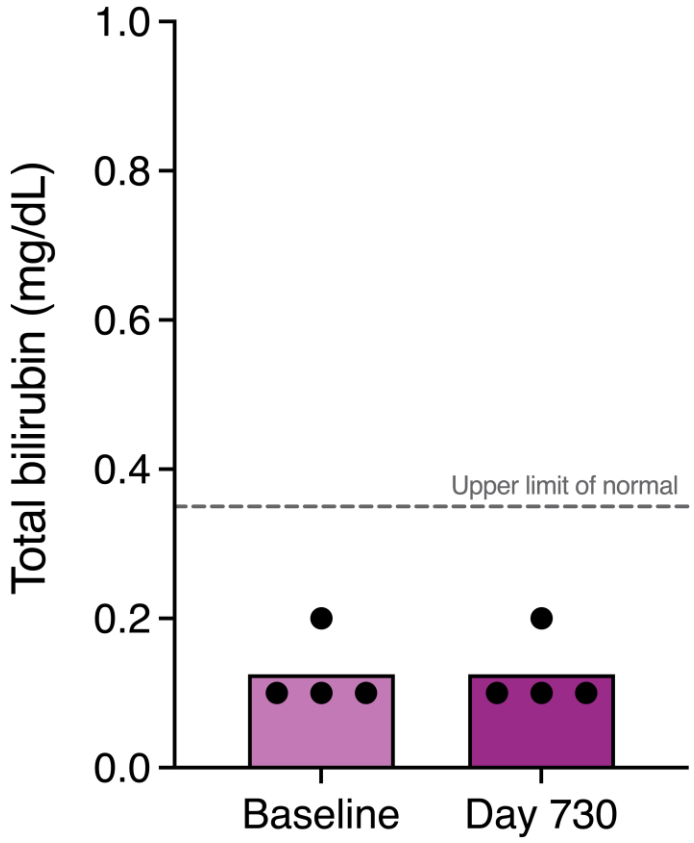
- Day 15 biopsy: 61%
- Day 730 necropsy: 61%



ANGPTL3 precursor in non-human primates
2-year data: no change from baseline in liver biomarkers detected





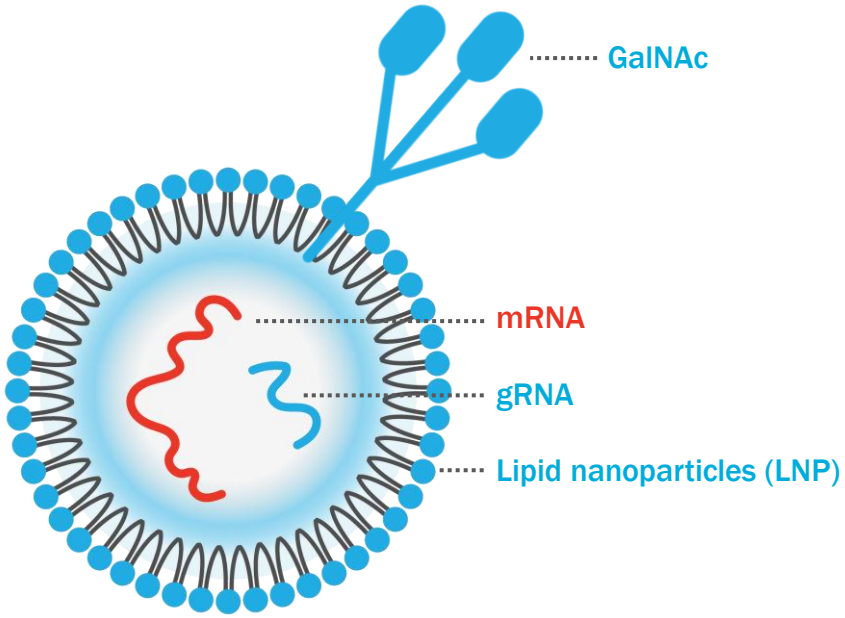


Mean and individual values displayed reflect measurement in each of 4 NHP prior to dosing with an ANGPTL3 precursor at 3 mg/kg and at time of necropsy.

Enabling efficient delivery in both LDLR-deficient and wild-type NHPs

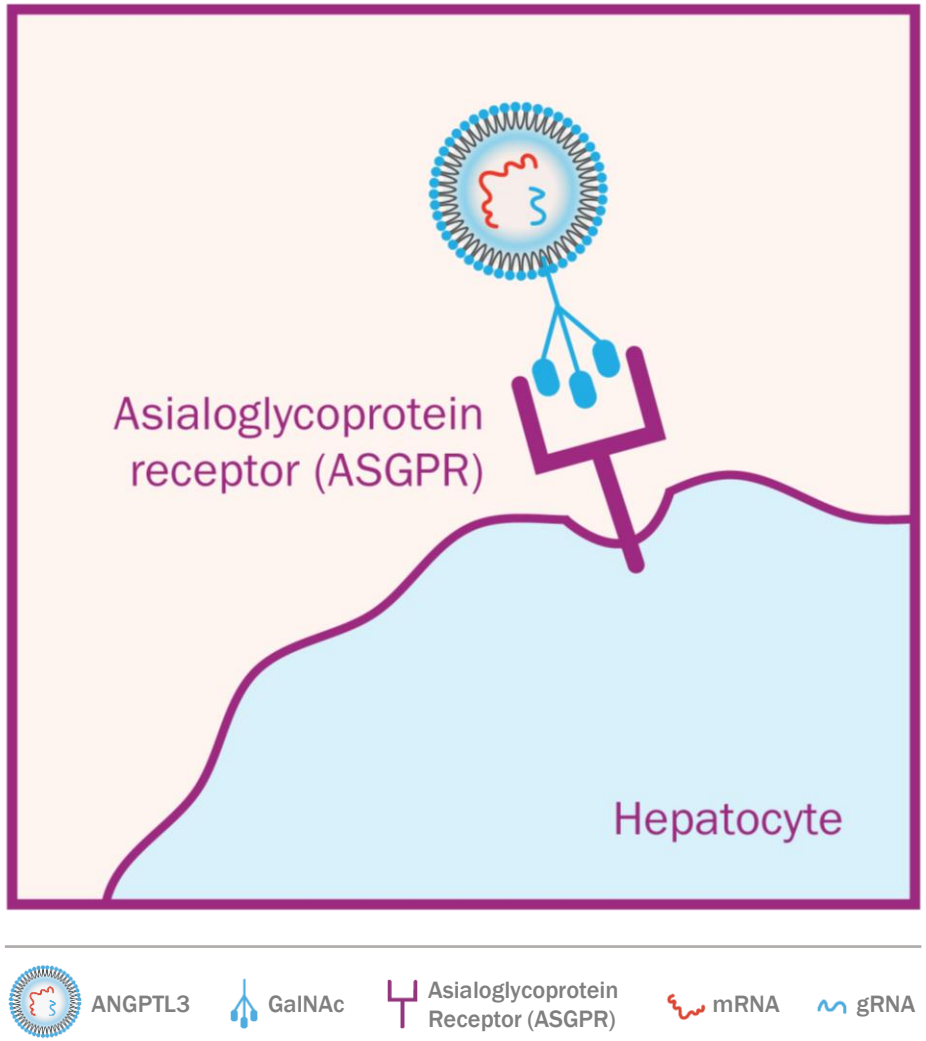
GalNAc LNP data

Addition of proprietary GalNAc targeting ligand to LNP enables hepatic delivery through ASGPR instead of LDLR

