In vivo CRISPR base editing of ANGPTL3 in a non-human primate model of homozygous familial hypercholesterolemia

Verve Company Update

November 9, 2021

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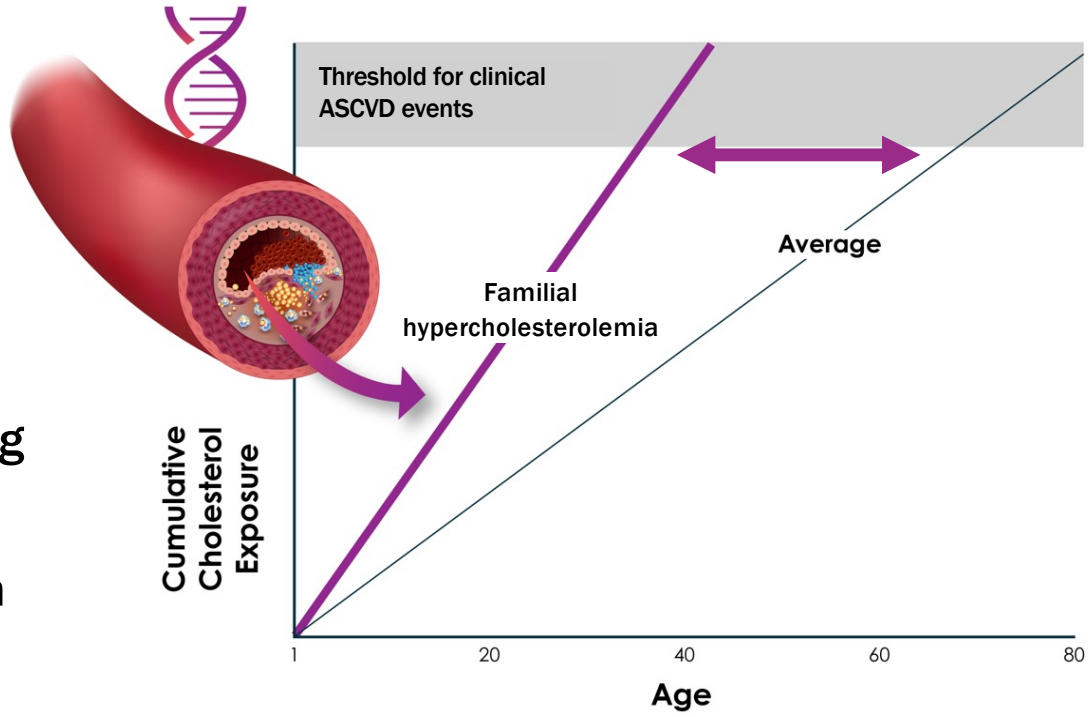
This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the initiation, and timing, of the Company's future clinical trials and its research and development. 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 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 its other product candidates; 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 and in other filings that the Company makes with the Securities and Exchange Commission in the future. 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.

Homozygous familial hypercholesterolemia (HoFH): a life-threatening genetic disease with very high cumulative exposure to LDL-C

- Usually caused by mutations in both copies of the LDLR gene, ~ 1,300 people in U.S.
- Lack of LDLR on hepatocytes leads to poor clearance of LDL-C from the blood
- LDL-C levels >500 mg/dL starting early in life
- Myocardial infarction common in 20s and 30s



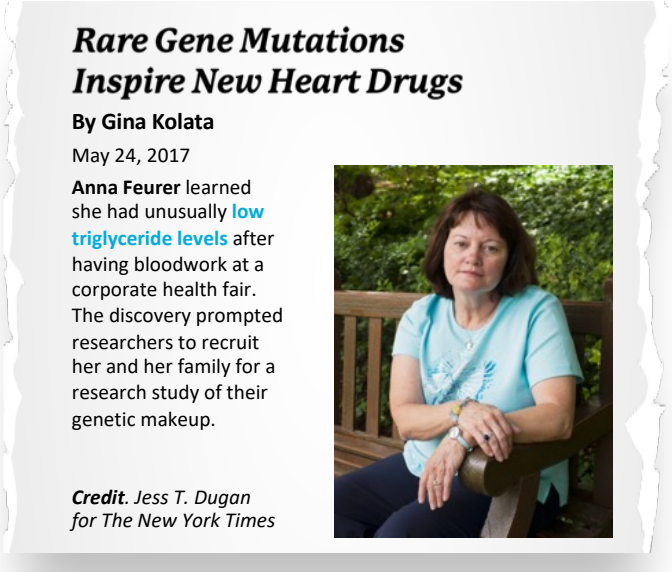
Adapted from Horton et al. J Lipid Res., 2009

Inactivation of ANGPTL3 gene is a compelling target for the treatment of HoFH: human genetics and human pharmacology

validated by human genetics

Heterozygous deficiency:
Low lipids in population
Resistant to heart attack

Human knockout:
Triglycerides: 19 mg/dL
LDL-C: 37 mg/dL



Rare Gene Mutations Inspire New Heart Drugs

By Gina Kolata

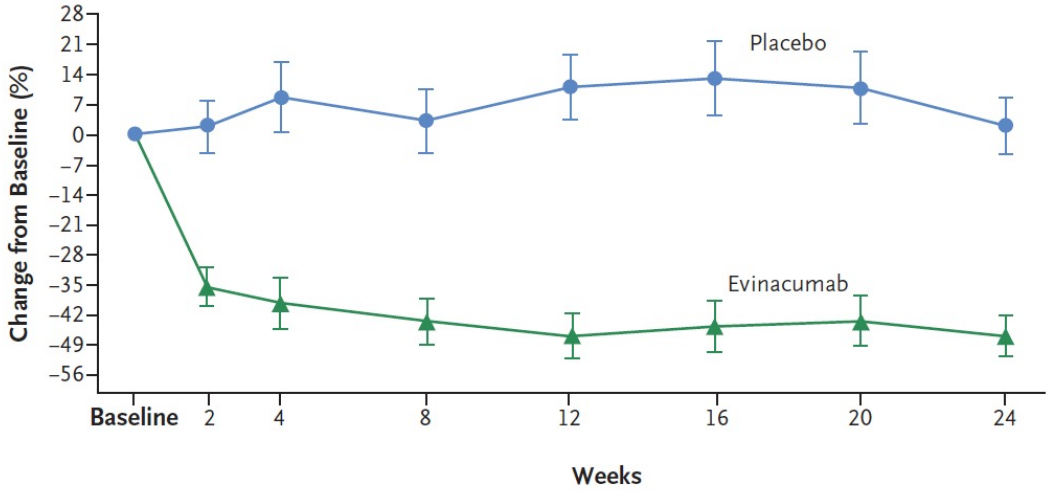
May 24, 2017

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.

