# Innovative LNPs for Gene Editing Applications


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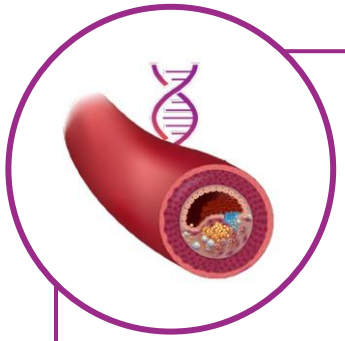
# Development of potential best-in-class LNPs for hepatic delivery

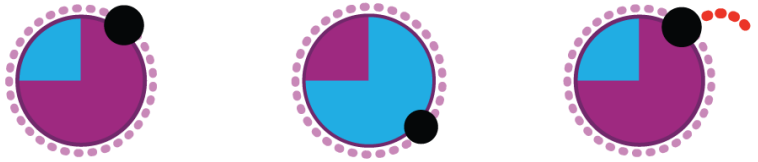
1. Challenges in hepatic delivery with current lipid nanoparticles(LNPs)
2. Formulation design and development of a scalable process for a stable drug product that can be tested in the clinic
3. Efficacy, biodistribution, durability and safety of the drug product in non-human primates (NHPs)

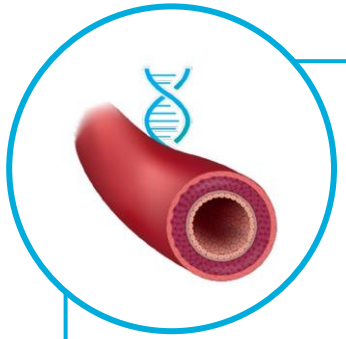
# What causes atherosclerotic cardiovascular disease (ASCVD) and what's a solution? Verve developing 'once and done' medicines for 3 causal drivers



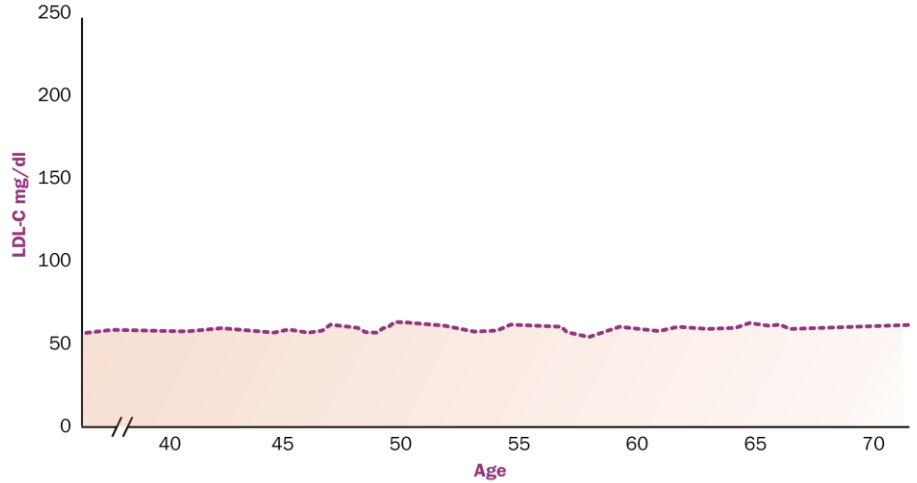
## High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:



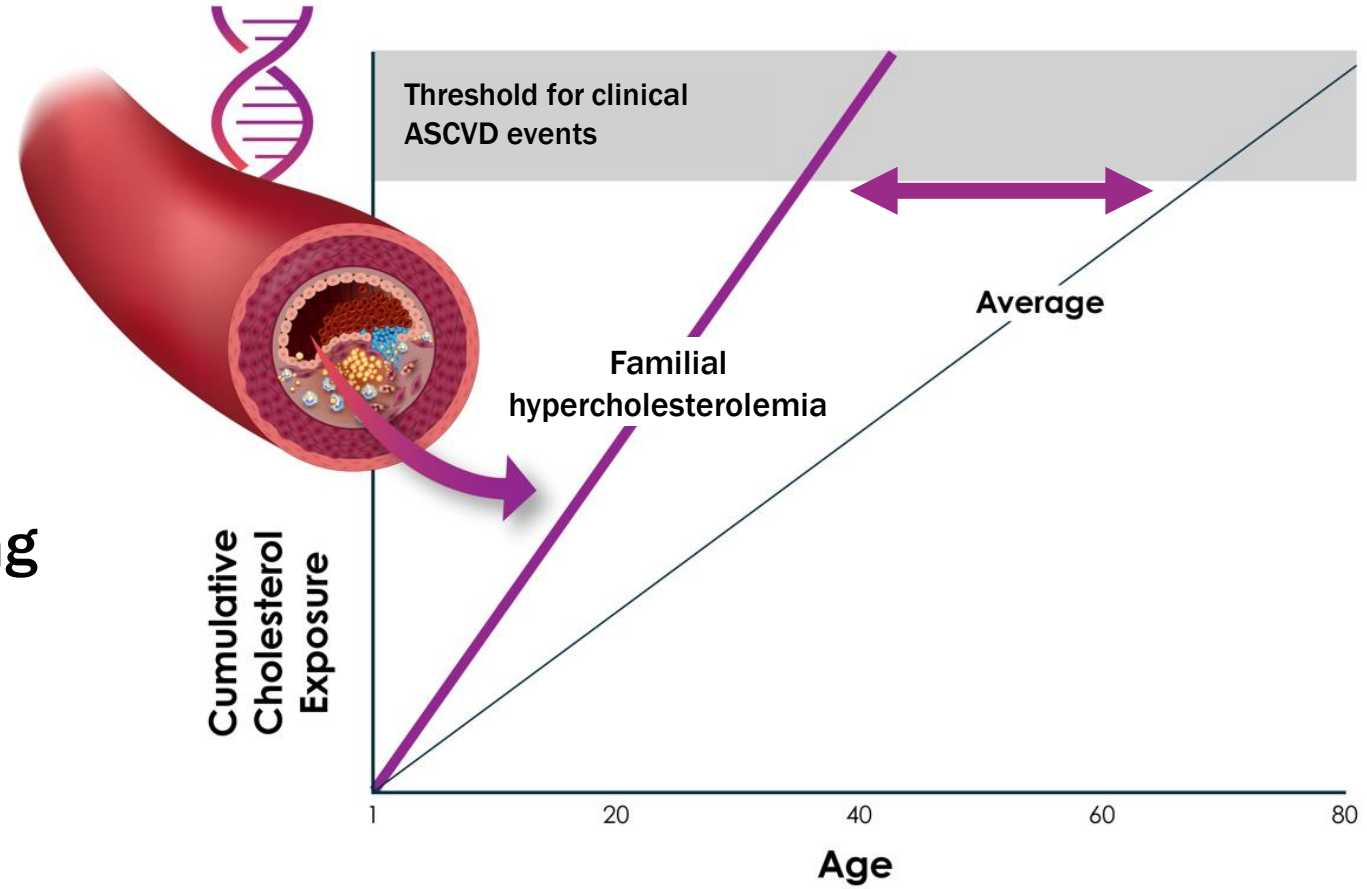



## Solution: keep blood cholesterol as low as possible for as long as possible



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

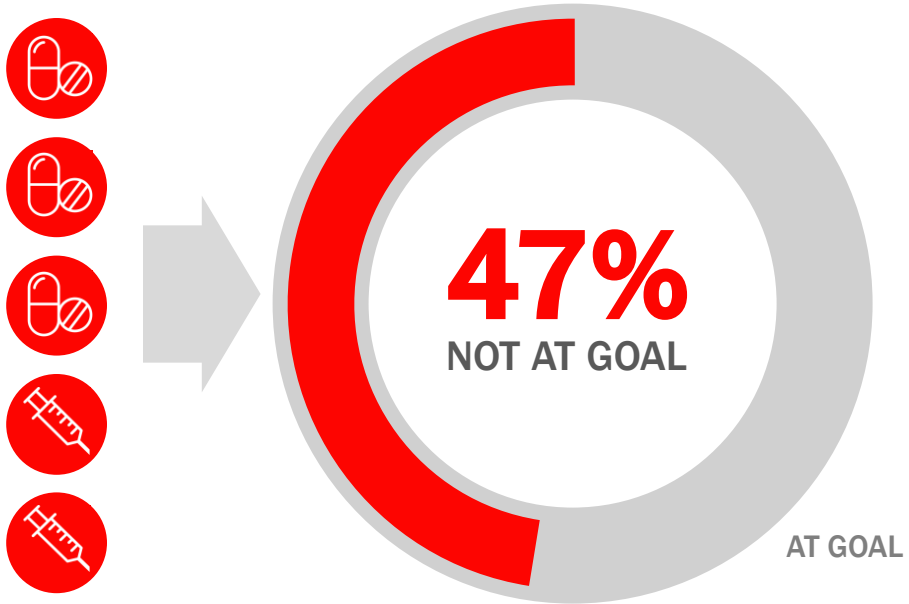
- Usually caused by mutations in both copies of the LDLR gene, ~ 1,300 people in U.S.
- Lack of LDLR on hepatocytes leads to poor clearance of LDL-C from the blood
- LDL-C levels >500 mg/dL starting early in life
- Myocardial infarction (heart attack) common in 20s and 30s