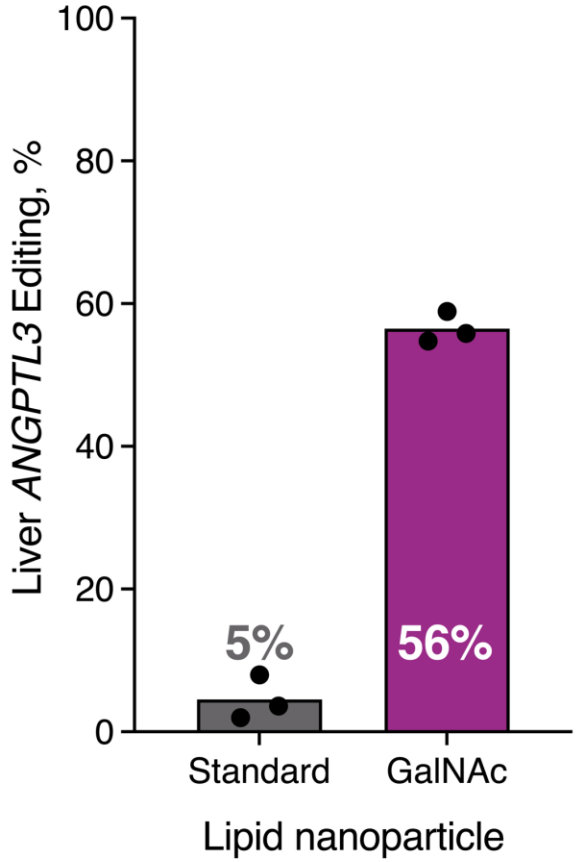


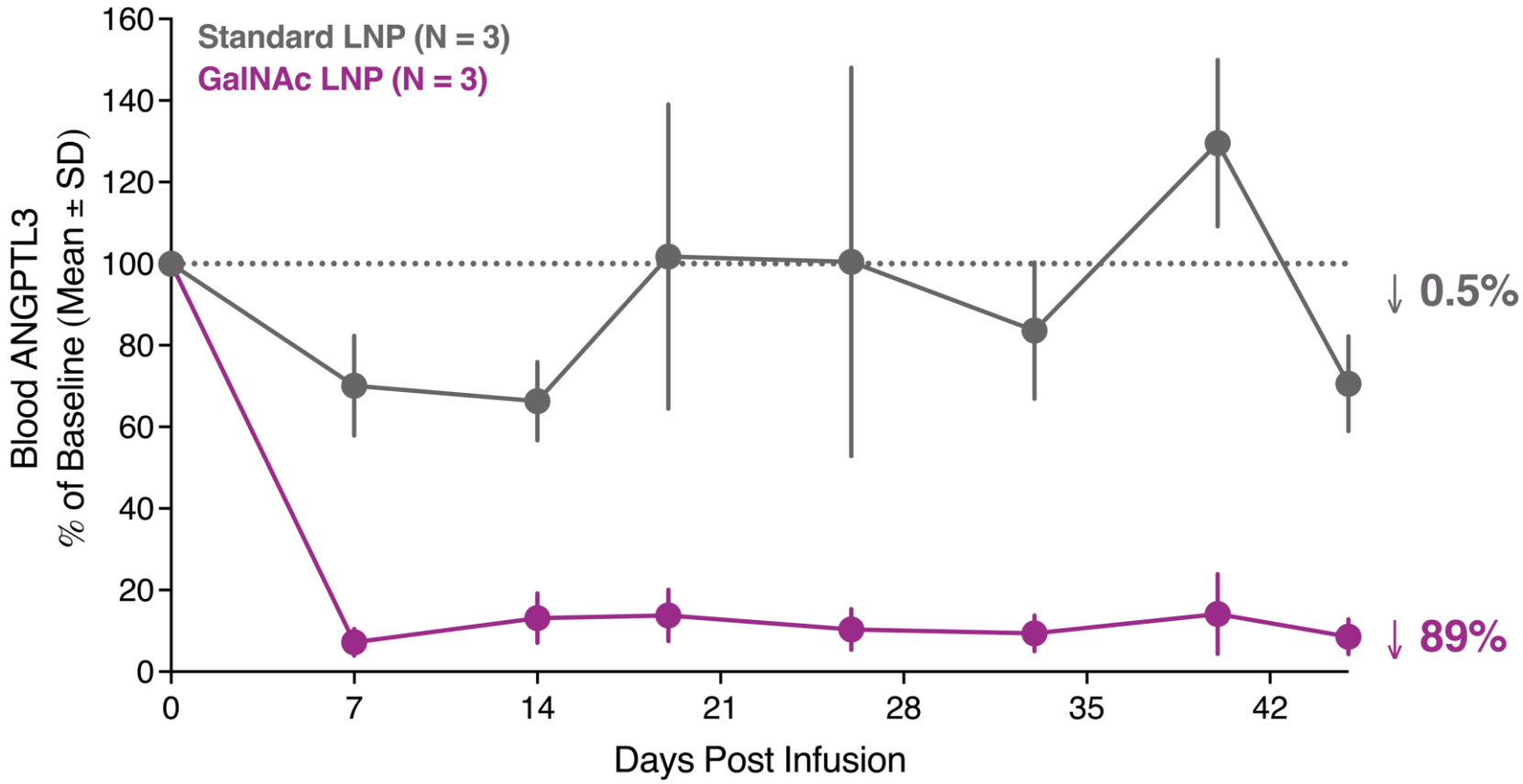
United States Patent
Rajeev et al.

Patent No.: US 11,207,416 B2
Date of Patent: Dec. 28, 2021



GalNAc LNP ANGPTL3 precursor enabled efficient liver editing in *LDLR*-deficient* NHPs