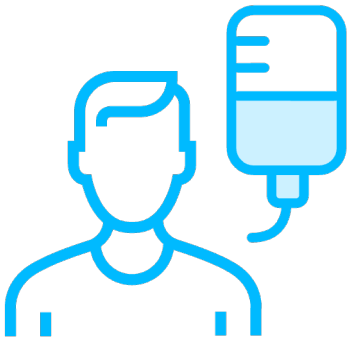
Credit. *Jess T. Dugan for The New York Times*

validated by human pharmacology

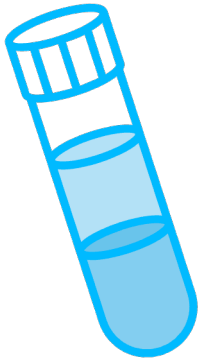
- ANGPTL3 inhibition with evinacumab lowered LDL-C by about 47% in a pivotal phase 3 trial in patients with HoFH
- Evinacumab now approved for HoFH



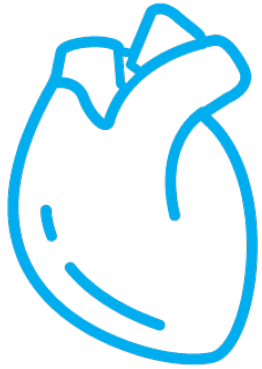
At Verve, we are developing...



a single-course gene editing treatment that would...

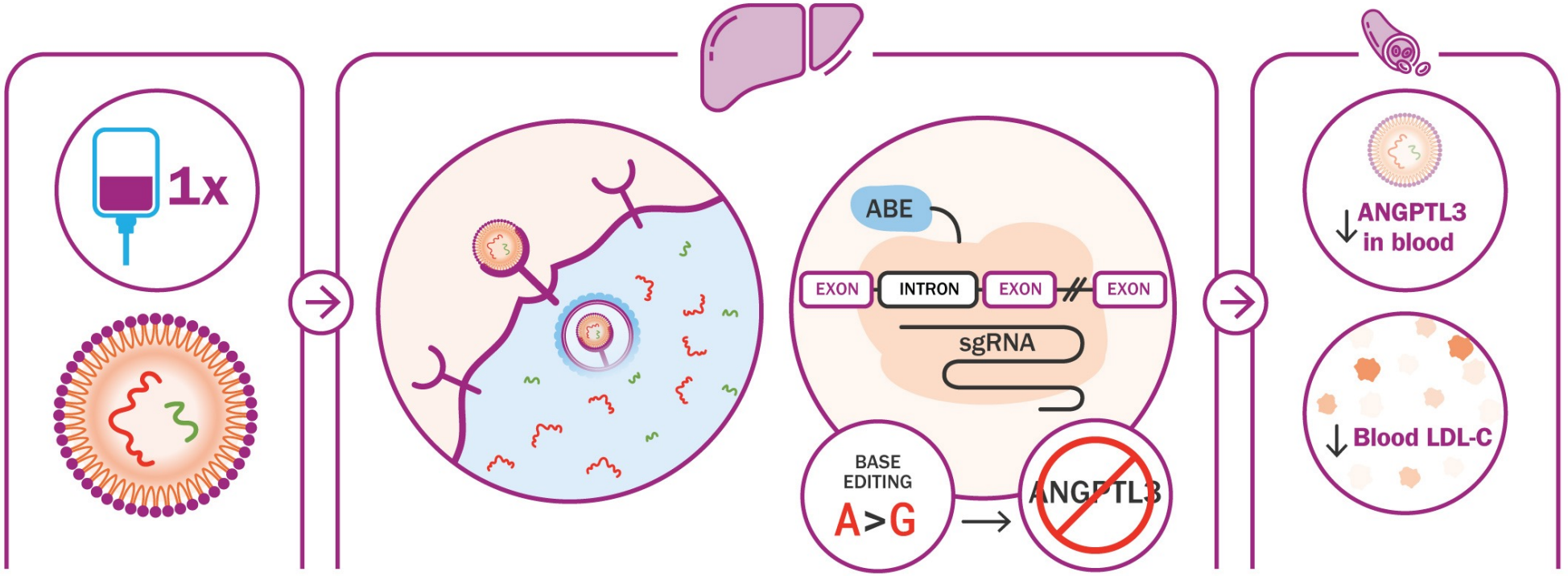


... durably and safely lowered blood LDL cholesterol...