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

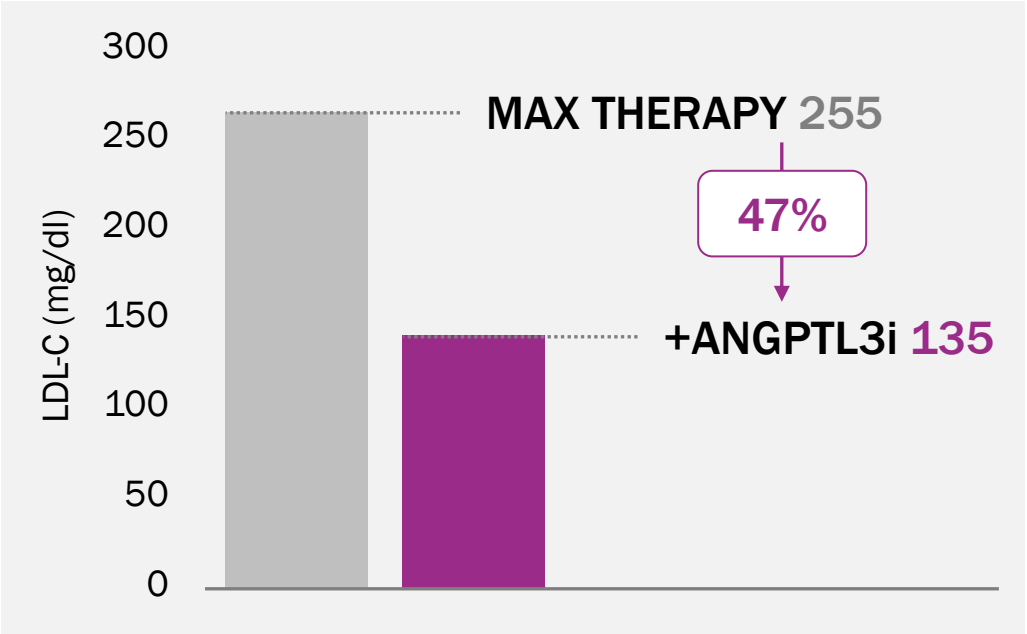
# HoFH: Severe orphan disease where medicine targeting ANGPTL3 is approved to lower LDL-C

## Unmet Medical Need




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

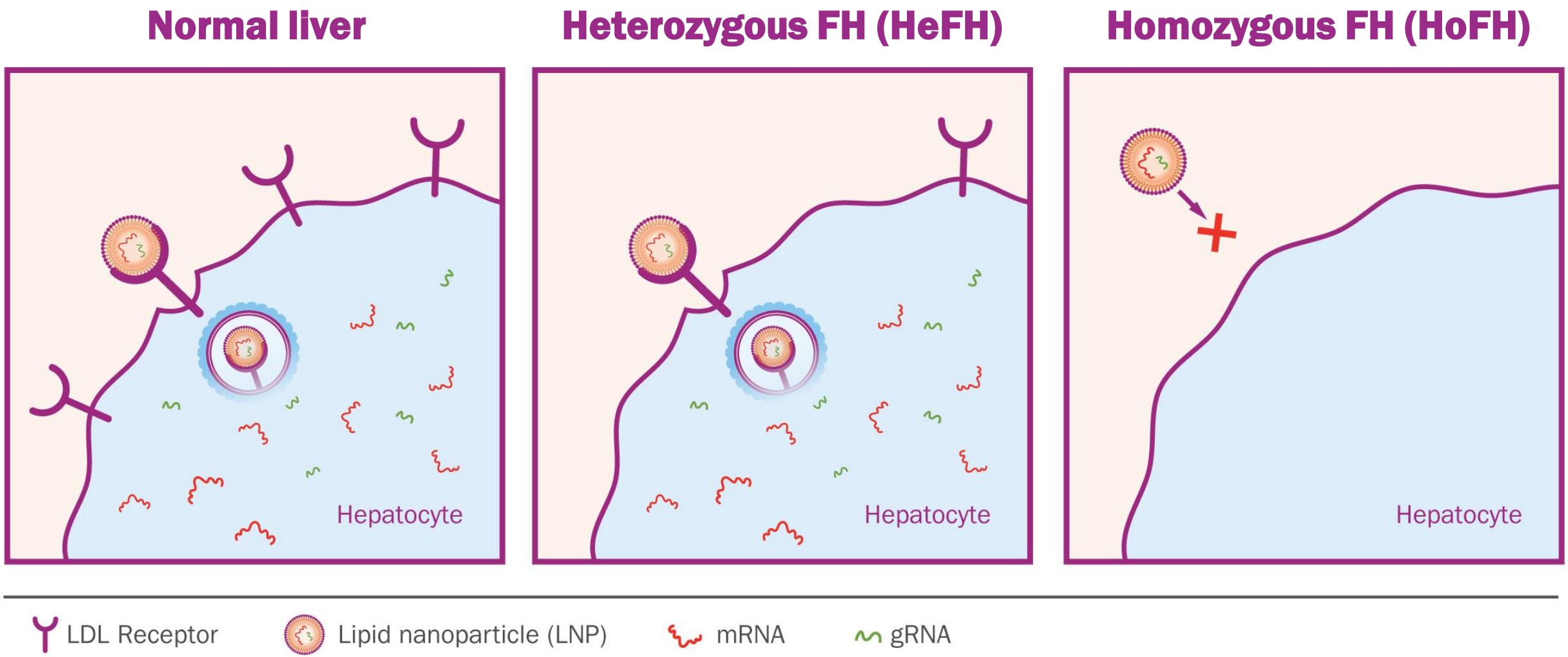
## Clinical Validation of ANGPTL3 Mechanism



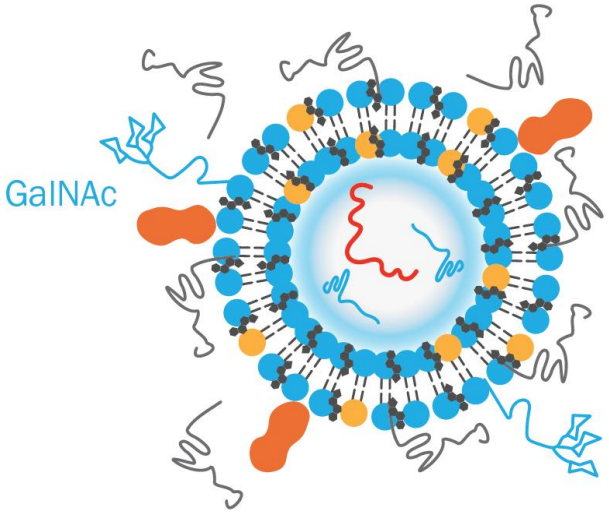

Registration trial of evinacumab (Evkeeza)
in HoFH patients
on maximum lipid-lowering therapy
ANGPTL3 inhibition ↓ LDL-C by 47%[2]

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.