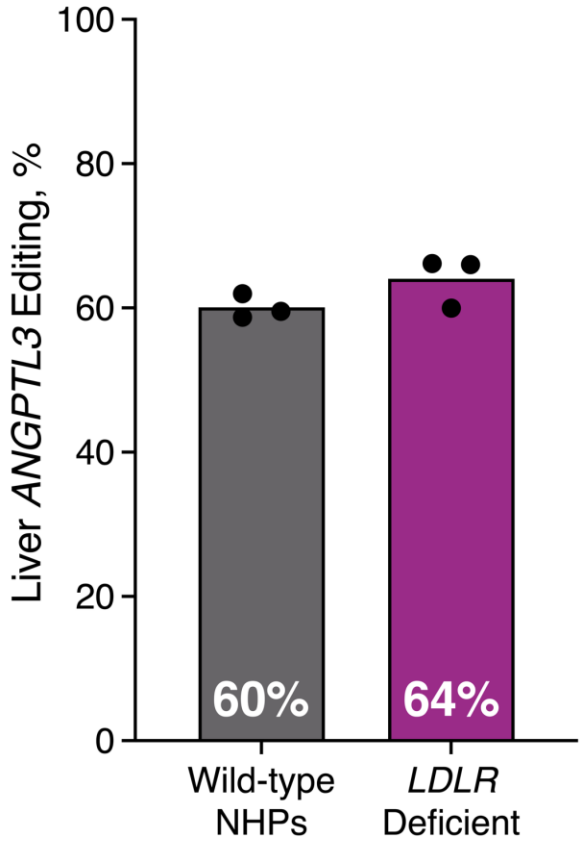


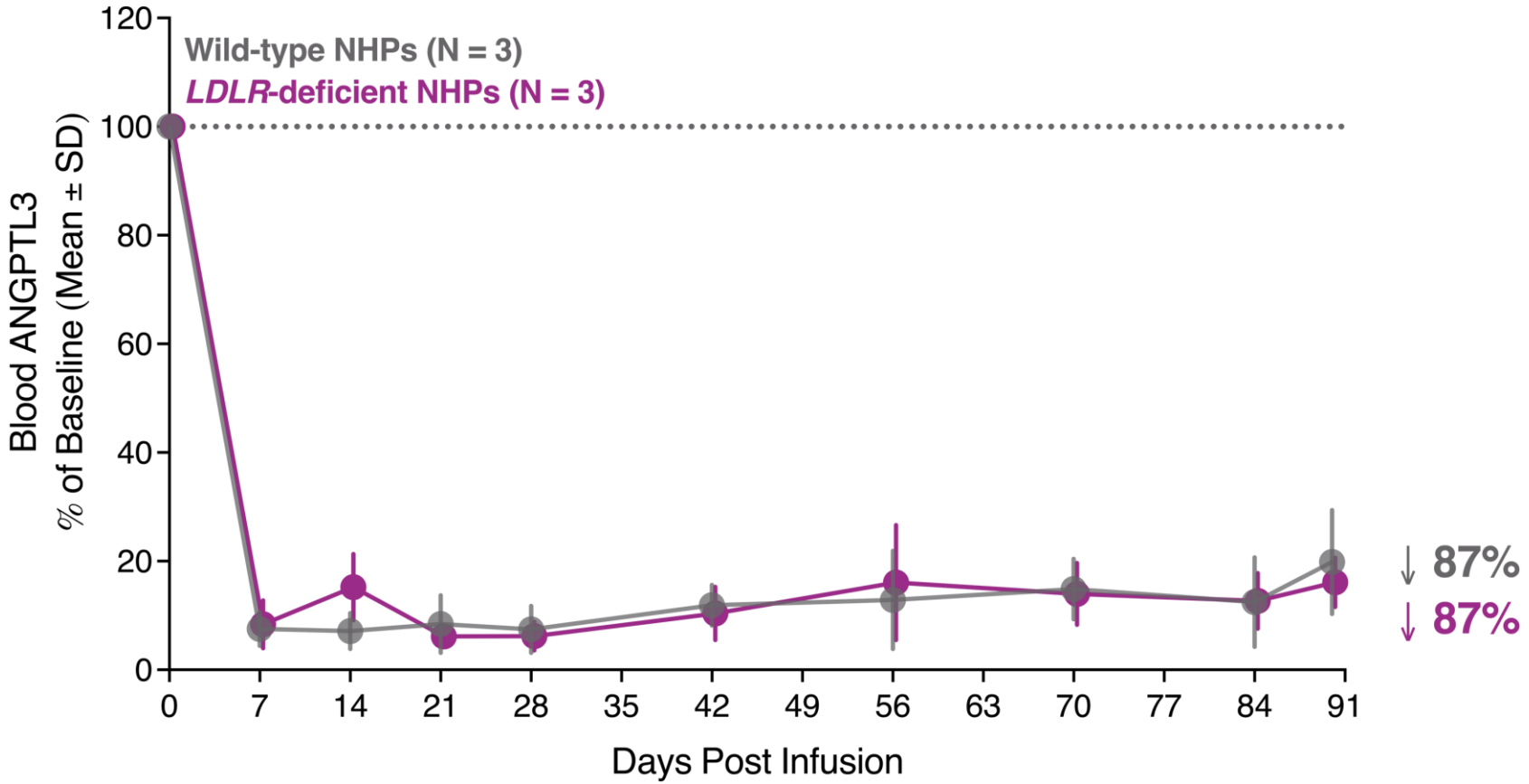


*Verve's NHP model of homozygous familial hypercholesterolemia with >90% reduction in liver *LDLR* protein (Kasiewicz et al., *biorXiv*, 2021)

Liver *ANGPLT3* editing displayed represent values for non-human primates treated with 2 mg/kg of an ANGPTL3 precursor using a standard or GalNAc LNP (N = 3 in each treatment group). Reductions in ANGPTL3 reported as time-weighted average % change from baseline from days 26 to 45.

GalNAc LNP ANGPTL3 precursor enabled similar editing efficiency in wild-type and *LDLR*-deficient* NHPs





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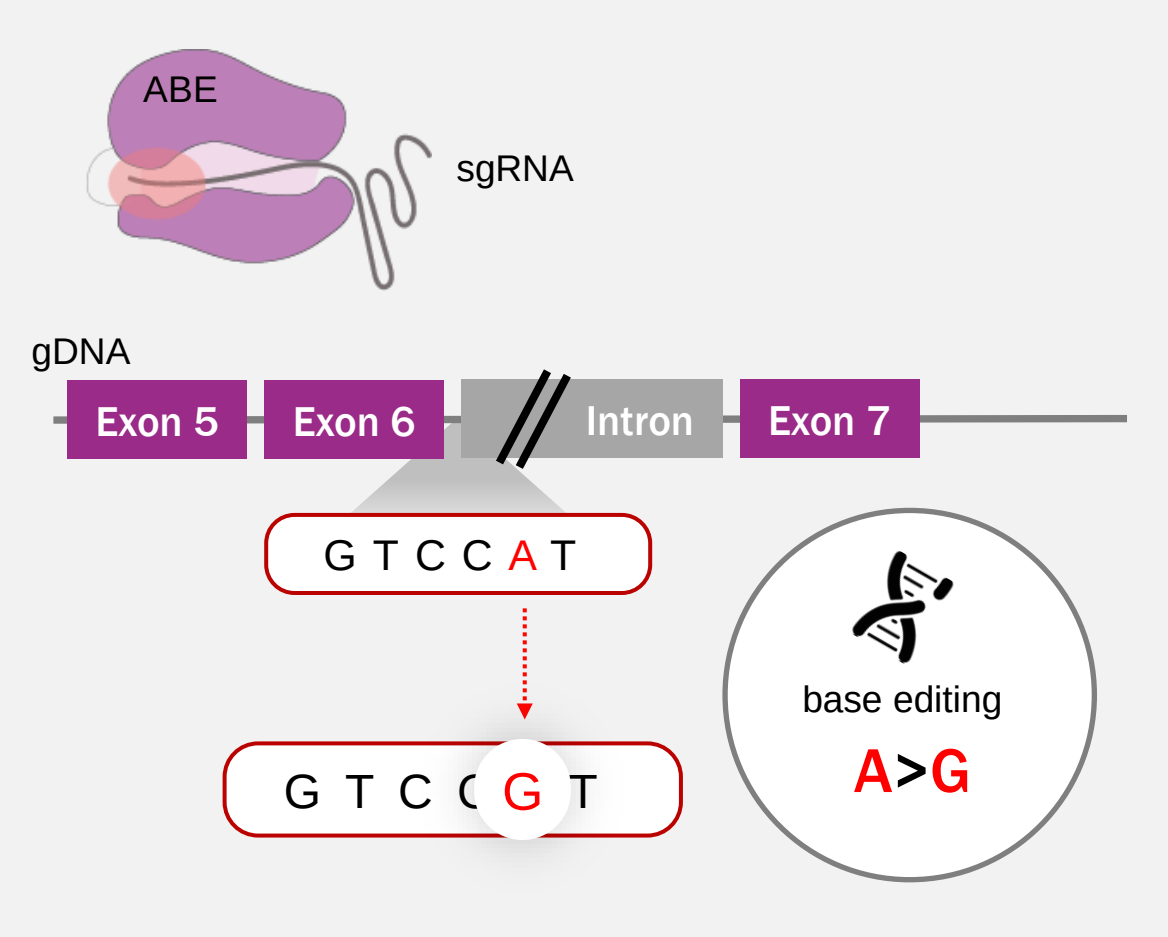
Liver *ANGPLT3* editing displayed represent values for wild-type or *LDLR*-deficient non-human primates treated with 2 mg/kg of an ANGPTL3 precursor (N = 3 in each group). Reductions in ANGPTL3 reported as time-weighted average % change from baseline from days 28 to 90.