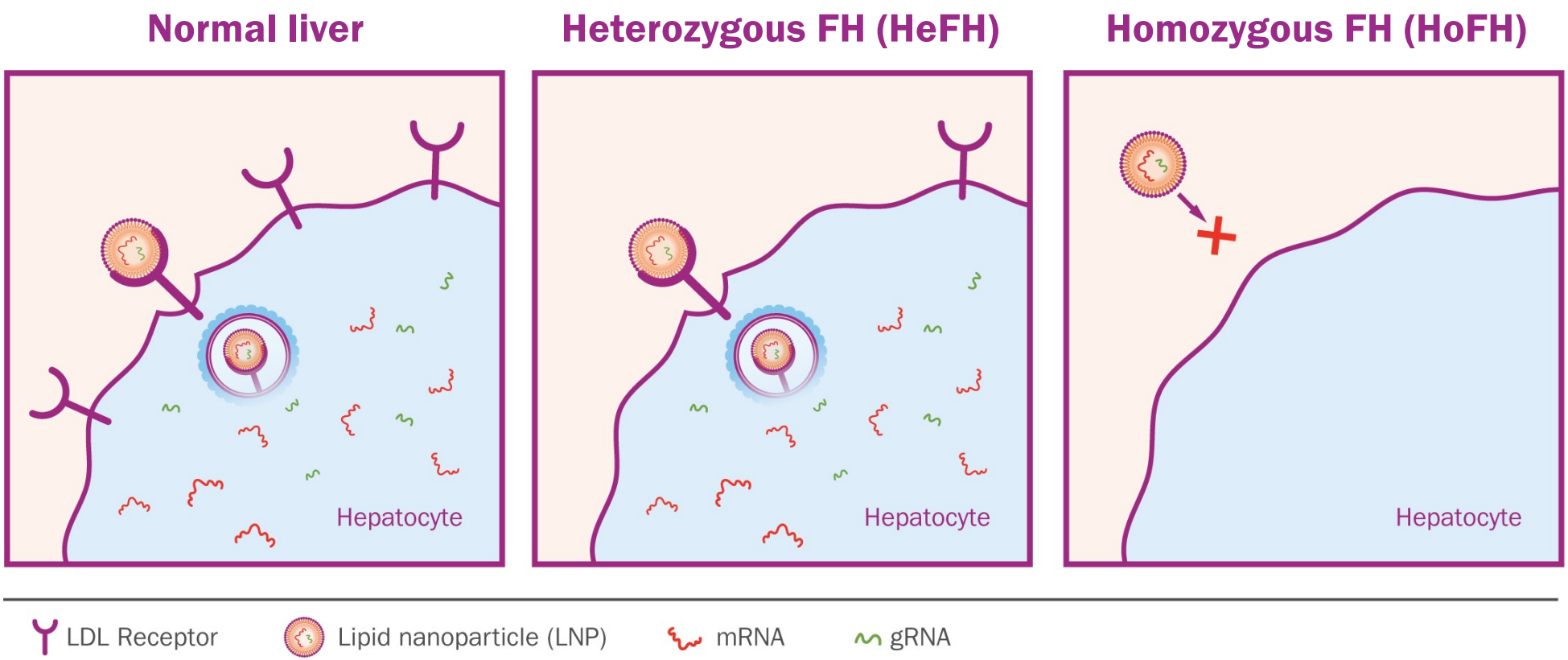


to treat FH and ASCVD

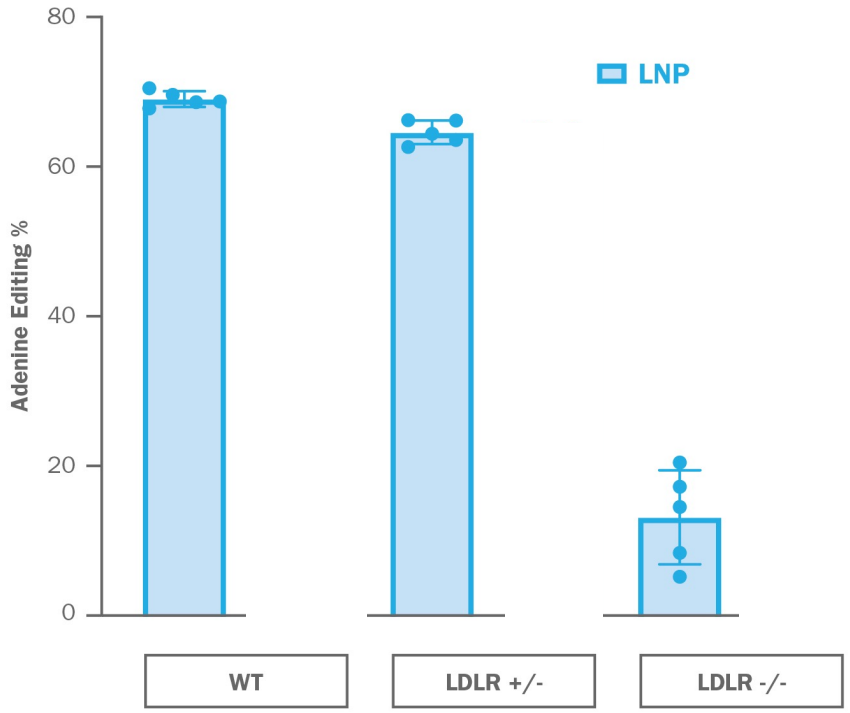
Our approach: in vivo liver base editing to permanently turn off disease-causing ANGPTL3 gene in the liver



Challenge: HoFH patients completely lack LDL Receptor; in this setting, delivery with standard LNPs doesn't work



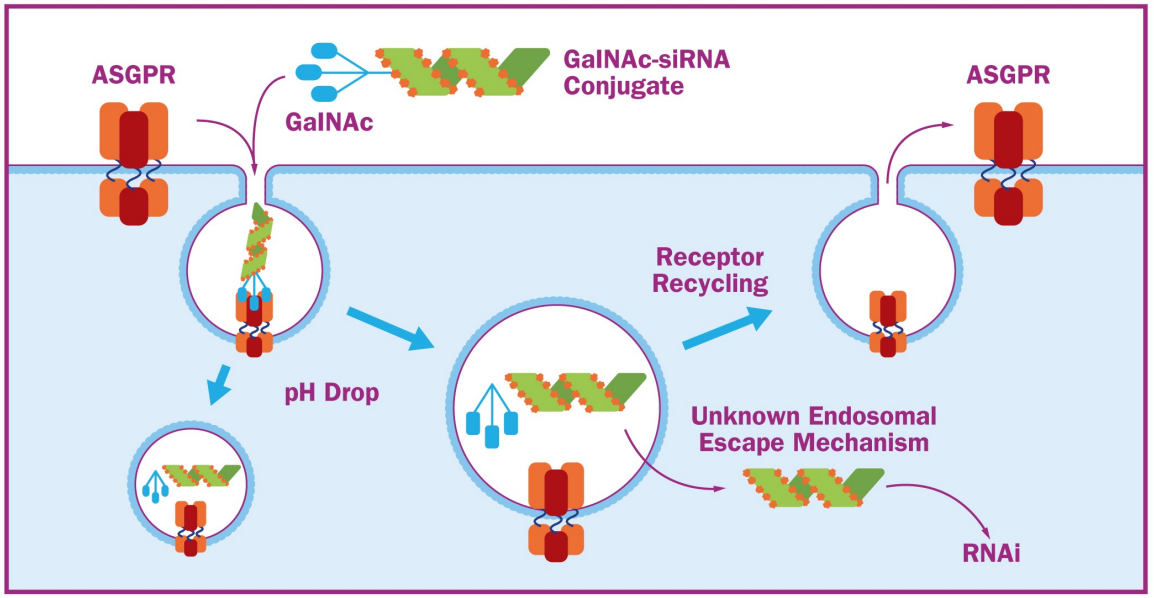
In mouse models of FH, standard LNPs deliver fine to HeFH mice but fail to deliver to HoFH (*Ldlr* -/-) mice



Goal: an LNP delivery system that would enable ANGPTL3 editing in both patients with HeFH and HoFH

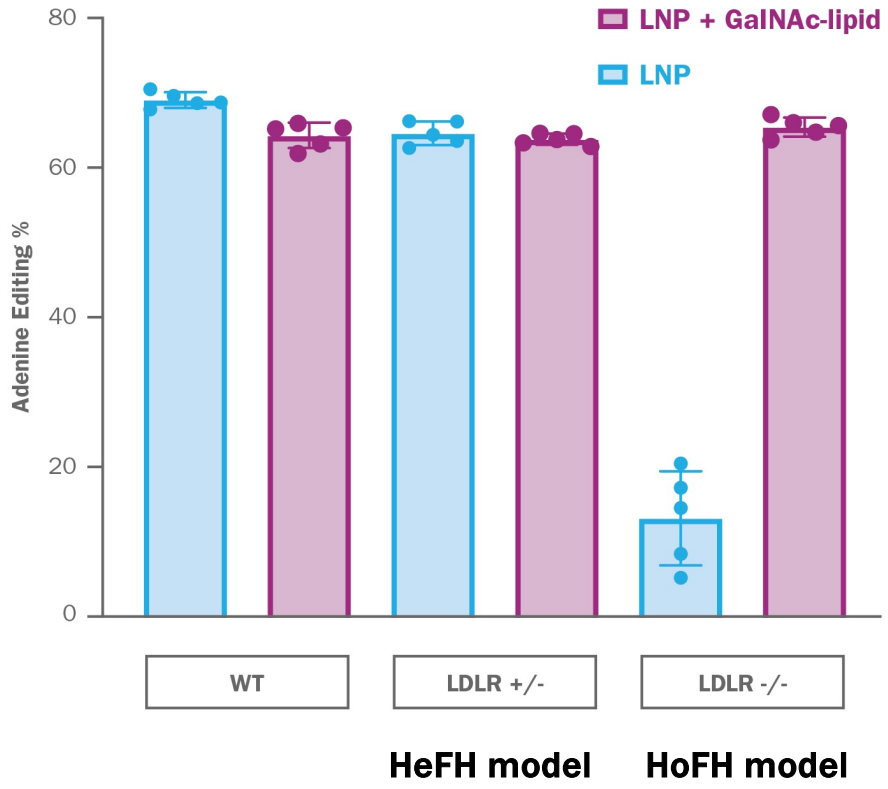
PROGRAM	INITIAL INDICATION	DEVELOPMENT STATUS			
		Research/ Lead optimization	IND-Enabling	Clinical	Development Milestones
Low-density lipoprotein cholesterol (LDL-C)					
VERVE-101 ABE-PCSK9	Heterozygous familial hypercholesterolemia				• IND Submission (2022) • Phase 1 Initiation (2022)
LDL-C and triglyceride-rich lipoprotein (TRL)					
ANGPTL3	Familial hypercholesterolemia				• Candidate selection (2022) • Begin IND-enabling studies (2022)