# HoFH patients completely lack LDL Receptor. In this setting, standard LNP delivery to liver is challenging!



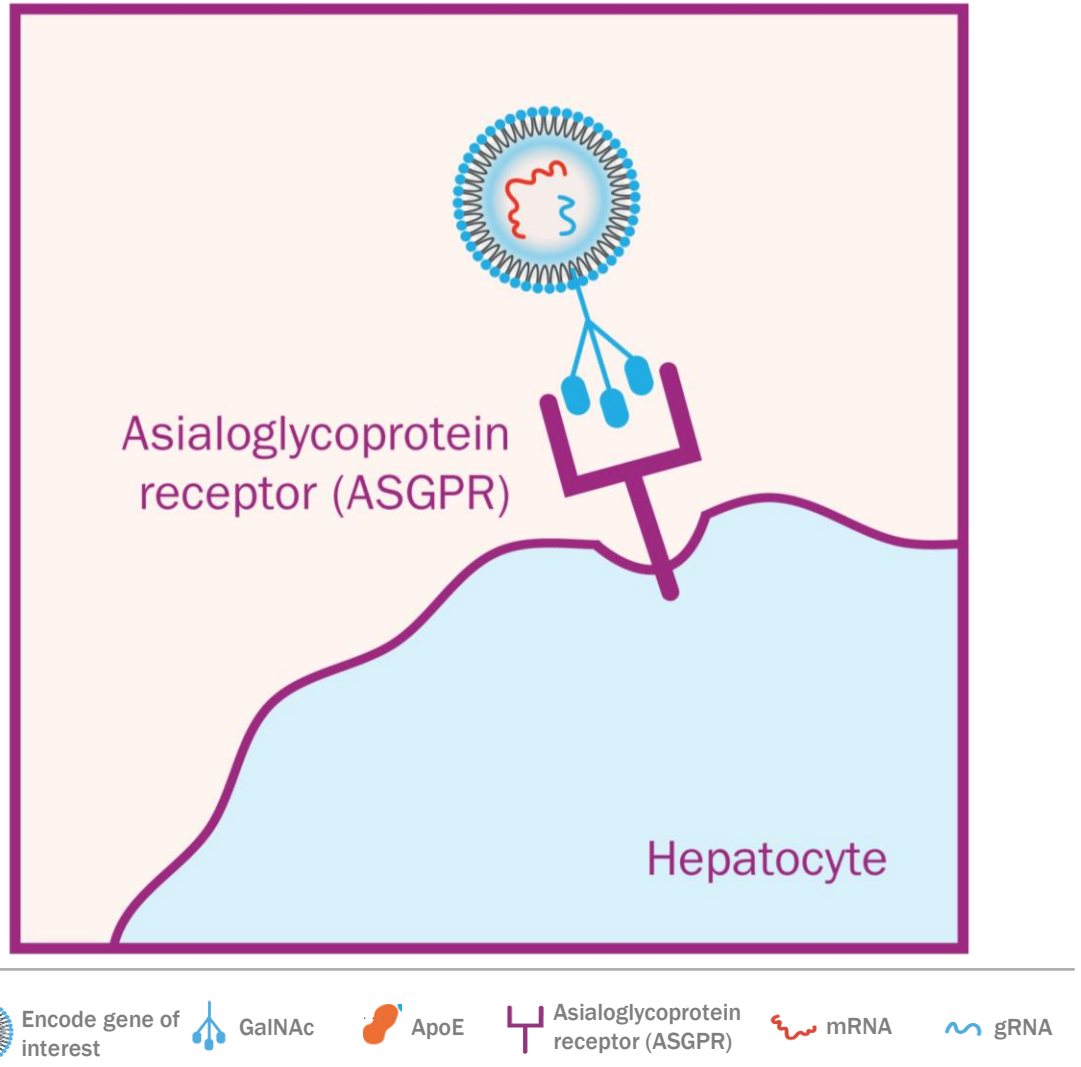
# Developed ASGPR-targeted GalNAc-LNPs with proprietary ionizable lipid (iLipid) and GalNAc ligand: potential best-in-class for delivery of genetic medicines to liver



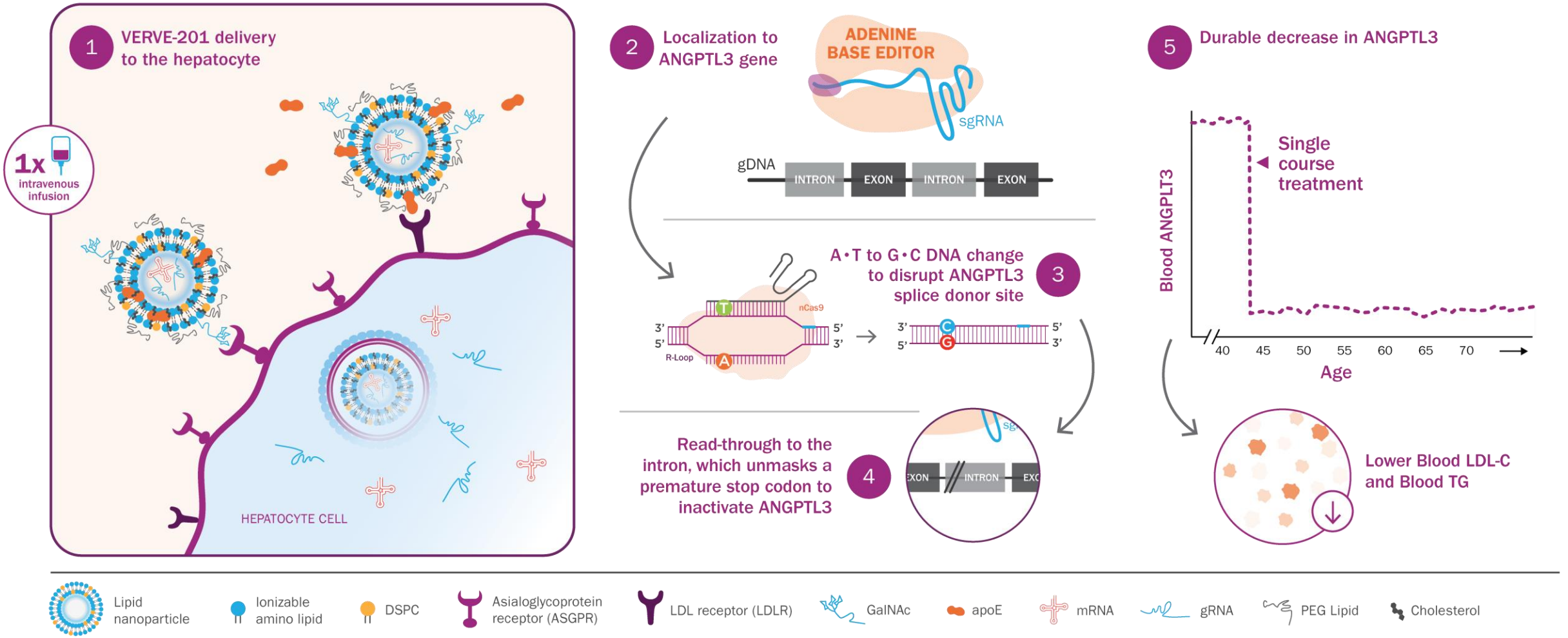

mRNA

gRNA

Lipid nanoparticles (LNP)



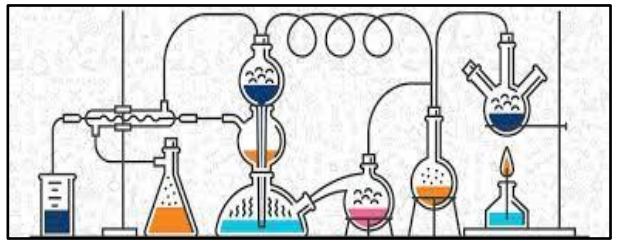
# Verve GalNAc-LNPs (VERVE-201) deliver base editing medicine designed to inactivate hepatic gene of interest and lower LDL-C and Triglycerides (TG)



