Verve Therapeutics: In Vivo CRISPR Base Editing to Treat ASCVD

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Disclosure

I am an employee of Verve Therapeutics.

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Chronic care model results in poor control of cumulative blood LDL-C exposure

Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44.
Single-course treatment for ASCVD could address key unmet need: getting LDL-C as low as possible for as long as possible

Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who was treated with a single-course treatment after suffering a heart attack at age 44.
Advancing a pipeline of single-course *in vivo* gene editing programs to safely and durably lower LDL-C and treat ASCVD

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<th>PROGRAM</th>
<th>INDICATIONS</th>
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<td>Research/Lead optimization</td>
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<td>Low-density lipoprotein cholesterol (LDL-C)</td>
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<td>VERVE-101 PCSK9</td>
<td>Heterozygous familial hypercholesterolemia</td>
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<td>ASCVD not at LDL-C goal on oral therapy</td>
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<td>LDL-C &amp; Triglyceride-rich lipoprotein (TRL)</td>
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<tr>
<td>ANGPTL3</td>
<td>Homozygous familial hypercholesterolemia</td>
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<td>ASCVD not at LDL-C goal on oral + PCSK9i</td>
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New Zealand
CTA cleared
Global regulatory strategy: VERVE-101

- New Zealand CTA cleared (2Q22)
- U.K. CTA and U.S. IND expected (2H22)
- Initial clinical data expected (2023)
- First patient treated expected (mid-2022)
Today sharing three new data streams

Updated durability and safety data in non-human primates for VERVE-101 precursor out to 616 days and VERVE-101 out to 1 year following infusion

New data from VERVE-101mu GLP toxicology study in mouse heterozygous FH disease model

Enhanced potency of proprietary GalNAc-modified LNPs to deliver gene editing therapies to wild-type NHPs
VERVE-101 precursor given to non-human primates: 616 days following infusion, durable 88% reduction in blood PCSK9

VERVE-101 Precursor
3.0 mg/kg
N = 4

↓ 88% from baseline
VERVE-101 precursor given to non-human primates: 616 days following infusion, durable >60% reduction in LDL-C
VERVE-101 has been potent, durable, and well tolerated in NHPs

Primary endpoints
1. Whole liver DNA editing
2. Blood PCSK9 levels
3. Blood LDL-C levels

GROUP 1
Vehicle control
(N=10)

GROUP 2
VERVE-101
1.5 mg/kg
(N=22)

GROUP 3
VERVE-101
0.75 mg/kg
(N=4)

Safety endpoints
1. Liver function testing
2. Glucose homeostasis

T = 0
T = 2 weeks
T = 16 weeks
T = 3+ years

liver biopsy
VERVE-101: one-time intravenous infusion in non-human primates
89% blood PCSK9 reduction one year after therapy

Vehicle control (N = 10)
VERVE-101 .75 mg/kg (N = 4)
VERVE-101 1.5 mg/kg (N = 22)
VERVE-101: one-time intravenous infusion in non-human primates
68% LDL-C reduction one year after therapy

Vehicle control (N = 10)
VERVE-101 0.75 mg/kg (N = 4)
VERVE-101 1.5 mg/kg (N = 22)
VERVE-101: one-time intravenous infusion in non-human primates
No impact on fasting glucose

Vehicle control (N = 10)
VERVE-101 0.75 mg/kg (N = 4)
VERVE-101 1.5 mg/kg (N = 22)
VERVE-101: one-time intravenous infusion in non-human primates
Transient impact on alanine aminotransferase (ALT)

Vehicle control (N = 10)
VERVE-101 0.75 mg/kg (N = 4)
VERVE-101 1.5 mg/kg (N = 22)
VERVE-101: one-time intravenous infusion in non-human primates

No impact on total bilirubin
VERVE-101mu GLP toxicity study in wild-type and HeFH mouse models

Supports efficacy and safety
6-month GLP toxicity study of VERVE-101 mouse surrogate
528 mice: wild-type or Ldlr\textsuperscript{+/-} (HeFH model)

100-fold dose range
from 0.05 to 5 mg/kg

Wild-type mice
Vehicle Control (N = 66)
0.05 mg/kg (N = 66)
0.5 mg/kg (N = 66)
5.0 mg/kg (N = 66)

Ldlr\textsuperscript{+/-} Mice (HeFH model)
Vehicle Control (N = 66)
0.05 mg/kg (N = 66)
0.5 mg/kg (N = 66)
5.0 mg/kg (N = 66)

Key endpoints:
• PCSK9 protein and liver editing
• Clinical pathology
• Histopathology

Day 1
Day 2
Day 16
Day 180

Three necropsy timepoints
No observed difference in PCSK9 editing or protein reduction between wild-type and HeFH mouse models with VERVE-101mu

Liver PCSK9 editing

<table>
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<tr>
<th>% Adenine Editing (Mean)</th>
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<tr>
<td>Vehicle Control</td>
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<tr>
<td>0.05 mg/kg</td>
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<td>0.5 mg/kg</td>
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Blood PCSK9

