Innovative LNPs for Gene Editing Applications

Padma Malyala
Vice President- Formulation and Analytical Development, Verve Therapeutics

TIDES USA 2023
7 May 2023
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 company’s research and development plans and the potential advantages and therapeutic potential of the company’s programs, including VERVE-201. 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, its product candidates; advance its product candidates in clinical trials; initiate, enroll and complete its ongoing and future 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 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.
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:
- LDL
- TRL
- Lp(a)

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

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

- **Normal liver**: LDL Receptor present.
- **Heterozygous FH (HeFH)**: LDL Receptor partially present.
- **Homozygous FH (HoFH)**: LDL Receptor completely absent.
Developed ASGPR-targeted GaINAc-LNPs with proprietary ionizable lipid (iLipid) and GaINAc ligand: potential best-in-class for delivery of genetic medicines to liver.
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

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

Rodent screening

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

Formulation design space

Lipids

- iLipid
- DSPC
- Cholesterol
- GalNAc-Lipid
- PEG-Lipid

Lipid molar composition

Drug substances, Concentration, pH

Buffers Cryoprotectants

Excipients

Process

- Flow rate
- Mixer geometry
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

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

Intravenous infusion of single dose

2 mg/kg RNA dose
In NHPs, GalNAc-LNPs enabled mean liver ANGPTL3 editing of 63% at higher dose.

Study of 34 NHPs

Intravenous infusion of single dose

GROUP 1
Vehicle control (N = 12)

GROUP 2
1.5 mg/kg (N = 6)

GROUP 3
3.0 mg/kg (N = 16)

Liver ANGPTL3 editing

- Vehicle Control (N = 12)
- 1.5 mg/kg (N = 6)
- 3.0 mg/kg (N = 16)

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

Vehicle control (N = 12)
1.5 mg/kg (N = 6)
3.0 mg/kg (N = 16)

↓ 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

Vehicle Control (N=12)
GalNAc-LNPs 1.5 mg/kg (N=6)
GalNAc-LNPs 3 mg/kg (N=12)
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.

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

Aaron Beach
Souvik Biswas
Lisa Kasiewicz
Kallanthottathil Rajeev

Nicholas Cox
Andrew Dorsey
Zach Glass
Ash Nagpal
Huiyan Ren

Alexandra Chadwick
Chris Cheng
Chaitali Datta
Sara Garcia
Anne Marie Mazzola
Kiran Musunuru
Ellen Rohde
Kui Wang

Andrew Ashe
Andrew Belling
Sekar Kathiresan