Optimizing *ANGPTL3* target site and base editor/gRNA configuration

minimizes risk of off-target editing

VERVE-201 is designed to inactivate *ANGPTL3* in the liver with a precise A-to-G base-pair DNA change

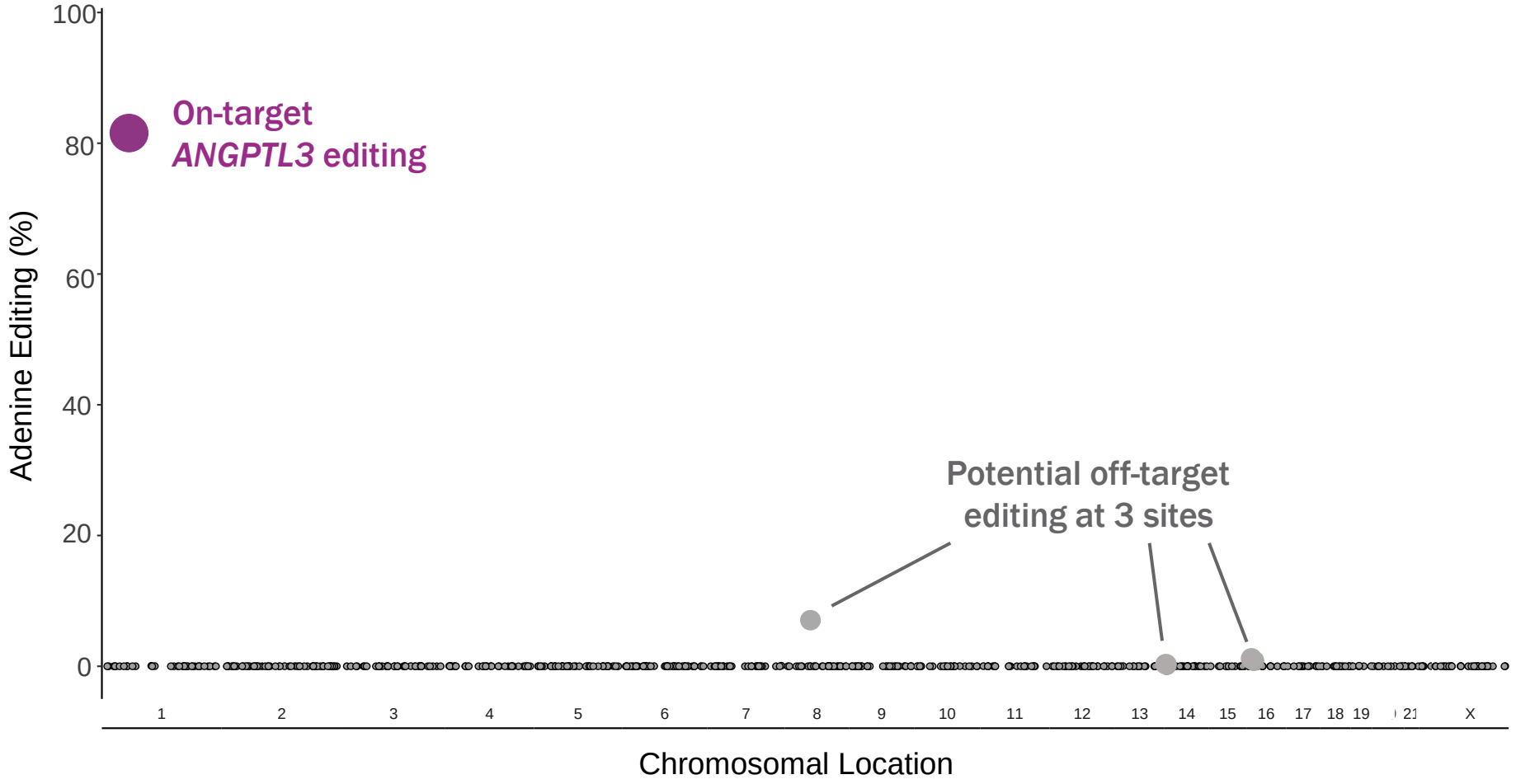


Site selected based on results of screening assays performed for 29 potential sites in the *ANGPTL3* gene.

Key features of *ANGPTL3* target DNA site:

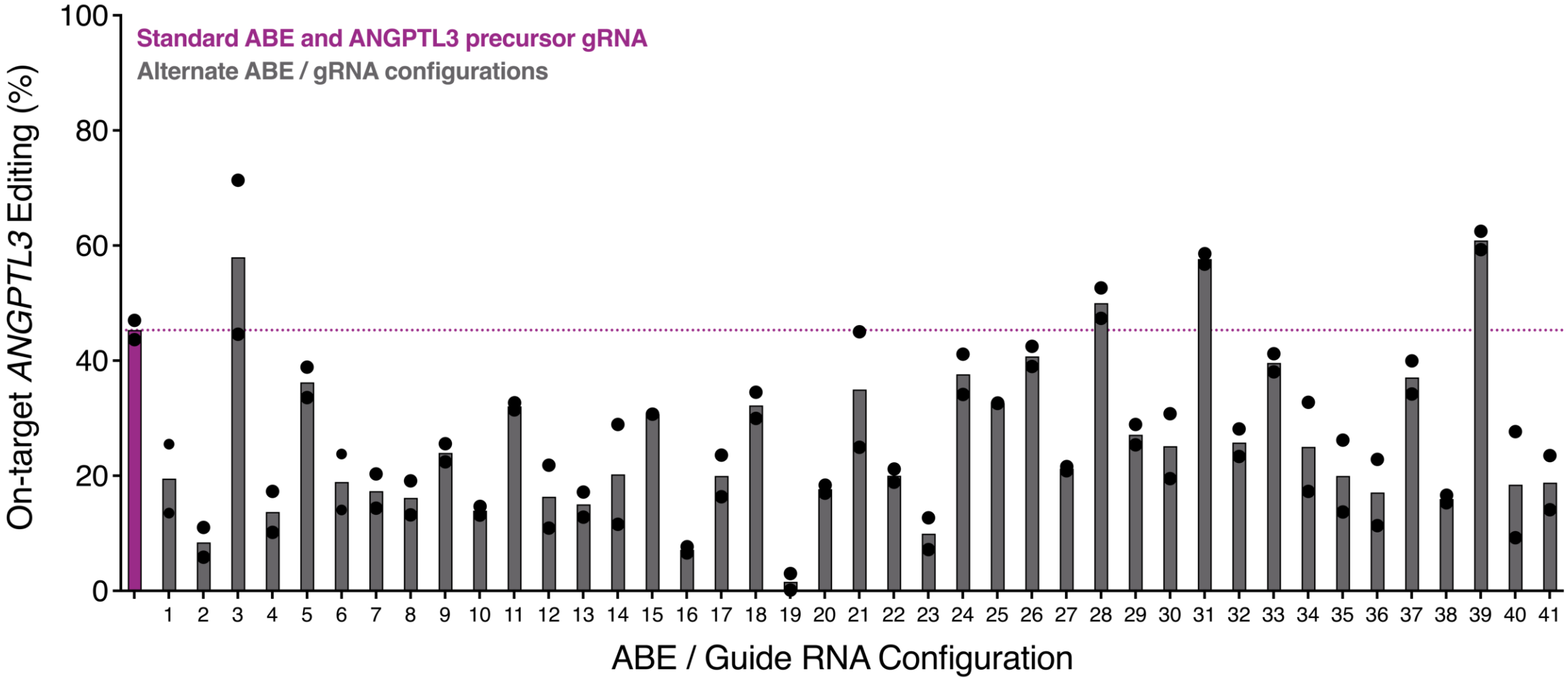
- Precise A to G base-pair substitution disrupts splice donor site and introduces a downstream premature stop codon
- Site is unique: 23 DNA base pair protospacer/PAM sequence not found anywhere else in the human genome, expected to minimize potential off-target editing
- Site is consistent: >99.98% of sequenced individuals have two *ANGPTL3* alleles that perfectly match the protospacer/PAM sequence, expected to maximize consistency of treatment response
- Silent bystander editing: at the single additional A in the editing window—should it occur—does not affect protein-coding sequence or *ANGPTL3* inactivation

Challenge: A standard ABE with ANGPTL3 precursor gRNA identified potential off-target editing at up to 3 sites