# LNP development approach at Verve

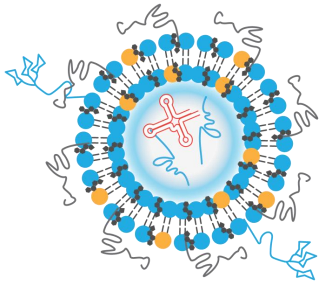
## Chemistry

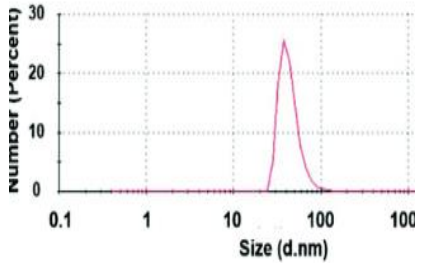
Design and synthesis



## Formulation Screening and Analytics

Screening and Analysis






## *In vivo* pharmacology

Rodent screening

- Formulation design and Process Development
- Analytics and Quality Control
- Large-scale production
- GMP production for clinical trials

Active LNP in NHP

# Formulation and Manufacturing:

## Design and Scale up

# Verve GalNAc-LNPs : mRNA + gRNA packaged in a GalNAc-LNP; edit designed to turn off *select gene*

## DRUG SUBSTANCES

RNA components encode base editor and a guide targeting *select* gene

- mRNA for adenine base editor
- gRNA localizes editor to select gene

+

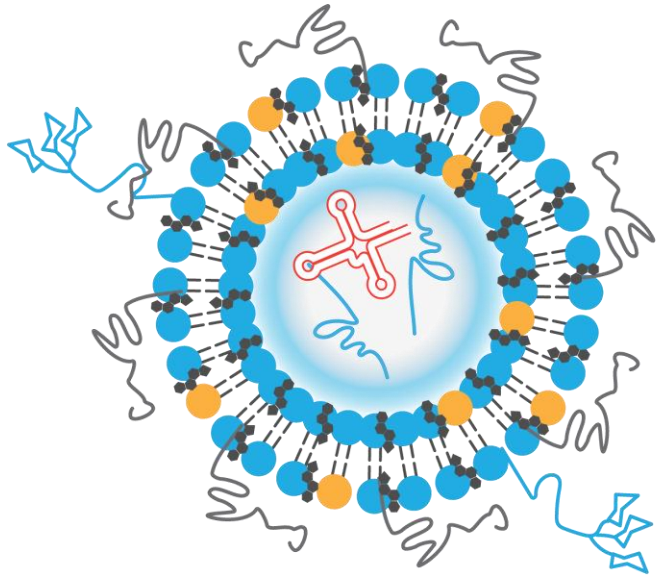
## DELIVERY VEHICLE

Lipid nanoparticle for delivery to liver cell includes 5 components

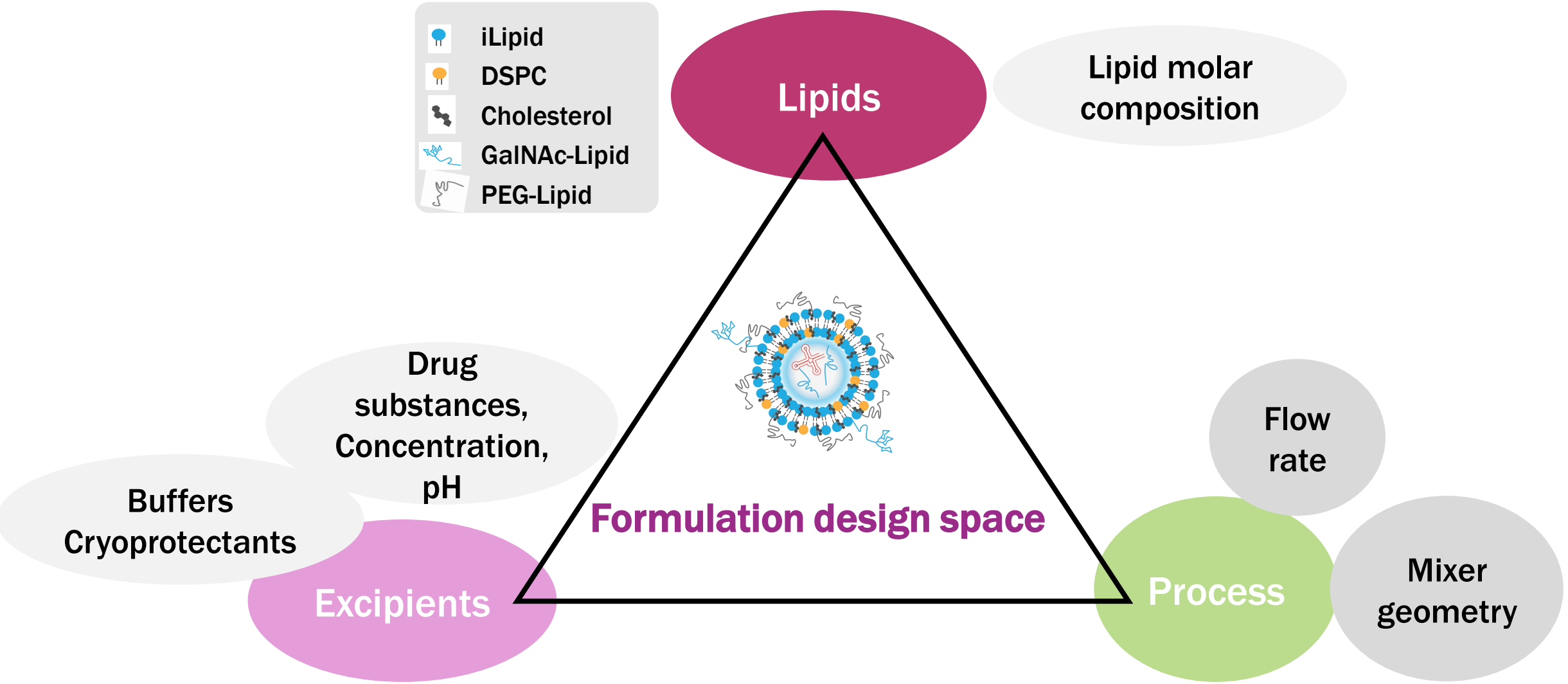
- Ionizable amino lipid
- DSPC
- Cholesterol
- GalNAc-Lipid
- PEG-Lipid