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<th>Blood PCSK9 (% Change from Baseline)</th>
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<tbody>
<tr>
<td>Vehicle Control</td>
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<tr>
<td>0.05 mg/kg</td>
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<tr>
<td>0.5 mg/kg</td>
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<tr>
<td>5.0 mg/kg</td>
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* Outliers at 0.05 mg/kg dose being investigated
VERVE-101: on track to treat first FH patient mid-2022
VERVE-101: on track for clinical trial initiation in mid-2022

~40 patients with HeFH
LDLR mutation, ASCVD, LDL>100, not on PCSK9 Tx

Part A: Single Ascending Dose
- High dose
- Int. dose
- Low dose
- Starting dose
- n=3-6 per group participant staggering, sentinels

Expansion Cohorts
- Part B: 12–20 additional participants get one selected dose
- Part C: Second dose offered to participants in part A who received lower dose than part B

Study Timing
- Screening and stabilization
- VERVE-101 IV administration
- 3-months
- End of interventional study
- Long-term follow-up

Periodic interim analyses of 3-month data expected to enable early readouts of:
- Safety and tolerability
- Blood PCSK9 reduction
- LDL-C, ApoB reduction

Final clinical trial design subject to IND/regulatory discussions
Significant unmet need in achieving target LDL-C for patients with HeFH and ASCVD

Precise A-to-G edit inactivates liver PCSK9 with a single intravenous infusion

Durable and potent effect – LDL-C ↓ by 68% in non-human primates 1 year after dosing

Well-tolerated in mice GLP toxicity study, across a 100-fold dosing range

CTA submission cleared in New Zealand with additional global filings in process

VERVE-101 Summary: on track for clinical trial initiation in mid-2022
Innovation in delivery of *in vivo* gene-editing products

standard LNPs have limited uptake in HoFH models
Verve solution: addition of proprietary GalNAc targeting ligand to LNP allows delivery through ASGPR.

**United States Patent**
Rajeev et al.

**Date of Patent:** Dec. 28, 2021
Base editing of ANGPTL3 via GalNAc-LNPs reduced blood ANGPTL3 by 94% - 97% in NHP model of HoFH

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

- ~ 94% reduction
- ~ 97% reduction
How do GalNAc-LNPs perform in wild-type NHP?

Dose ranging study of ANGPTL3 precursor in NHP

Intravenous infusion

- Standard LNP
  - 0.75 mg/kg (N = 3)
  - 1.5 mg/kg (N = 3)
  - 3.0 mg/kg (N = 3)

- LNP + GalNAc
  - 0.75 mg/kg (N = 3)
  - 1.5 mg/kg (N = 3)
  - 3.0 mg/kg (N = 3)

LNPs are identical other than the addition of GalNAc-lipid

Key endpoints at Day 15 necropsy
- Liver ANGPTL3 editing
- Blood ANGPTL3 protein level
- Biodistribution

Day 0

Day 15
In wild-type NHPs, GaINAc-LNP leads to increased ANGPTL3 editing potency compared with standard LNP.

<table>
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<tr>
<th>Dose of ANGPTL3 Precursor</th>
<th>Mean Adenine Editing, %</th>
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<tbody>
<tr>
<td>.75 mg/kg</td>
<td>5.4%</td>
</tr>
<tr>
<td>1.5 mg/kg</td>
<td>15%</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>64%</td>
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</table>

Standard LNP (N = 3)  
LNP + GaINAc (N = 3)
In wild-type NHPs, GalNAc-LNP shows up to 98% reduction in blood ANGPTL3, reflecting improved consistency versus standard LNP.
Addition of GalNAc to LNP did not alter safety profile
Transient impact on alanine aminotransferase

Standard LNP 0.75 mg/kg (N = 3)
LNP + GalNAc 0.75 mg/kg (N = 3)

1.5 mg/kg (N = 3)
3.0 mg/kg (N = 3)
Specific delivery to the liver with LNP + GalNAc

Standard LNP 1.5 mg/kg (N = 3)
LNP + GalNAc 1.5 mg/kg (N = 3)
Proprietary GalNAc-LNPs are a potentially best-in-class technology to deliver genetic medicines to the liver

**DESIGNED TO**
- bypass LDLR for HoFH patient population

**OBSERVED TO BE**
- Potent in wild-type NHPs
- Consistent
- Liver-specific ASGPR uptake
Conclusion #1: VERVE-101 first-in-human dosing on track for mid-2022

VERVE-101 reduced blood PCSK9 up to 89% and LDL-C up to 68% in non-human primates one year following infusion.

Conclusion #2: Growing proprietary tool kit for therapeutic delivery

Mouse surrogate of VERVE-101 achieves efficient editing of Pcsk9 and is well-tolerated in both wild-type and HeFH mouse models.

Proprietary Verve LNPs enable delivery of ANGPTL3 precursor in HoFH NHP model, with new evidence of enhanced potency in wild-type NHPs as well.

Verve is on track to deliver on key milestones of first-in-human dosing of VERVE-101 and announcement of ANGPTL3 drug candidate in 2022.