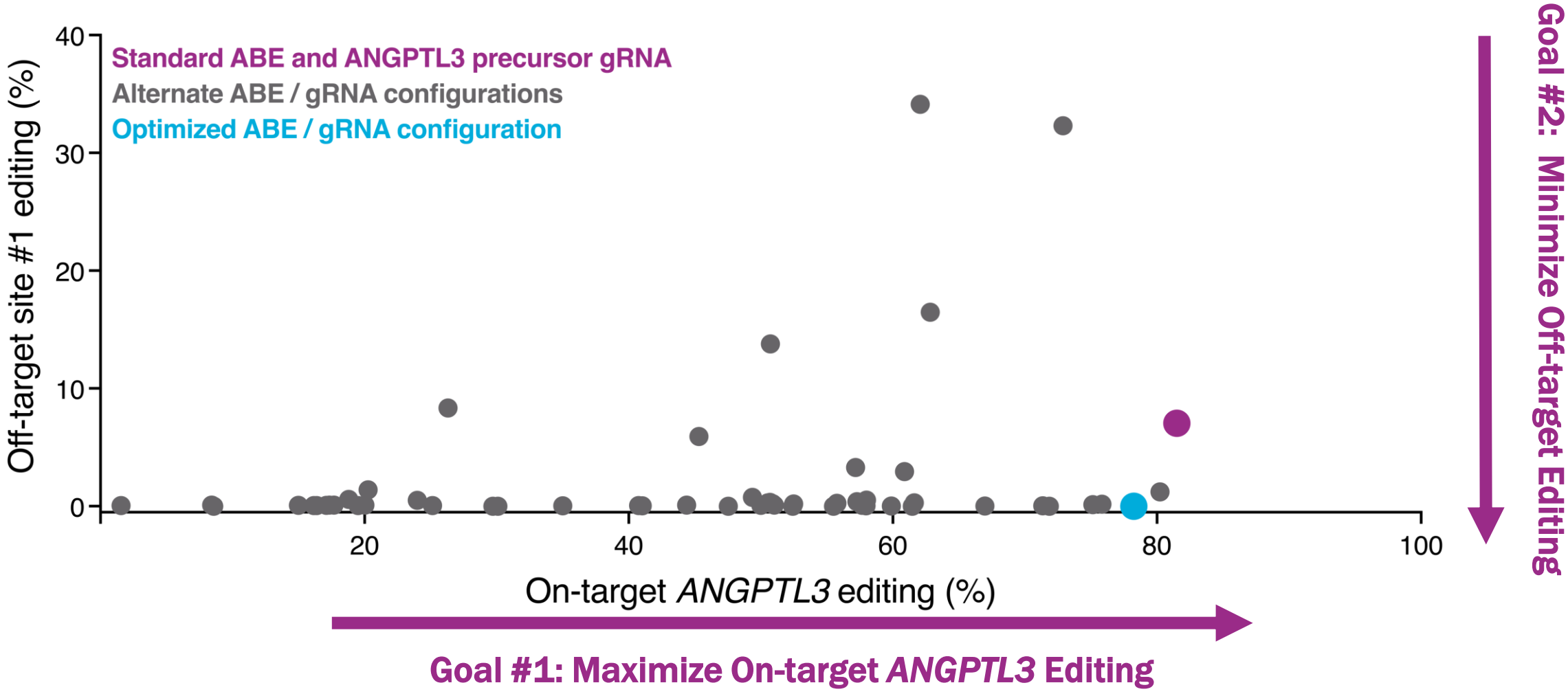
- 600+ candidate sites nominated by ONE-seq evaluated using SureSelect screening assay in adult primary human hepatocyte cells
- As compared to on-target editing of 82%, potential off-targeting editing at 3 additional sites ranging from 0.2 to 7.1%

Potential solution: Screened >200 rationally engineered and chemically modified ABE / gRNA configurations



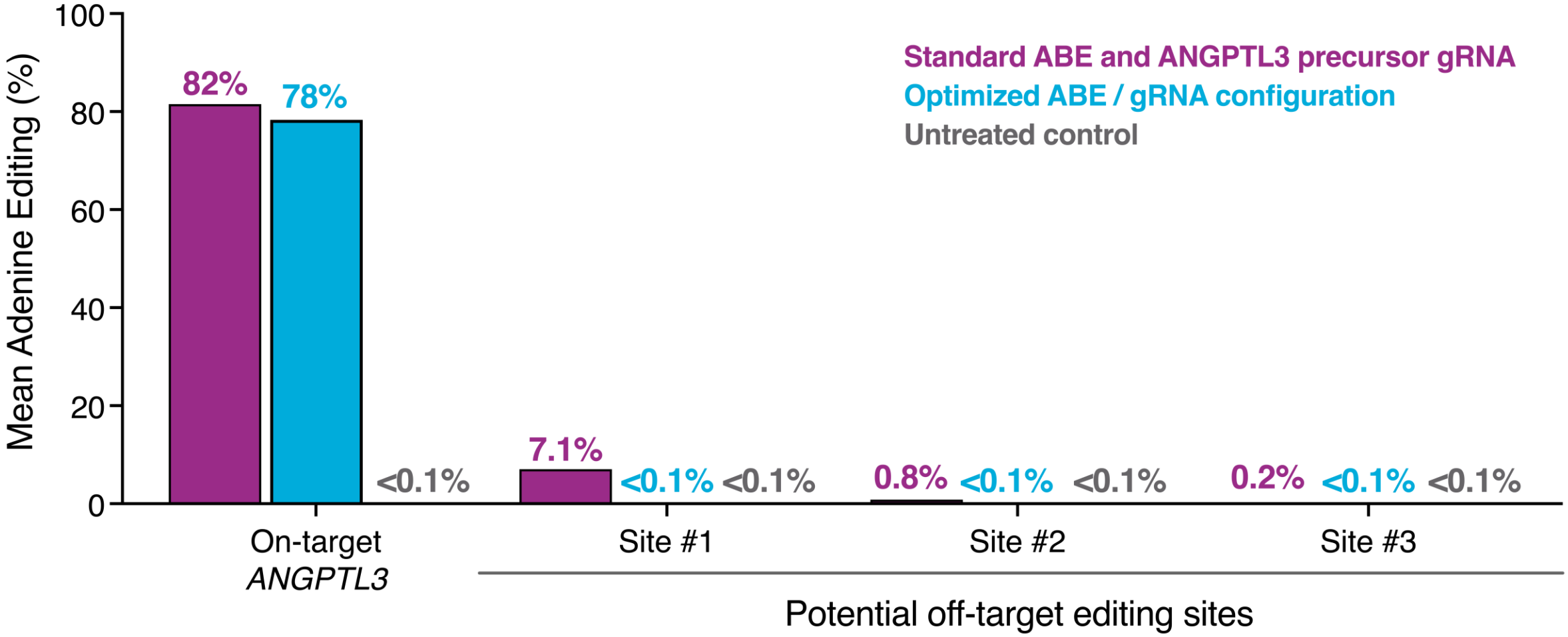
Data aggregated from 2 representative screening experiments assessing on-target *ANGPTL3* editing in adult primary human hepatocytes.
As compared to mean editing of 45% with standard ABE and ANGPTL3 precursor gRNA, noted editing ranging from 1.6 to 61% with 41 alternate ABE / gRNA configurations.

Screening* of ABE / guide RNA configurations in vitro
Goals: maximize on-target editing, minimize off-target editing



* Data aggregated from 3 representative screening experiments in primary human hepatocytes of a standard ABE and ANGPTL3 precursor gRNA and >50 alternate ABE / gRNA configurations.