=

## Verve GalNAc-LNP

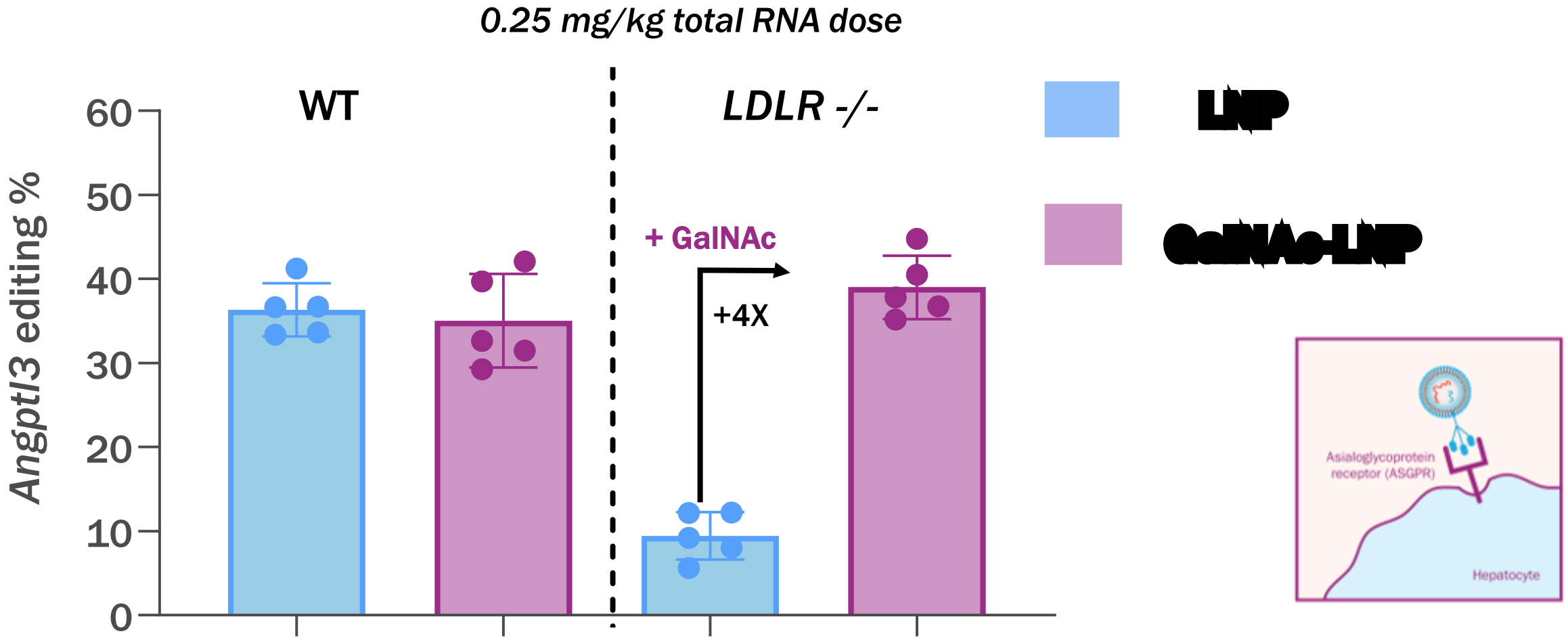


# LNP formulation considerations: Scalability and Reproducibility



# Mouse Data

# Verve's novel GalNAc-LNPs are capable of enabling editing efficiency in *LDLR knock out* mice



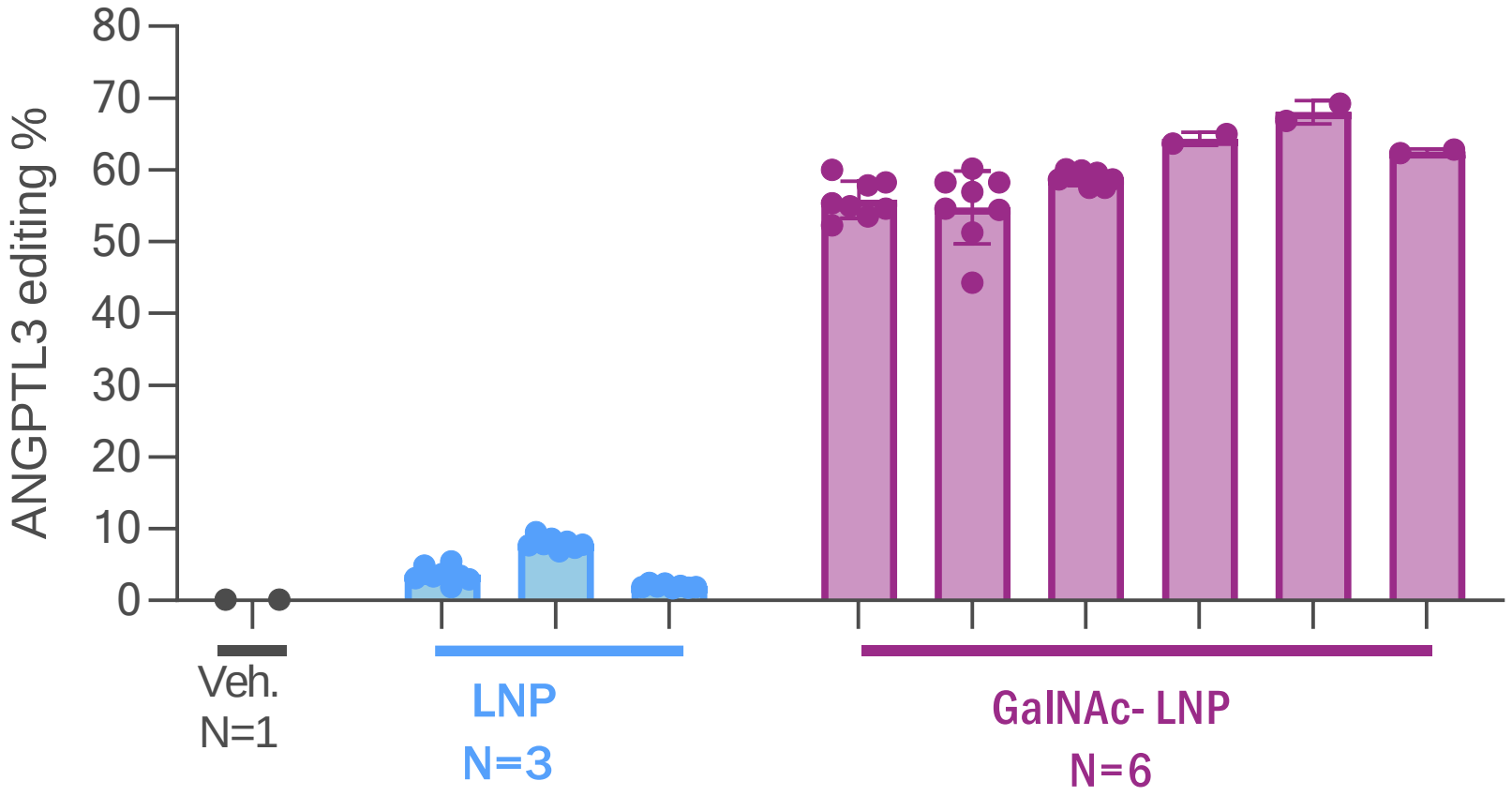

Demonstrated similar liver editing in a dose responsive manner (data not shown)

