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

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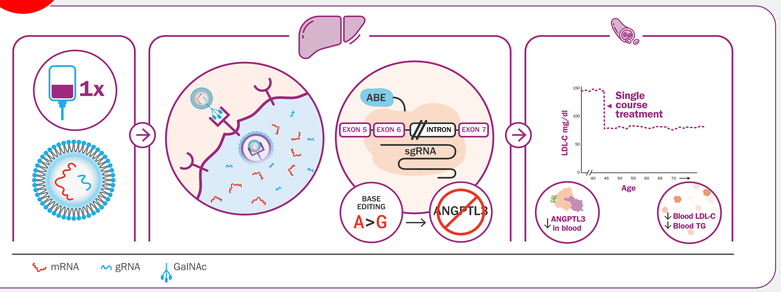
GOAL

GOAL OF VERVE'S ANGPTL3 PROGRAM: turn off gene (permanently) in liver with base editing to lower LDL-C and treat ASCVD



BACKGROUND:

- Lowering cumulative exposure to low-density lipoprotein cholesterol (LDL-C) is the primary treatment for atherosclerotic cardiovascular disease (ASCVD)
- The majority of patients in the current chronic care model fail to achieve adequate LDL-C lowering.
- Durable inactivation in the liver of a cholesterol-raising gene with a one-time therapy offers potential to address this unmet need.

TWO PATIENT POPULATIONS WITH HIGH UNMET NEED:

- **ASCVD not at LDL-C goal on oral standard of care (SOC) therapy + PCSK9i:** in the ORION-9, -10, and -11 studies of inclisiran, 32% of patients did not attain LDL-C <70 mg/dl even on oral (statin) + PCSK9 siRNA (inclisiran)ev (Wright et al. 2021)
- **Homozygous familial hypercholesterolemia:** In a global registry of HoFH patients, 47% did not attain LDL-C goal even on 5 lipid-lowering therapies (Tromp et al. 2022)

ANGPTL3 – VALIDATION FROM HUMAN PHARMACOLOGY

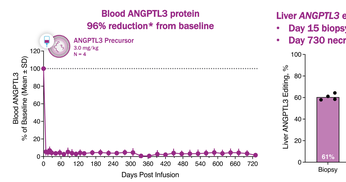
- **ASCVD not at LDL-C goal on oral SOC + PCSK9i:** LDL-C reduced by 50% with evinacumab in trial of ASCVD patients with LDL-C ≥ 70 mg/dl on oral+PCSK9i therapy (Rosenson et al. 2020)
- **Homozygous familial hypercholesterolemia:** LDL-C reduced by 52% in registrational trial of evinacumab (Evkeeza™) in HoFH patients on maximum lipid-lowering therapy (Raal et al. 2020)
- **Blood ANGPTL3 reduction of ~90%** has lowered LDL-C by ~40% in prior studies of an antisense oligonucleotide or siRNA targeting ANGPTL3

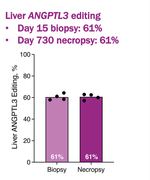
ANGPTL3 – VALIDATION FROM HUMAN GENETICS

- **Homozygous *ANGPTL3* deficiency** ('human knockout') individuals with very low LDL-cholesterol and no known adverse effects (Minicocci et al. 2012)
- **Heterozygous *ANGPTL3* deficiency** individuals with lower LDL-C and resistant to ASCVD (Stitziel et al. 2017)

1 LIVER SAFETY: Is long-term and potent suppression of ANGPTL3 in NHPs associated with any detectable liver toxicity?

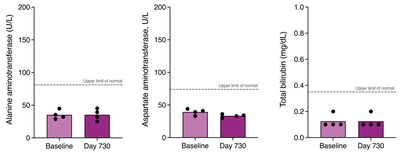
ANGPTL3 precursor: potent and durable in NHPs
2-year data: >90%↓ in blood ANGPTL3, >60% liver editing





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

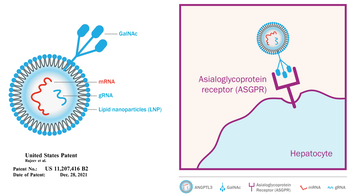
ANGPTL3 precursor in non-human primates
2-year data: no change from baseline in liver biomarkers detected



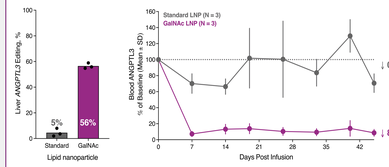
Mean and individual values displayed reflect measurement in each of 4 NHP prior to dosing with an ANGPTL3 precursor at 3 mg/kg and at time of necropsy.