Liver-specific ASGPR is an alternative receptor for entry into hepatocytes using a GalNAc ligand



Adapted from Springer and Dowdy, Nucleic Acid Therapeutics 2018, 28, 109

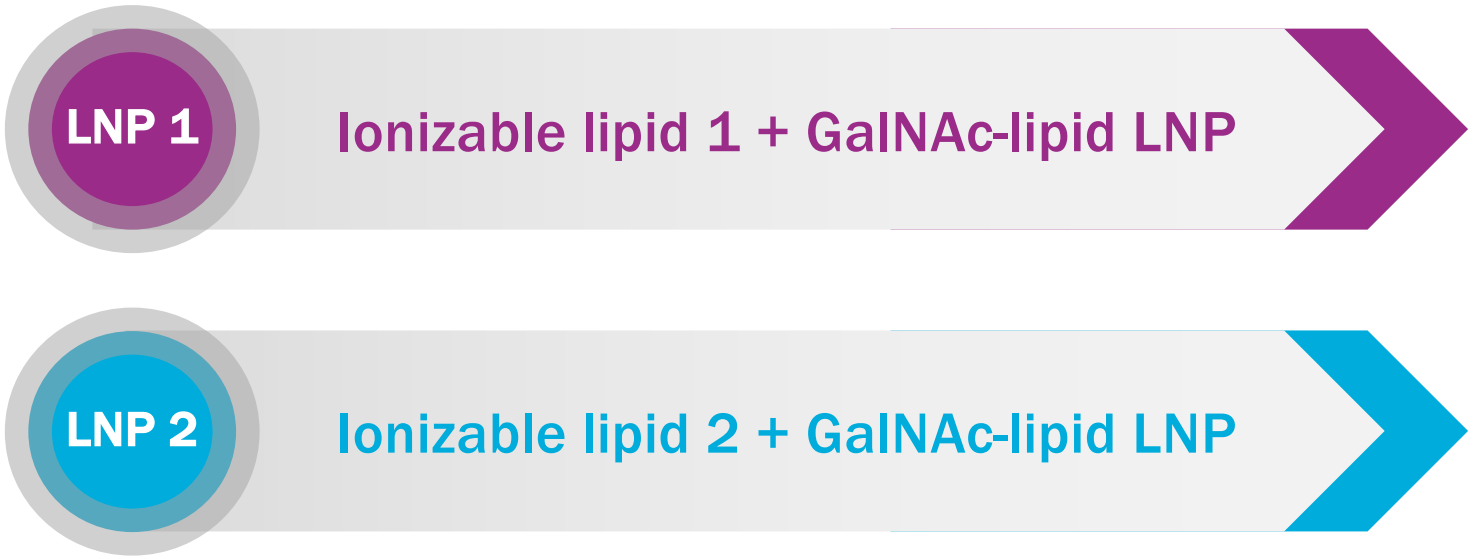
Verve solution: ASGPR targeting proprietary GalNAc ligand that, when added to LNP, enables liver delivery in HoFH mouse model



Editing data are from analyses of liver necropsy specimens at 1 week

Will GalNAc-LNP efficacy translate to larger animal models such as NHP?

Two proprietary GalNAc-LNPs created at Verve



Drug development problem: need for an NHP model of HoFH

Translation of LNP delivery from mouse to human has historically been poor

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Will GalNAc-LNPs truly bypass LDLR in primates and humans?

Need a model of HoFH in NHP to evaluate if ANGPTL3 drug candidates are likely to allow delivery to HoFH patients (as well as HeFH)

Creation of a HoFH model in NHP through liver editing

Eliminate LDLR protein expression just from the liver by targeted editing of the *LDLR* gene in hepatocytes

Use Cas9 and a dual gRNA strategy, encapsulated in LNPs that deliver to the liver, in wild-type NHPs to delete a ~50 bp portion of the LDLR gene and efficiently disrupt LDLR protein expression just in the liver

Creating a model of HoFH in NHP

Model creation
LDLR editing

Intravenous administration to *healthy wild-type cynomolgus monkey (Macaca fascicularis)*

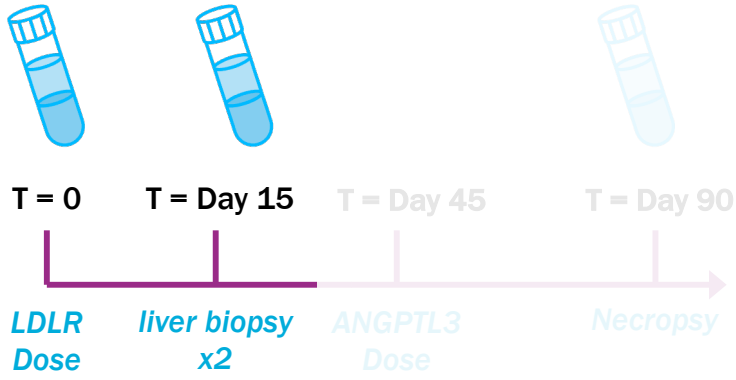
- Standard LNP 2 mg/kg
  mRNA: spCas9
  Dual gRNA: LDLR
  (N=10)
- Vehicle Control (N=9)

Testing LNPs in Model
ANGPTL3 editing

LNPs +/- GalNAc
ABE8.8
gRNA: ANGPTL3
2 mg/kg
(N=3 each group)

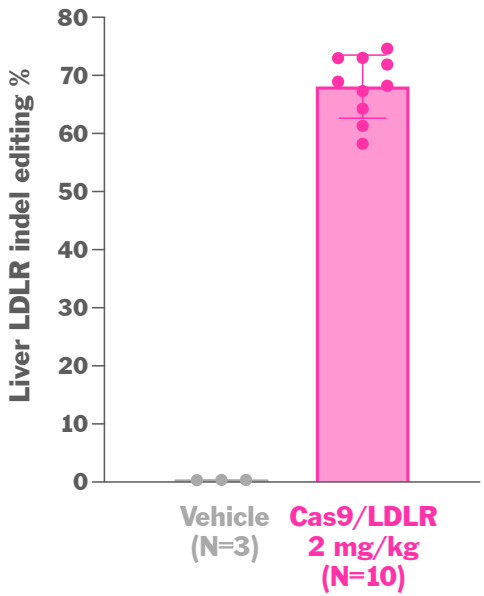
Primary endpoints – LDLR
1. Liver biopsy *LDLR* DNA editing
2. Liver biopsy LDLR expression
3. Blood LDL-C levels