# NHP Data

# GalNAc-LNPs enabled efficient base editing in *LDLR knock out* NHPs

**Intravenous infusion of single dose**

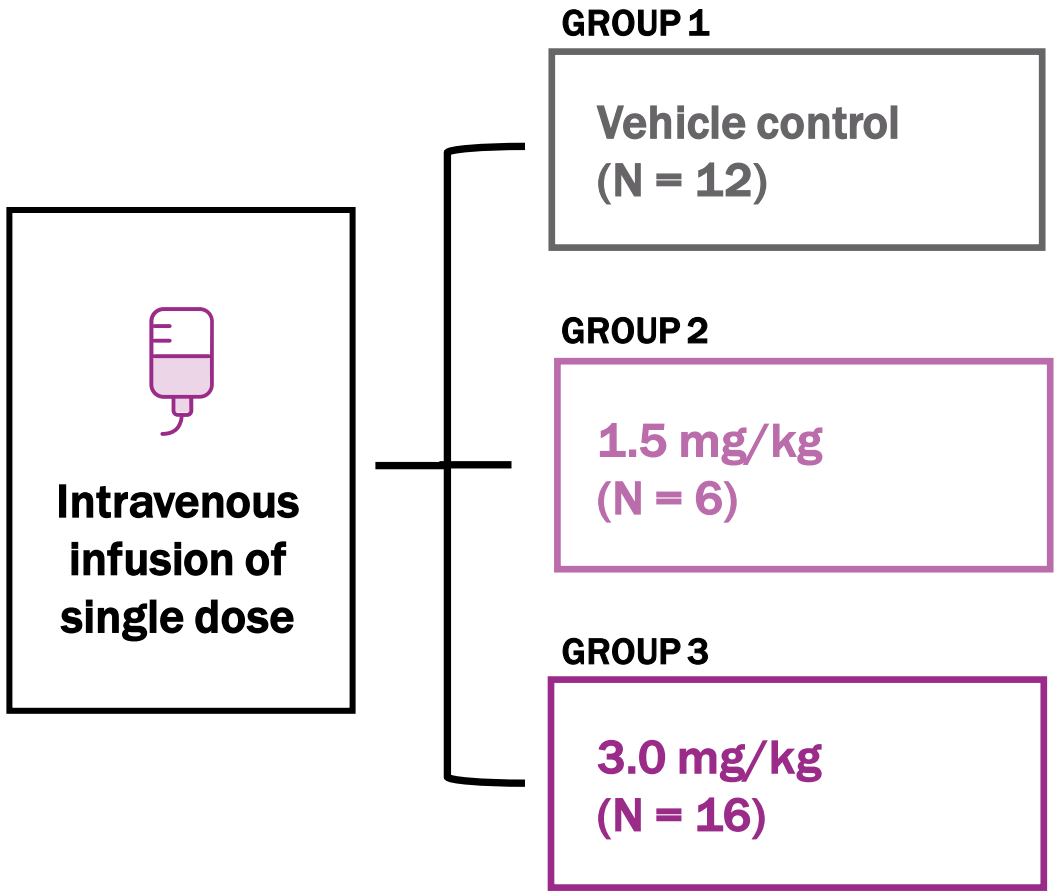
*2 mg/kg RNA dose*



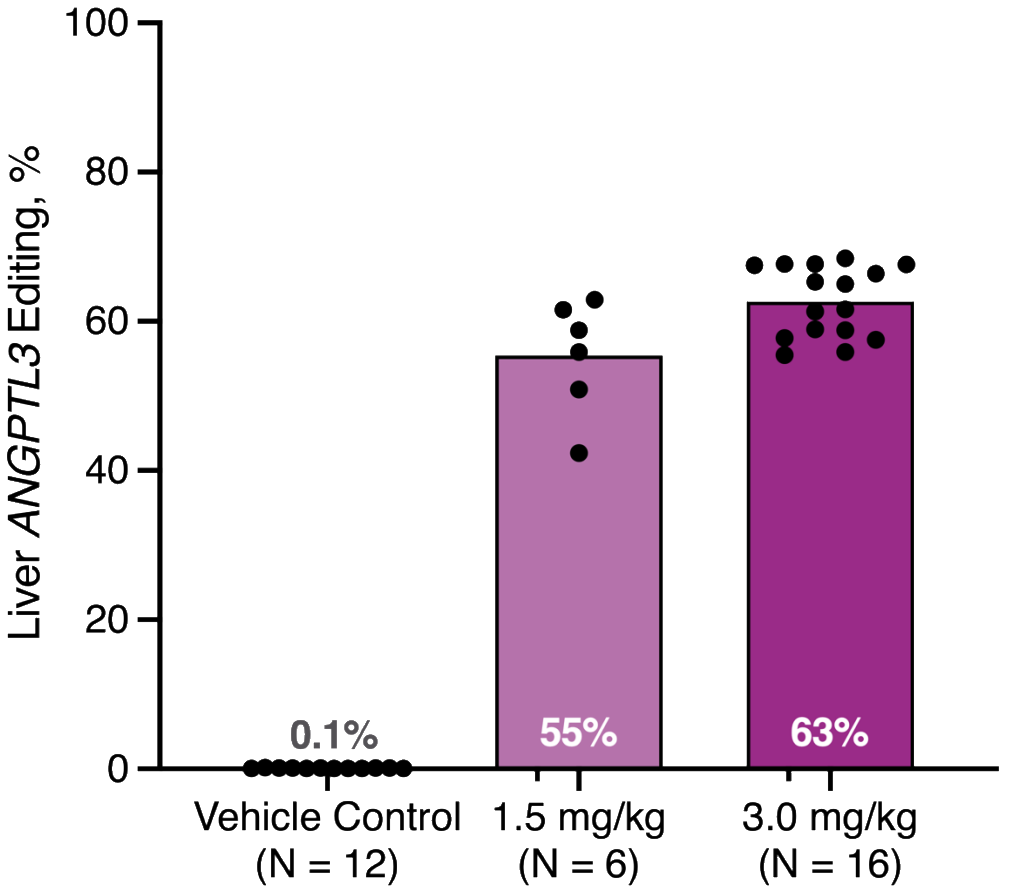

Data demonstrates ASGPR mediated robust delivery of GalNAc-LNPs to hepatocytes

# In NHPs, GalNAc-LNPs enabled mean liver *ANGPTL3* editing of 63% at higher dose

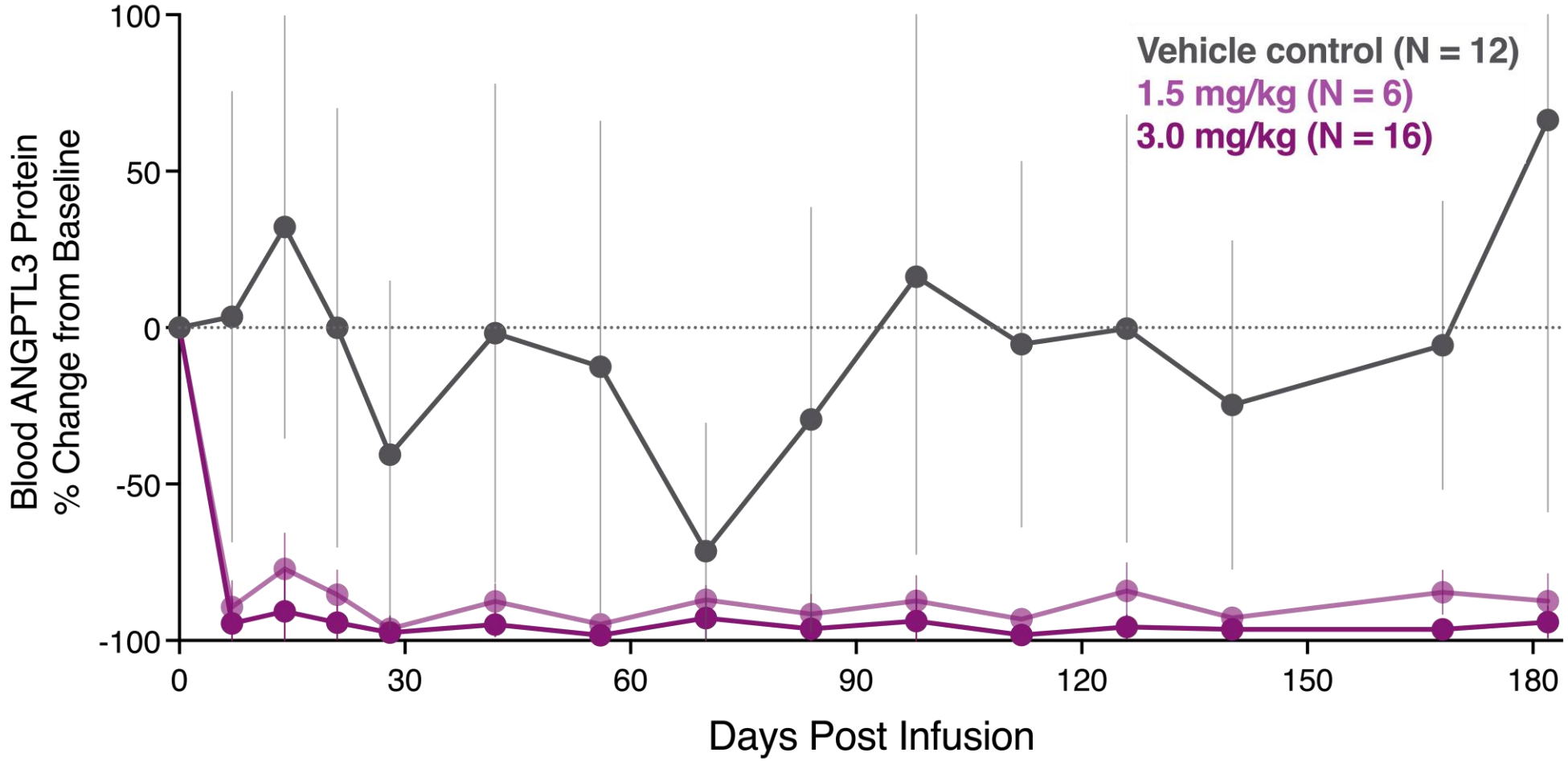
## Study of 34 NHPs




## Liver *ANGPTL3* editing



# In NHPs, VERVE GalNAc-LNPs