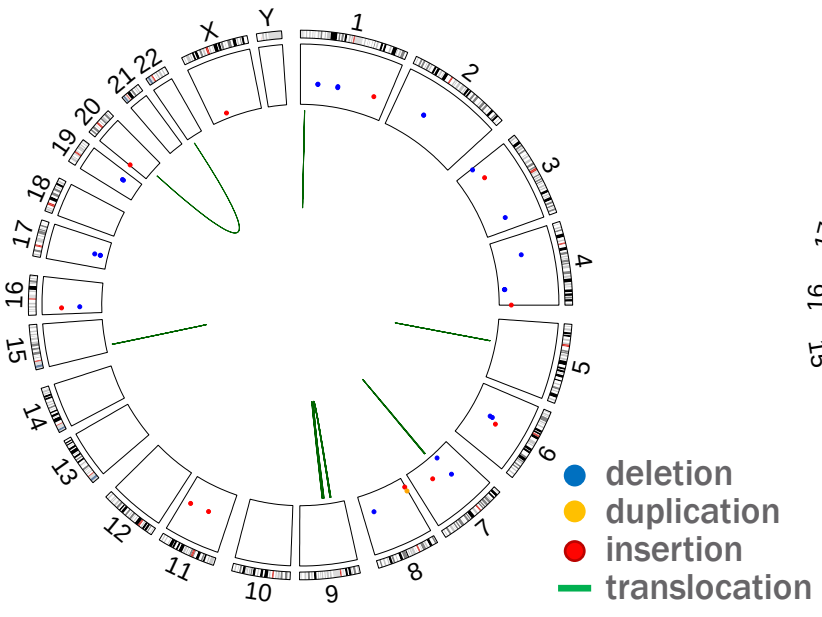
Optimized ABE / gRNA configuration with preserved potency and no detectable off-target editing at 3 candidate sites in PHH cells



Data display mean adenine editing noted at the on-target *ANGPTL3* site and 3 potential off-target editing sites assessed using a SureSelect assay of primary human hepatocytes treated with a standard ABE and ANGPTL3 gRNA, an optimized ABE / gRNA configuration, or untreated cells averaged across two replicates. No detectable differences in editing with the optimized configuration at any of the three potential off-target editing sites versus untreated cells was observed.

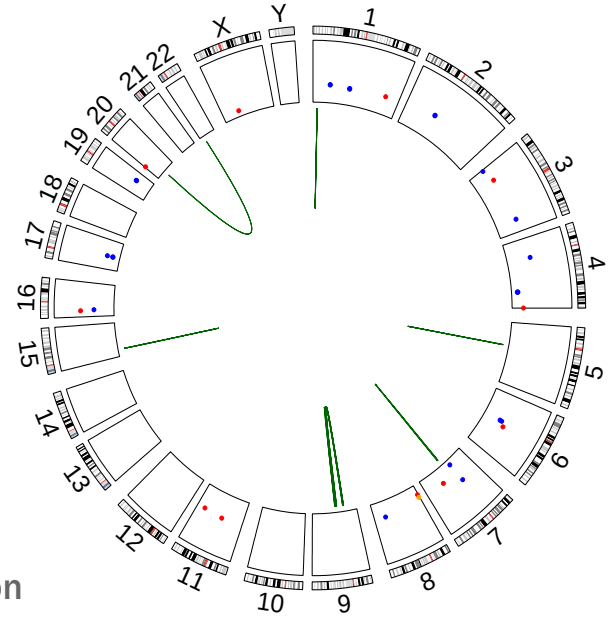
No structural variants observed from VERVE-201 treatment in primary human hepatocytes: whole genome optical mapping

Untreated



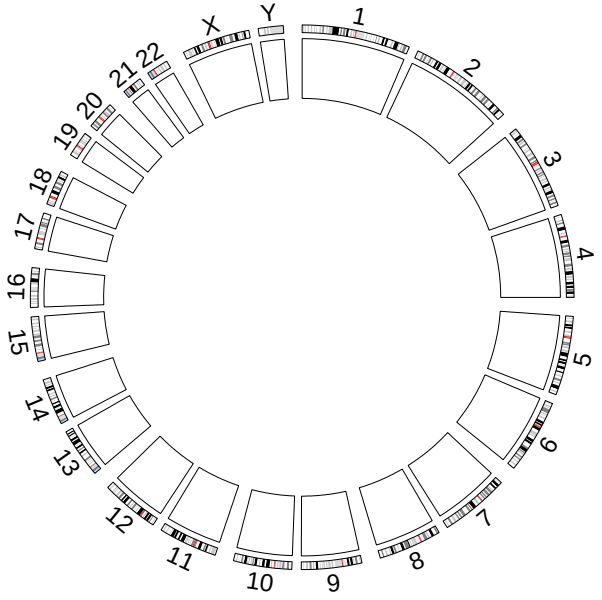
Structural variants are observed in control untreated PHH donor cells

VERVE-201 treated



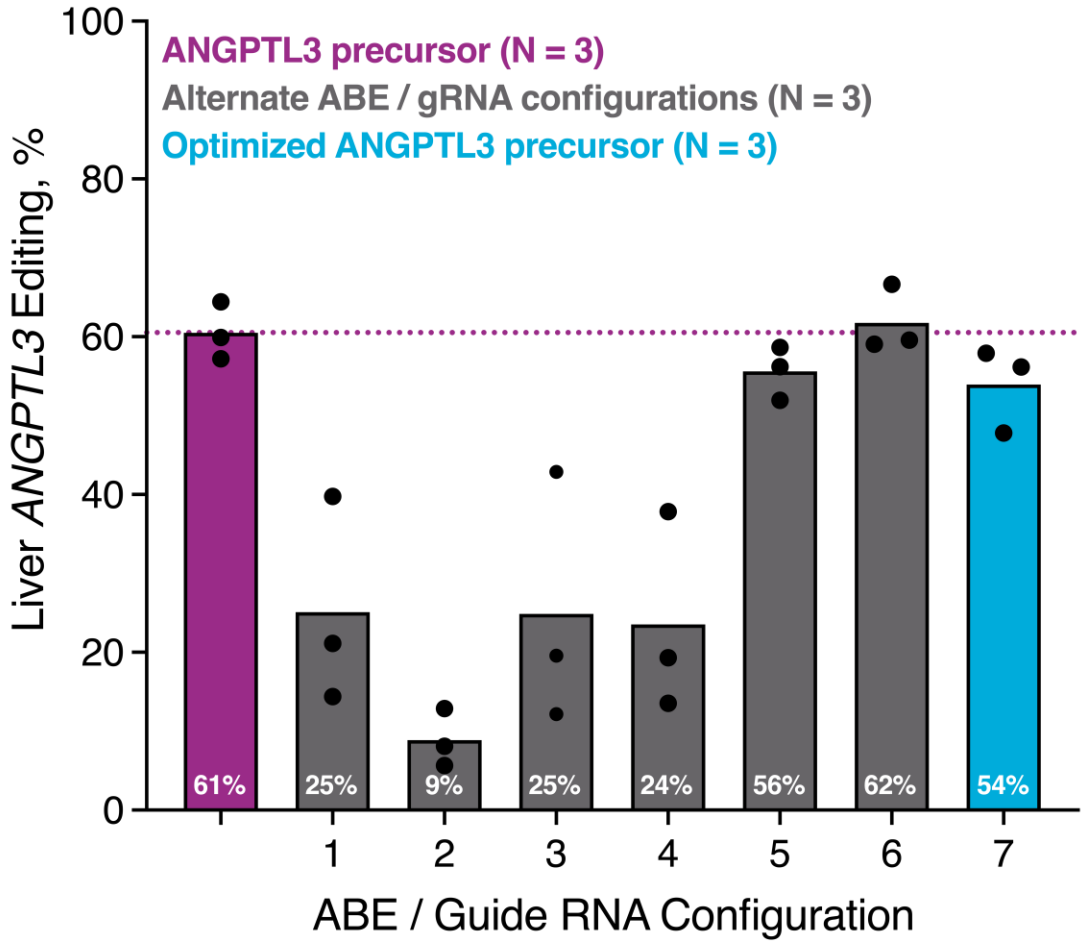
Identical structural variants are observed in the VERVE-201 treated PHH donor cells