Primary Endpoints – ANGPTL3
1. Liver biopsy ANGPTL3 editing
2. ANGPTL3 protein in blood
3. Blood LDL-C levels



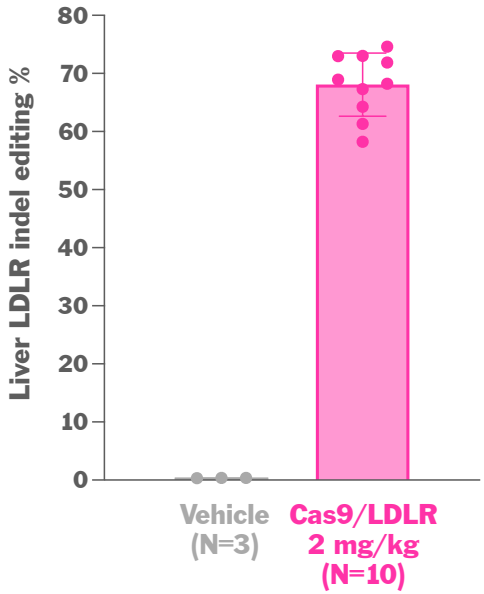
Efficient disruption of LDLR gene in NHP liver

Liver LDLR editing %
(indel creation) in liver biopsy

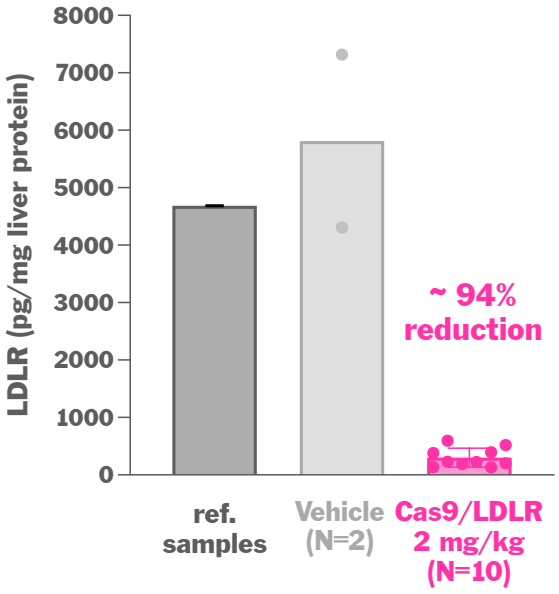


Liver editing disrupts LDLR gene: 94% reduction in LDLR protein

Liver LDLR editing % (indel creation) in liver biopsy

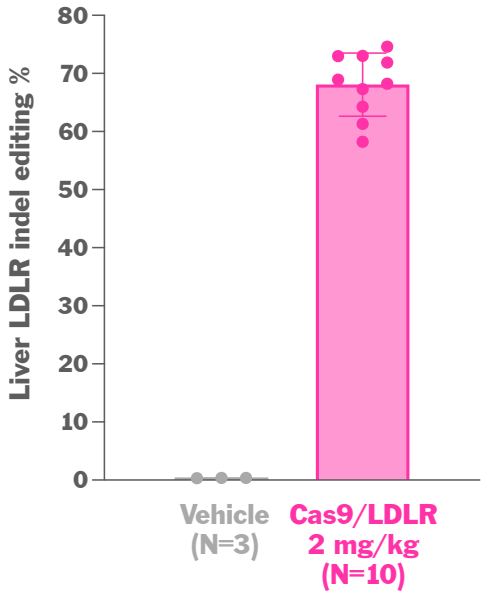


Liver LDLR expression by protein ELISA on liver biopsy

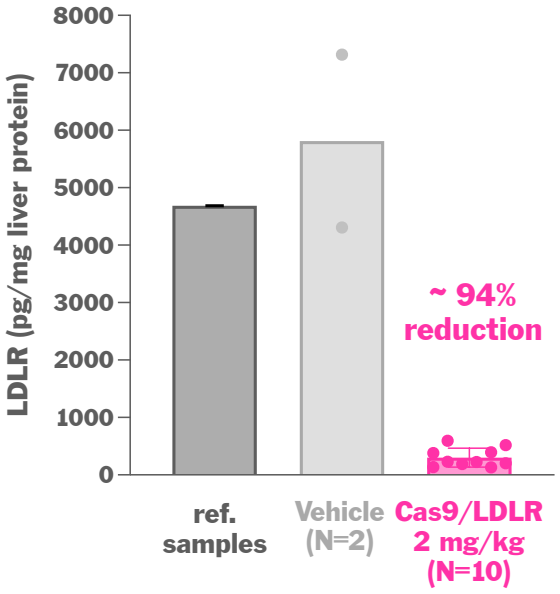


Liver editing disrupts LDLR gene: blood LDL-C rises six-fold

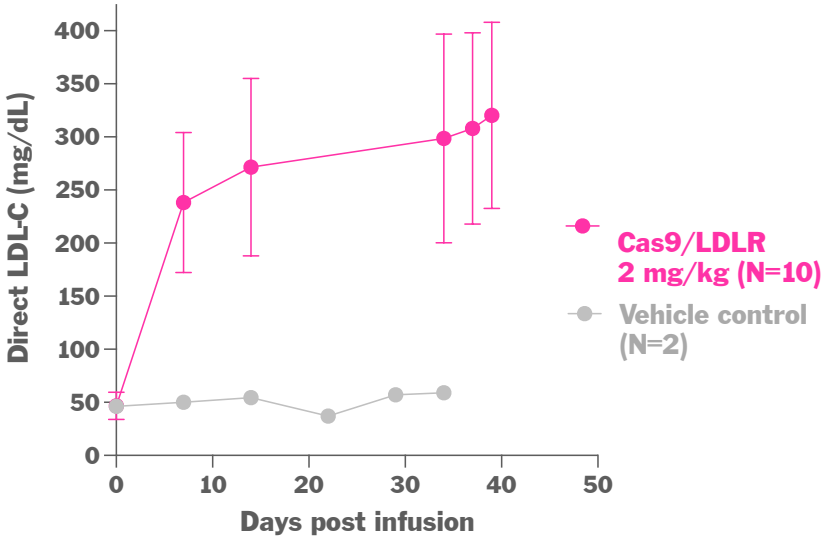
Liver LDLR editing % (indel creation) in liver biopsy