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

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



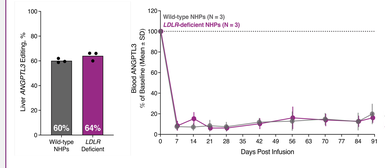
GalNAc LNP ANGPTL3 precursor enables efficient liver editing in LDLR-deficient* non-human primates



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

Liver *ANGPTL3* editing displayed represent values for non-human primates treated with 2 mg/kg of an ANGPTL3 precursor using a standard orGalNAc 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 enables similar editing efficiency in wild-type and LDLR-deficient* NHPs



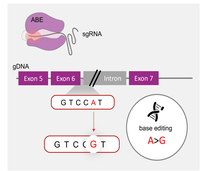
*Verve's NHP model of homozygous familial hypercholesterolemia with >90% reduction in liver *LDLR* protein (Kasiewicz et al., *bioRXiv*. 2021)

Liver *ANGPTL3* editing displayed represent values for wild-type or LDLR-deficient non-human primates treated with 2 mg/kg of an ANGPTL3precursor (N = 3 in each group). Reductions in ANGPTL3 reported as time-weighted average % change from baseline from days 28 to 90.

3 POTENCY AND POTENTIAL OFF-TARGET EDITING:

Can chemically modified base editing / gRNA configurations preserve potency while minimizing potential off-target editing?

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

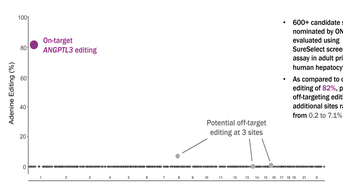


Site selected based on results of screening assays performed for 29 potential sites in the ANGPTL3 gene.

Key features of *ANGPTL3* target DNA site:

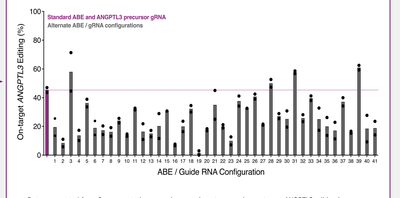
- Precise A-to-G base-pair change: disrupts splice donor site and introduces a downstream premature stop codon
- Site is unique: 23 DNA base pair protospacer/PAM sequence not found anywhere else in the human genome, expected to minimize potential off-target editing
- Site is consistent: >99.98% of sequenced 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



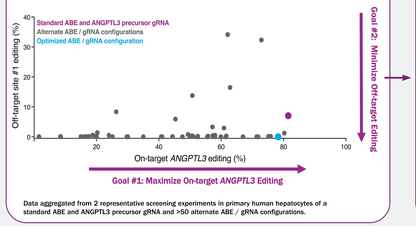
- 600+ candidate sites nominated by ONE-seq evaluated using SureSelect screening assay in adult primary human hepatocyte cells
- As compared to on-target editing of 82%, potential off-targeting editing at 3 additional sites ranging from 0.2 to 7.1%

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



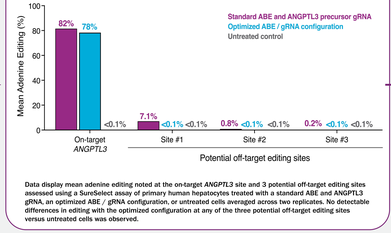
Data aggregated from 2 representative screening experiments assessing on-target *ANGPTL3* editing in adult primary human hepatocytes. As compared to mean editing of 45% with standard ABE and ANGPTL3 precursor gRNA, noted editing ranging from 1.6 to 61% with 41 alternate ABE / gRNA configurations.

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



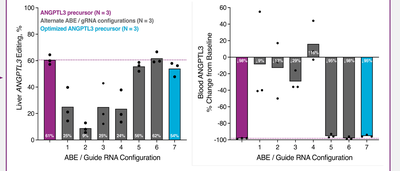
Data aggregated from 2 representative screening experiments in primary human hepatocytes of a standard ABE and ANGPTL3 precursor gRNA and >50 alternate ABE / gRNA configurations.

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



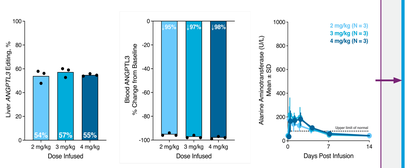
Data display mean adenine editing noted at the on-target *ANGPTL3* site and 3 potential off-target editing sites assessed using a SureSelect assay of primary human hepatocytes treated with a standard ABE and ANGPTL3 gRNA, an optimized ABE / gRNA configuration, or untreated cells averaged across two replicates.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

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



Data aggregated across two experiments In non-human primates 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%

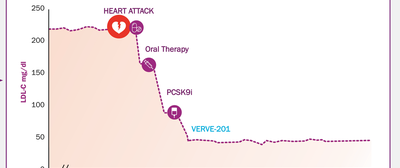


In NHPs dosed with 2, 3, or 4 mg/kg of VERVE-201cyno (N = 3 in each dosing group), observed liver *ANGPTL3* editing ranging from 54 to 57% and blood ANGPTL3 protein reduction assessed at day 15 ranging from 95 to 98%. Transient increases in ALT and AST resolved by day 7, no change in total bilirubin.

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

- **Significant unmet need** for additional LDL-C lowering in ASCVD not at goal on oral + PCSK9i therapy & HoFH
- **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 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.