enabled mean 96% reduction* in blood ANGPTL3 protein at higher dose



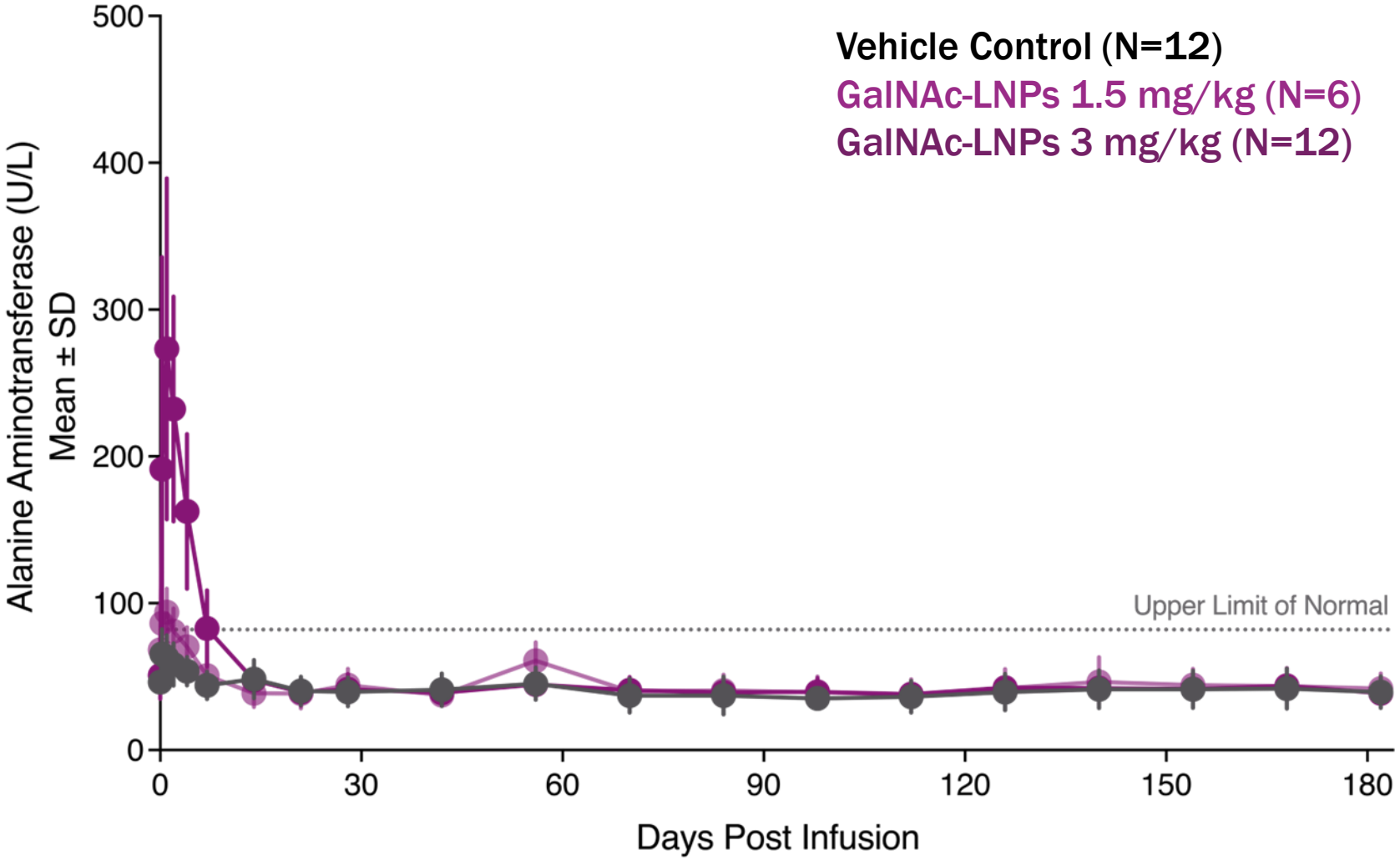

↓ 13%

↓ 89%

↓ 96%

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

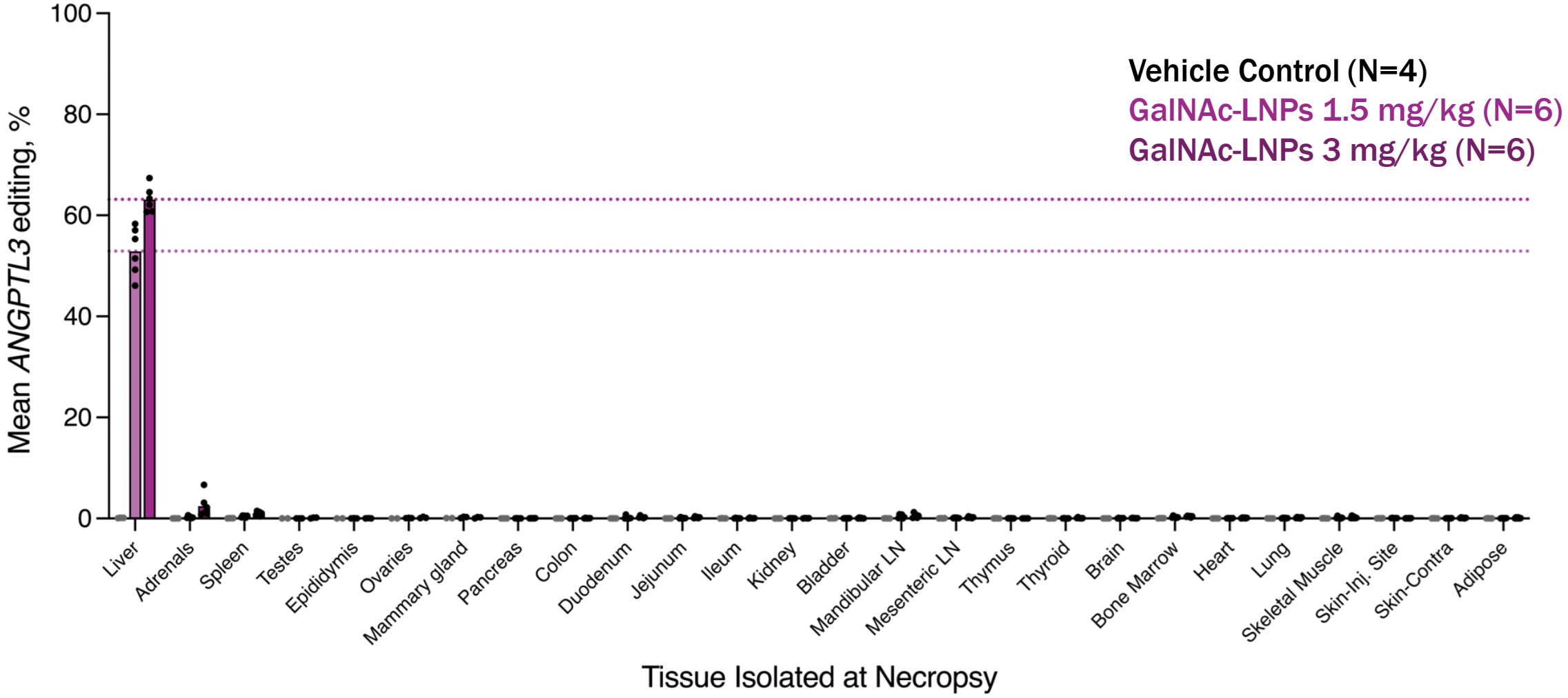
# In NHPs, VERVE GalNAc-LNPs were well-tolerated with only transient impact on ALT




## 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

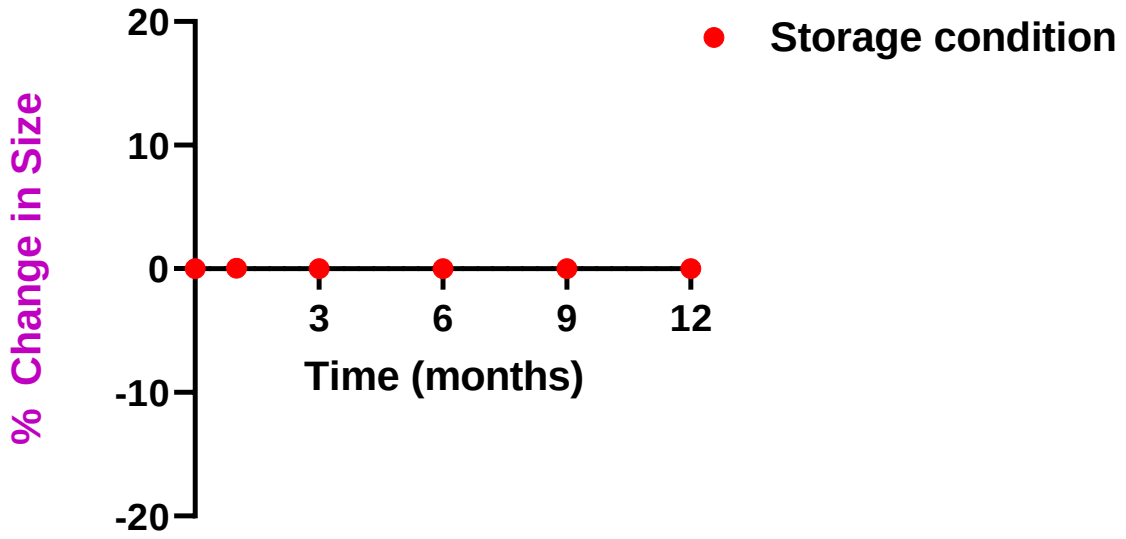
# In NHPs dosed with VERVE GalNAc-LNPs, on-target *ANGPTL3* editing* occurred mostly in the liver