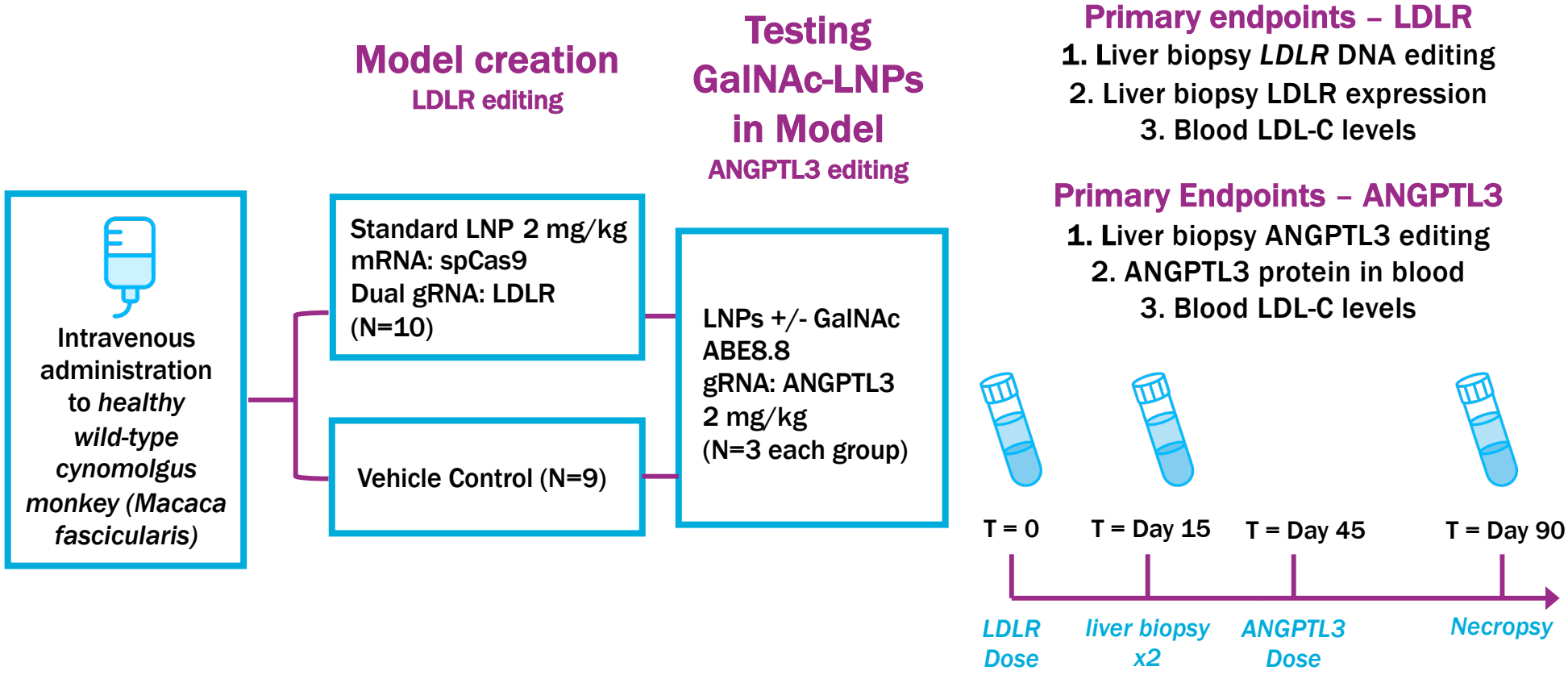
Liver LDLR expression by protein ELISA on liver biopsy



LDL-C rises from ~50 mg/dL to more than 300 mg/dL

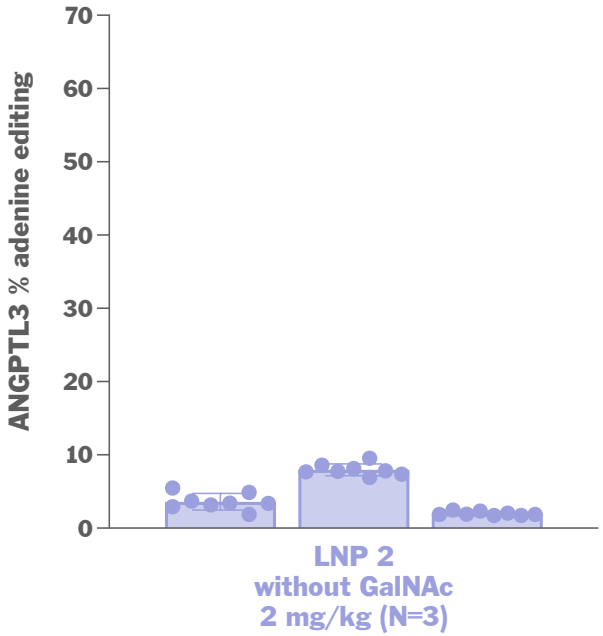


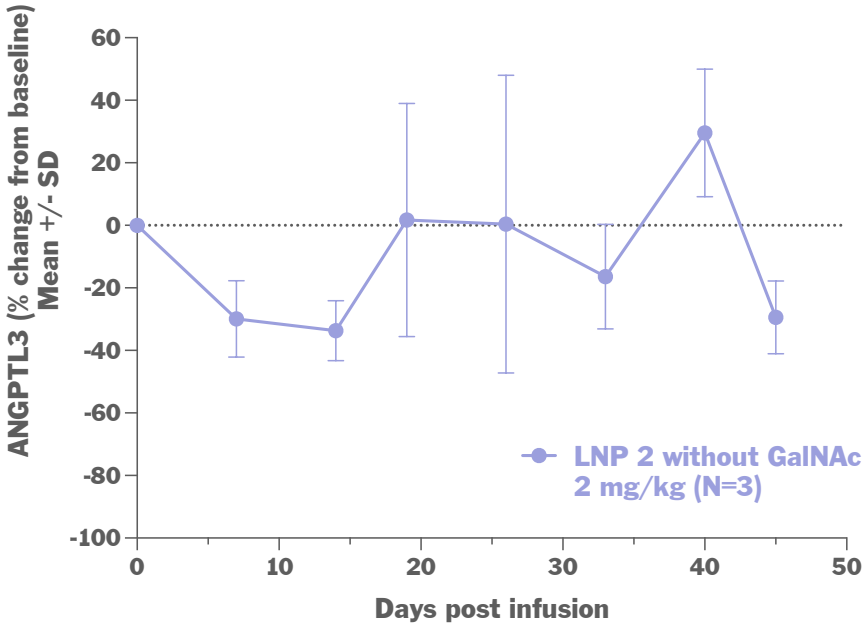
Testing GalNAc-LNPs in a model of HoFH in NHP



Standard LNPs (without GalNAc) do not achieve effective ANGPTL3 base editing in the liver of the HoFH NHPs