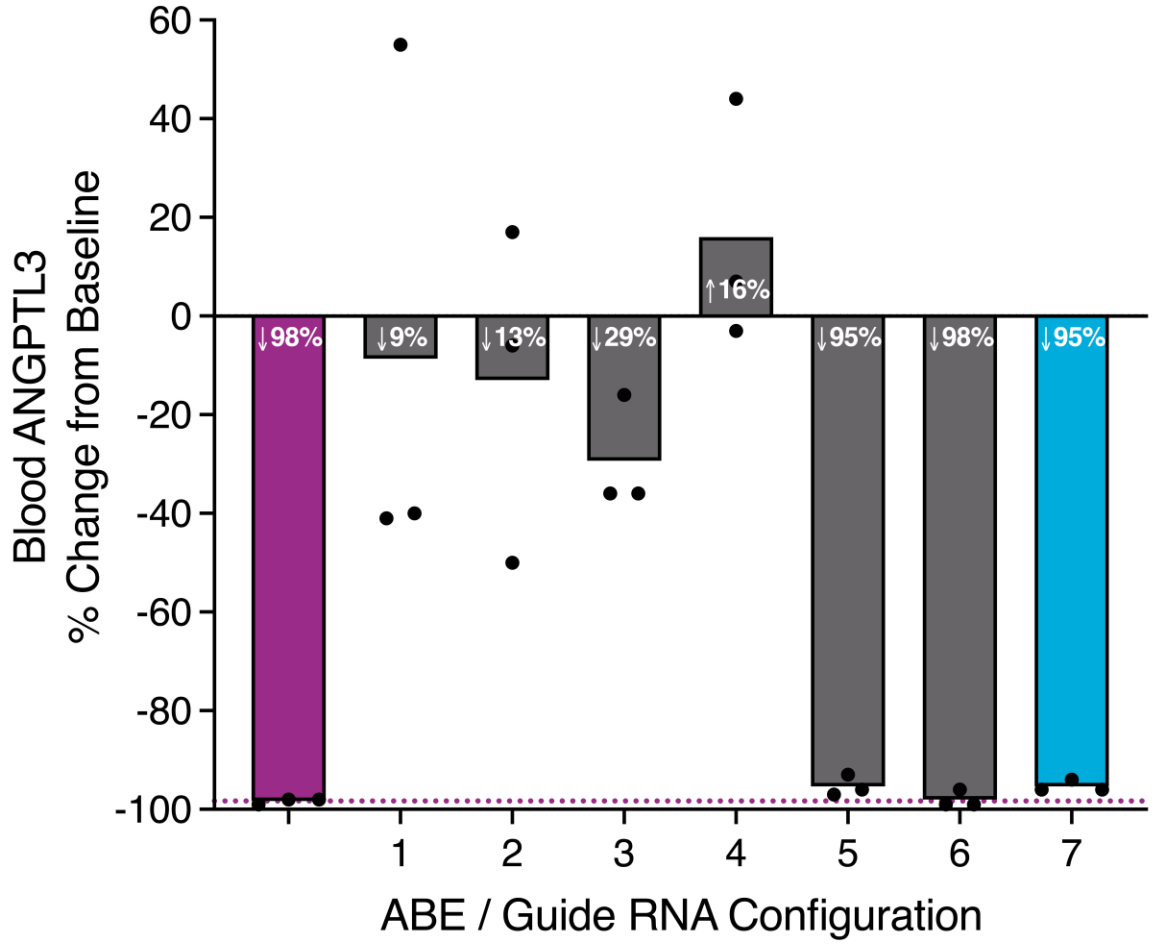
VERVE-201 minus Untreated



No treatment related structural variants are observed in VERVE-201 treated PHH donor cells

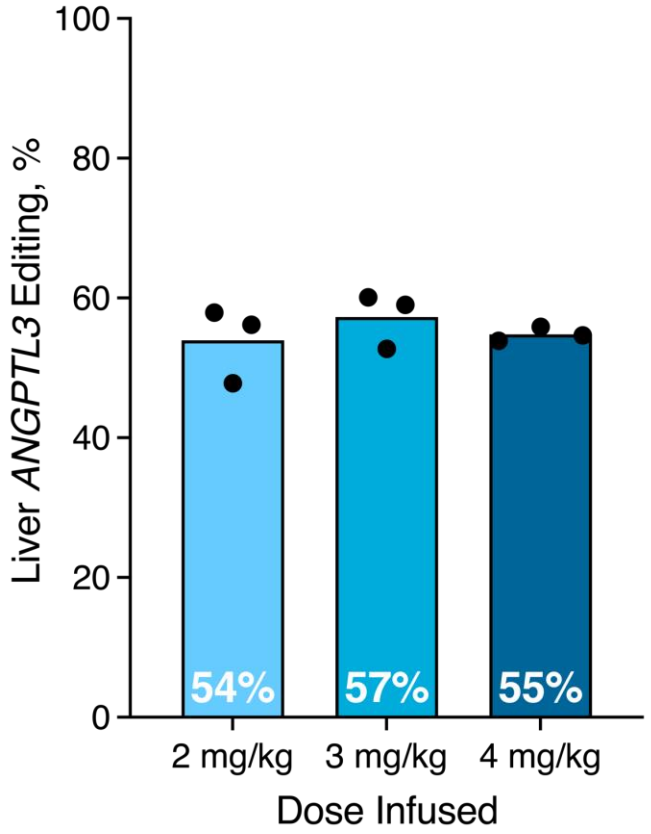
ANGPTL3 precursor and modified ABE/gRNA configurations assessment in non-human primates