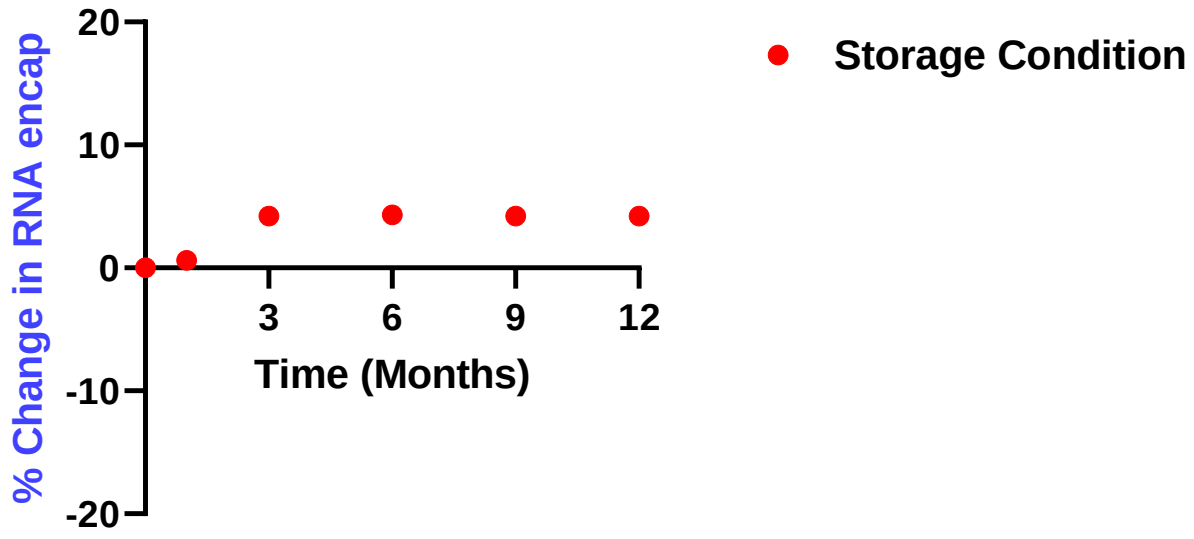

* ANGPTL3 editing assessed using targeted amplicon sequencing in tissues isolated at scheduled necropsy 6 months after dosing

# Stability of finished drug product in the storage container is an important factor for clinical supply, and ultimately commercialization.

## Particle size




## RNA encapsulation

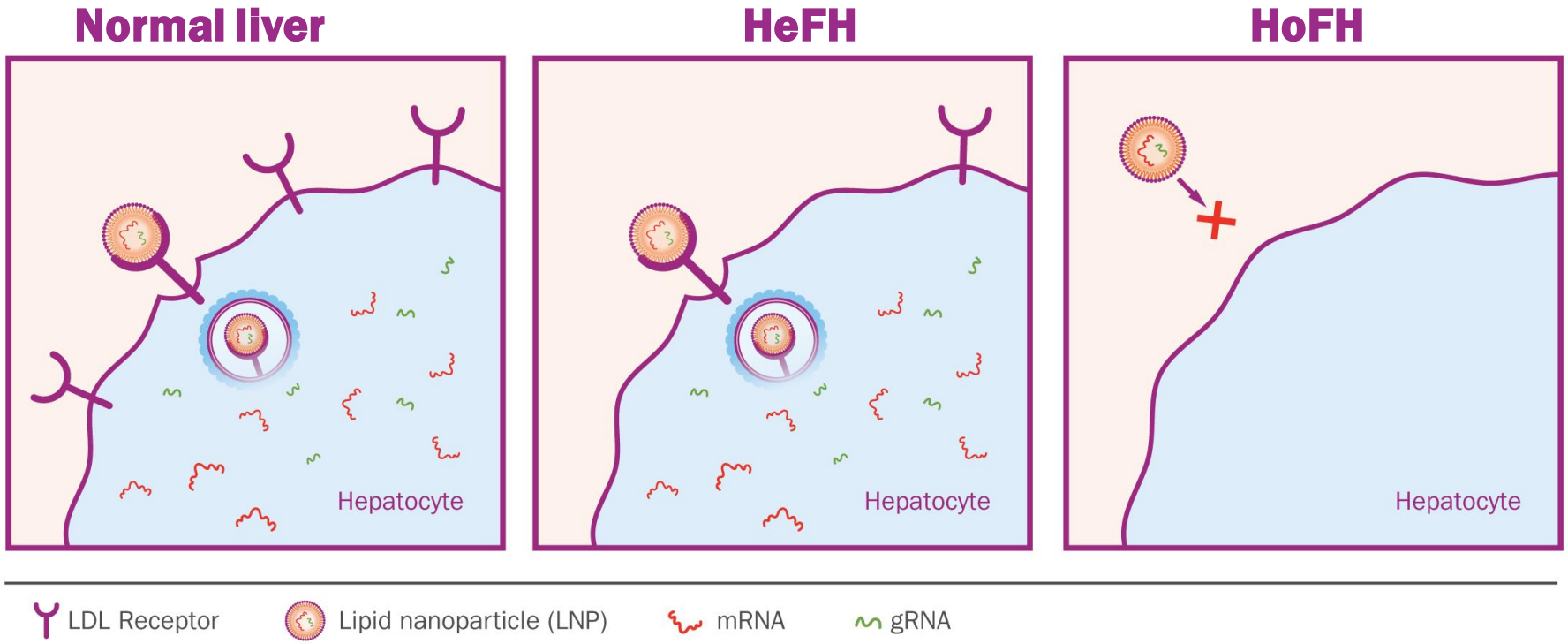


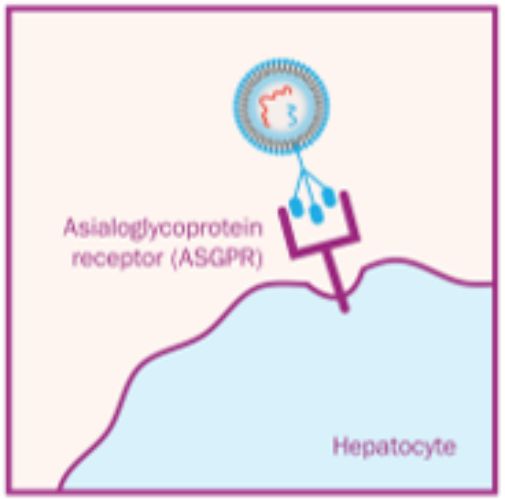

Drug product storage conditions can impact long term stability profile.

# In summary, Verve's proprietary GalNAc-LNP has a robust data package of efficacy, safety, durability and manufacturability.

- ✓ GalNAc-LNP yielded equivalent potency, regardless of LDLR status in NHP.
- ✓ Developed a scalable formulation process for well-characterized GalNAc-LNPs, that have shown a shelf-life of one year to date.
- ✓ Verve's GalNAc-LNP drug products, with proprietary GalNAc-lipid and iLipid, have demonstrated clinical readiness.

# Designed a GalNAc-LNP that bypasses the LDLR dependent pathway




**The area of hepatic LNPs is still in a maturation phase. We are one step closer to developing LNPs to advance potency, safety, and address specific patient populations**

# Acknowledgements


## Key Contributors

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