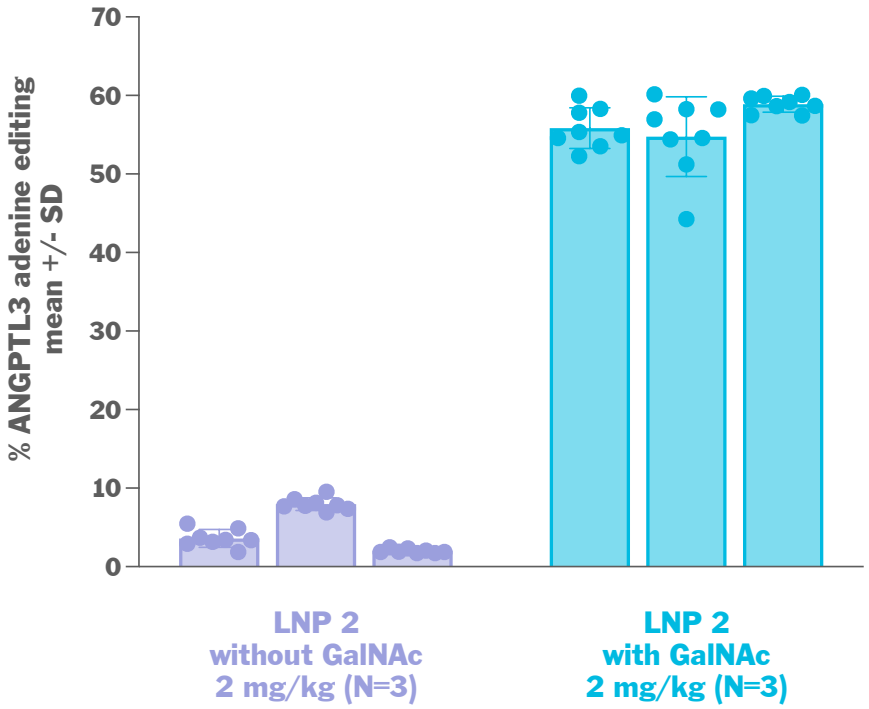
Standard LNP in HoFH NHP model

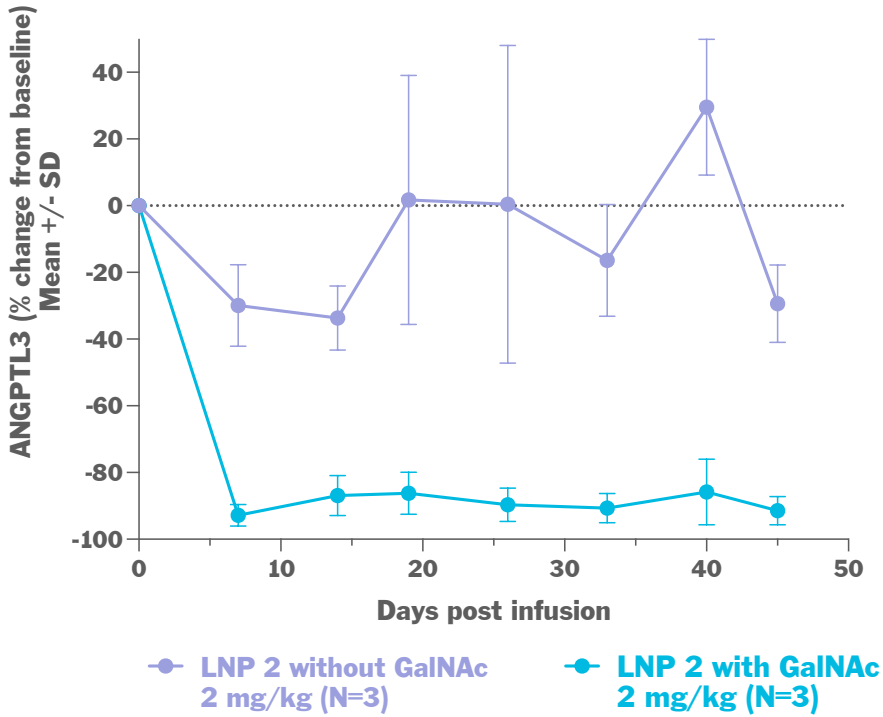




Verve's GalNAc-LNP achieves effective ANGPTL3 base editing in the HoFH NHP liver

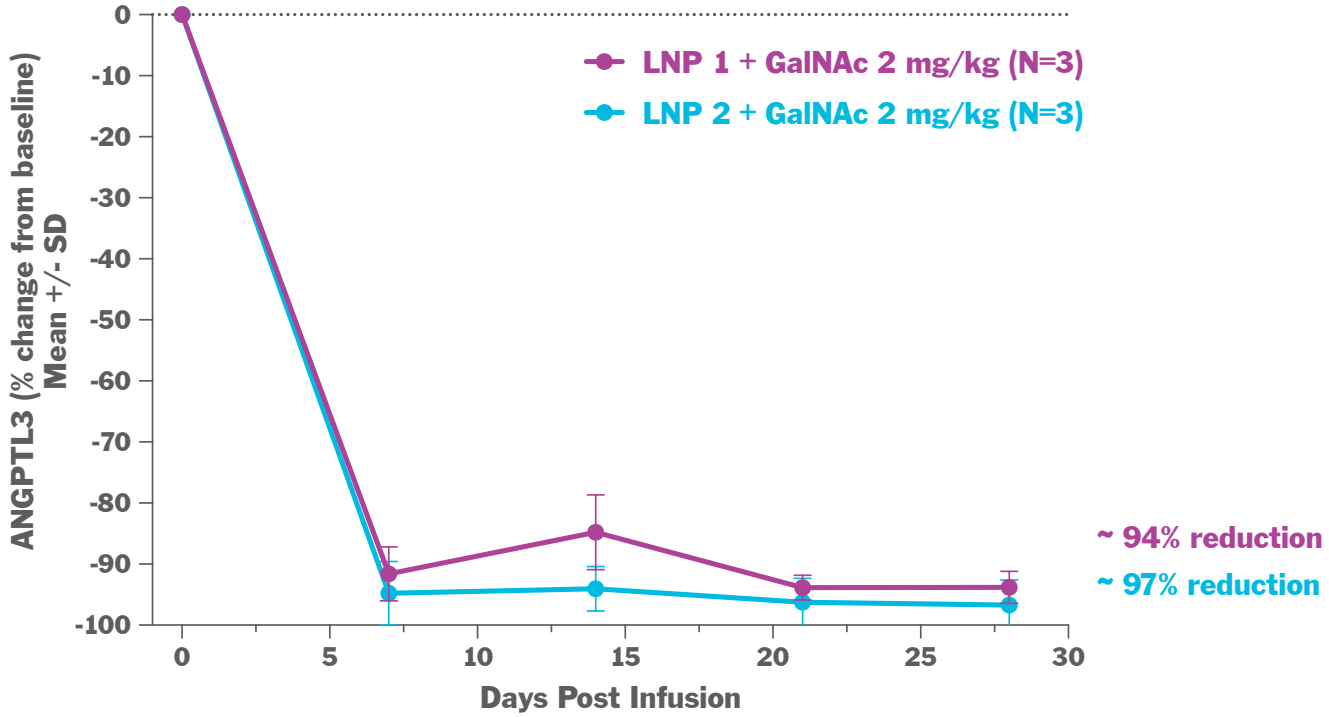
GalNAc-targeting bypasses LDLR and achieves liver editing





Base editing of ANGPTL3 via GalNAc-LNPs reduces blood ANGPTL3 by 94% - 97% in NHP model of HoFH