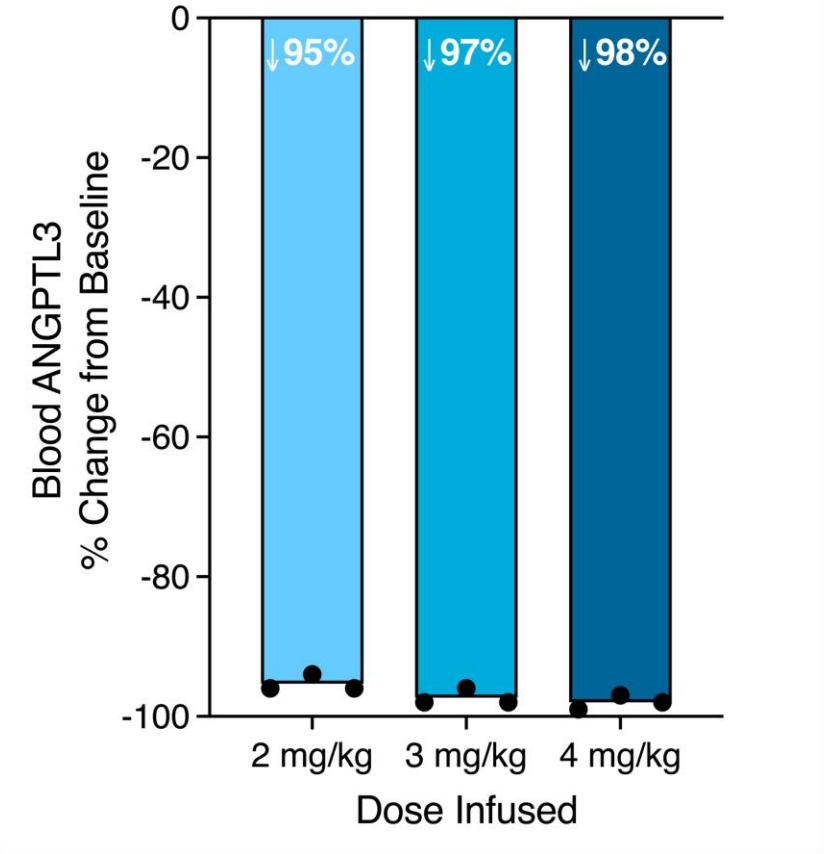


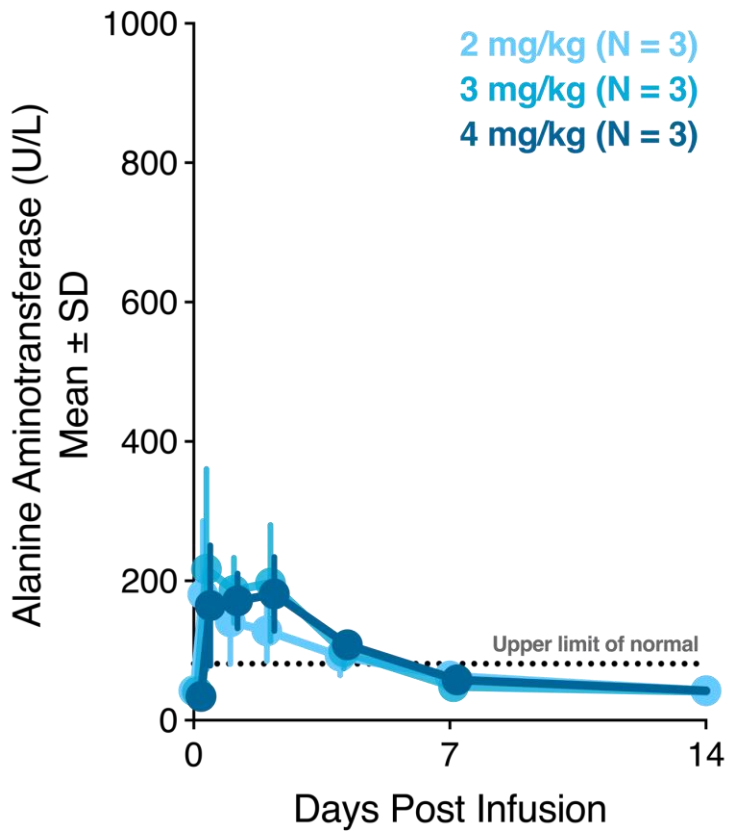


Data aggregated across 2 experiments In NHPs treated with 2 mg/kg of the ANGPTL3 precursor or modified ABE/cyno surrogate gRNA configurations (N = 3 for each treatment group). Reductions in blood ANGPTL3 assessed 15 days were >90% for 3 of 7 configurations screened.

Optimized ANGPTL3 precursor is well-tolerated in NHPs at a range of doses and potent in reducing blood ANGPTL3 >90%







In NHPs dosed with 2, 3, or 4 mg/kg of VERVE-201cyno (N = 3 in each dosing group), observed liver *ANGPTL3* editing ranging from 54 to 57% and blood ANGPTL3 protein reduction assessed at day 15 ranging from 95 to 98%. Transient increases in ALT and AST resolved by day 7, no change in total bilirubin.

VERVE-201 *ANGPTL3* drug candidate: IND-enabling activity ongoing, on track for first-in-human clinical trial initiation in 2024

High unmet need for additional LDL-C lowering HoFH and ASCVD not at goal on oral + PCSK9i therapy

Precise A-to-G DNA edit designed to inactivate liver *ANGPTL3* without double-strand DNA breaks

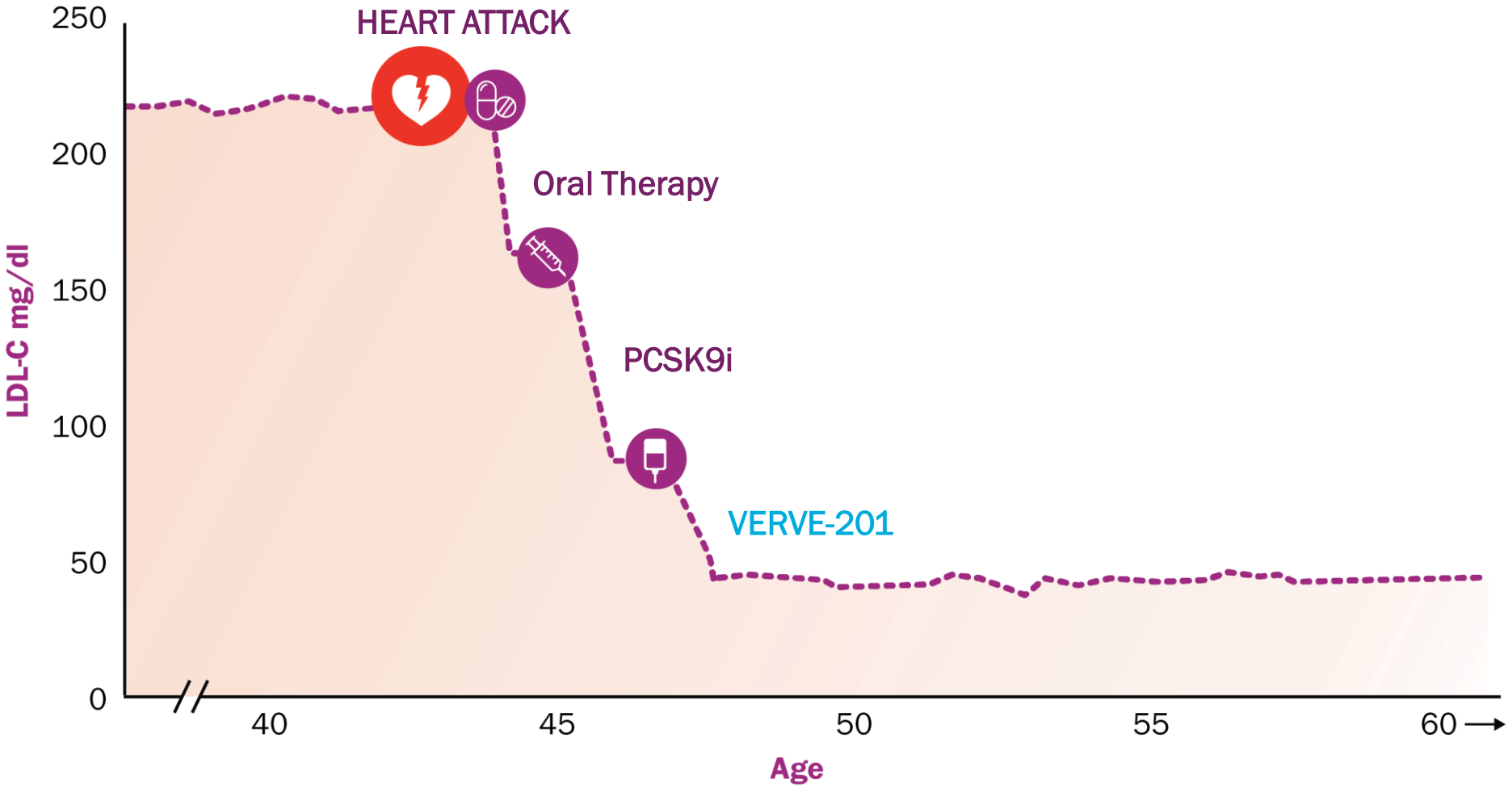
Durable and potent effect: >90%↓ in ANGPTL3 2 years after single dosing of ANGPTL3 precursor in NHP

Safety: No detectable long-term impact of ANGPTL3 suppression on liver biomarkers in NHP

Verve's proprietary GalNAc LNP expected to enable efficient liver delivery in all patients, including HoFH

Chemically modified ABE+gRNA preserves potency while minimizing risk of off-target modifications in PHH

Inactivation of ANGPTL3 with a single-course treatment to lower LDL-C has potential to address unmet need in HoFH and ASCVD



Illustrative graphic of a hypothetical patient with ASCVD and hypercholesterolemia treated with serial addition of lipid-lowering therapies to achieve goal LDL-C after suffering a heart attack at age 44.