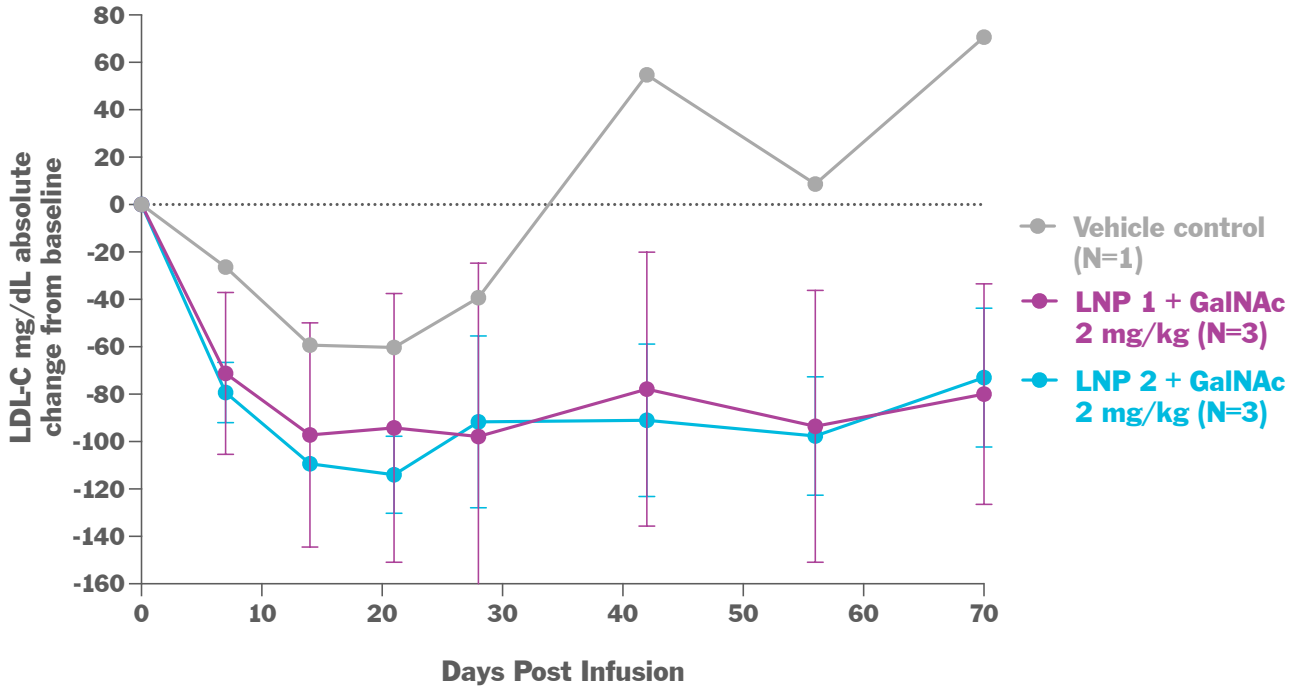
GalNAc LNPs (encapsulating ABE-ANGPTL3 base editing payload) dosed to HoFH NHPs that already have stable disruption of LDLR protein and markedly elevated LDL-C



Base editing of ANGPTL3 via GalNAc-LNPs reduces blood LDL-C in NHP model of HoFH

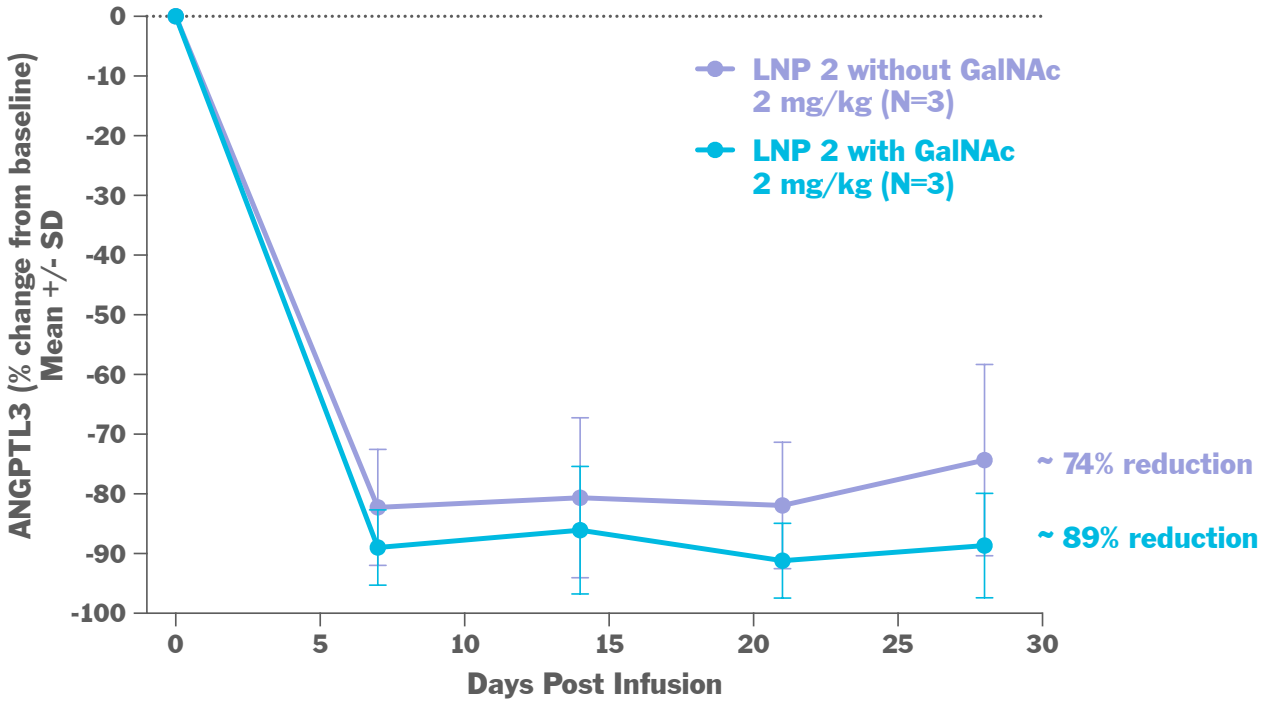
GalNAc LNPs (encapsulating ABE-ANGPTL3 base editing payload) dosed to HoFH NHPs that already have stable disruption of LDLR protein and markedly elevated LDL-C ~ 300 mg/dL

Baseline direct LDL-C ~ 300 mg/dL at time of test article dosing to HoFH NHPs



Is there relevance of the GalNAc-LNP delivery system to normal liver? Yes, may have improved potency when compared to standard LNPs

Wild-type NHPs administered the same LNP with and without inclusion of GalNAc-lipid



Large confirmatory dose-response studies in wild-type NHPs are ongoing

GalNAc-LNP delivery system will enable ANGPTL3 editing in both patients with HeFH and HoFH

Presented today ✓

- **Creation of an NHP model that recapitulates two key features of homozygous FH**
  - Liver deficiency of LDLR to model uptake of LNPs in HoFH
  - Marked hyperlipidemia to model circulating lipids and how that might impact LNP uptake by the liver
- **Demonstration that GalNAc LNPs enable highly efficient delivery and ANGPTL3 editing in the liver of the HoFH model in NHP**

Next steps →

- **Evaluation of dose response of GalNAc-LNPs as compared with standard non-GalNAc LNPs in wild-type NHP and mouse disease models**
- **Biodistribution and PK studies**
- **IND-enabling studies planned to initiate in 2022**

Thank you to our world-class team of problem solvers

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