

A decorative graphic on the left side of the slide consisting of several thick, curved, overlapping lines in shades of purple, green, and blue, extending from the top left towards the bottom center.

VERVE-101 – an investigational single-course gene editing medicine targeting *PCSK9* – durably and potently lowers *PCSK9* and LDL-C concentrations in non-human primates

**Amit V. Khera MD, MSc
Verve Therapeutics**

Paul Dudley White International Scholar Awardee
ATVB Council Outstanding Research Awardee
American Heart Association Scientific Sessions
November 6, 2022

Forward looking statements

This press release 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-101. All statements, other than statements of historical facts, contained in this press release, 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 press release 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.

Solution to ASCVD revealed by human genetics and pharmacology: get LDL-C as low as possible for as long as possible



ESC

European Society
of Cardiology

European Heart Journal (2022) **43**, 249–250

<https://doi.org/10.1093/eurheartj/ehab532>

Braunwald's Corner

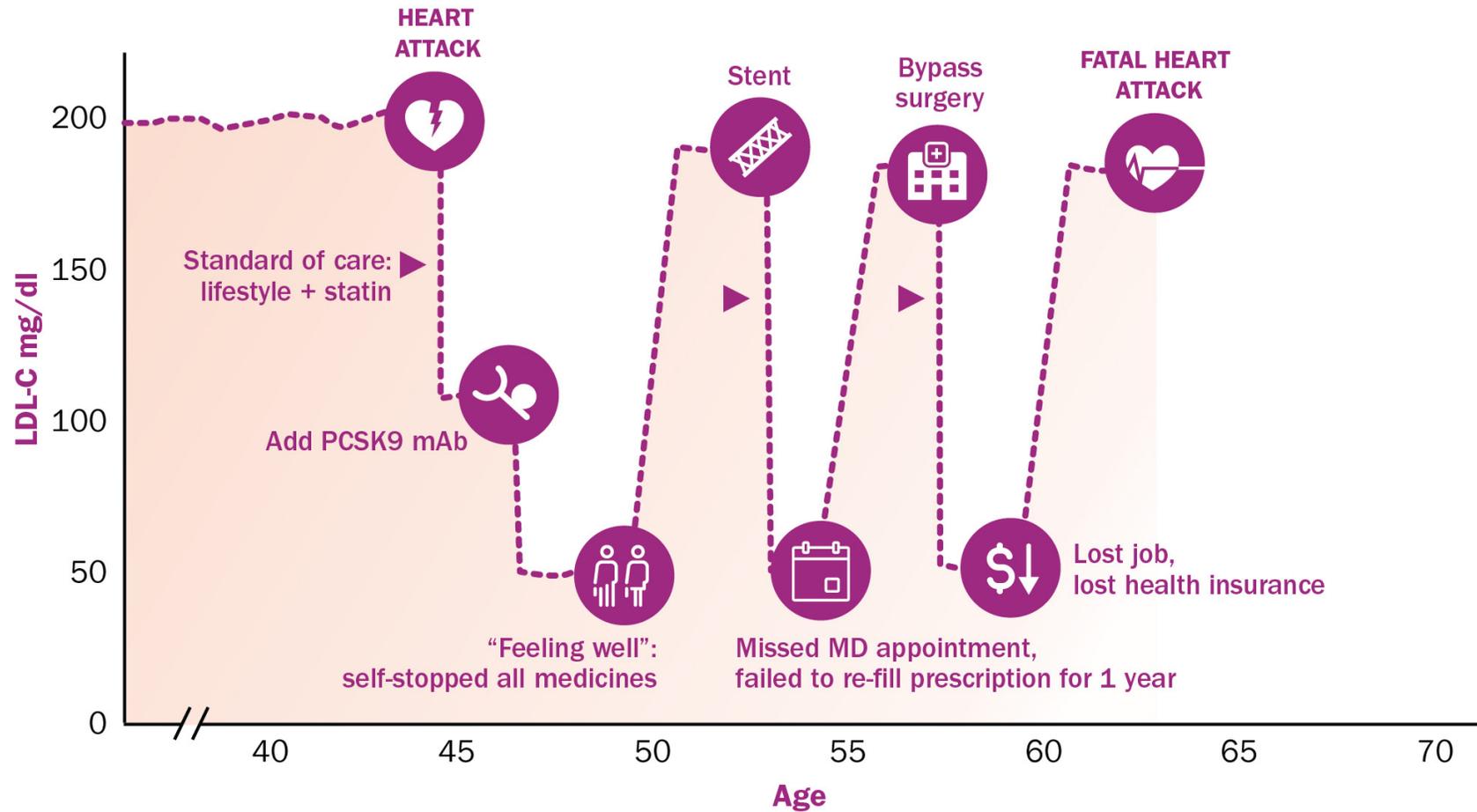
How to live to 100 before developing clinical coronary artery disease: a suggestion

Eugene Braunwald  ^{1,2*}

¹TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and ²Department of Medicine, Harvard Medical School, Boston, MA, USA

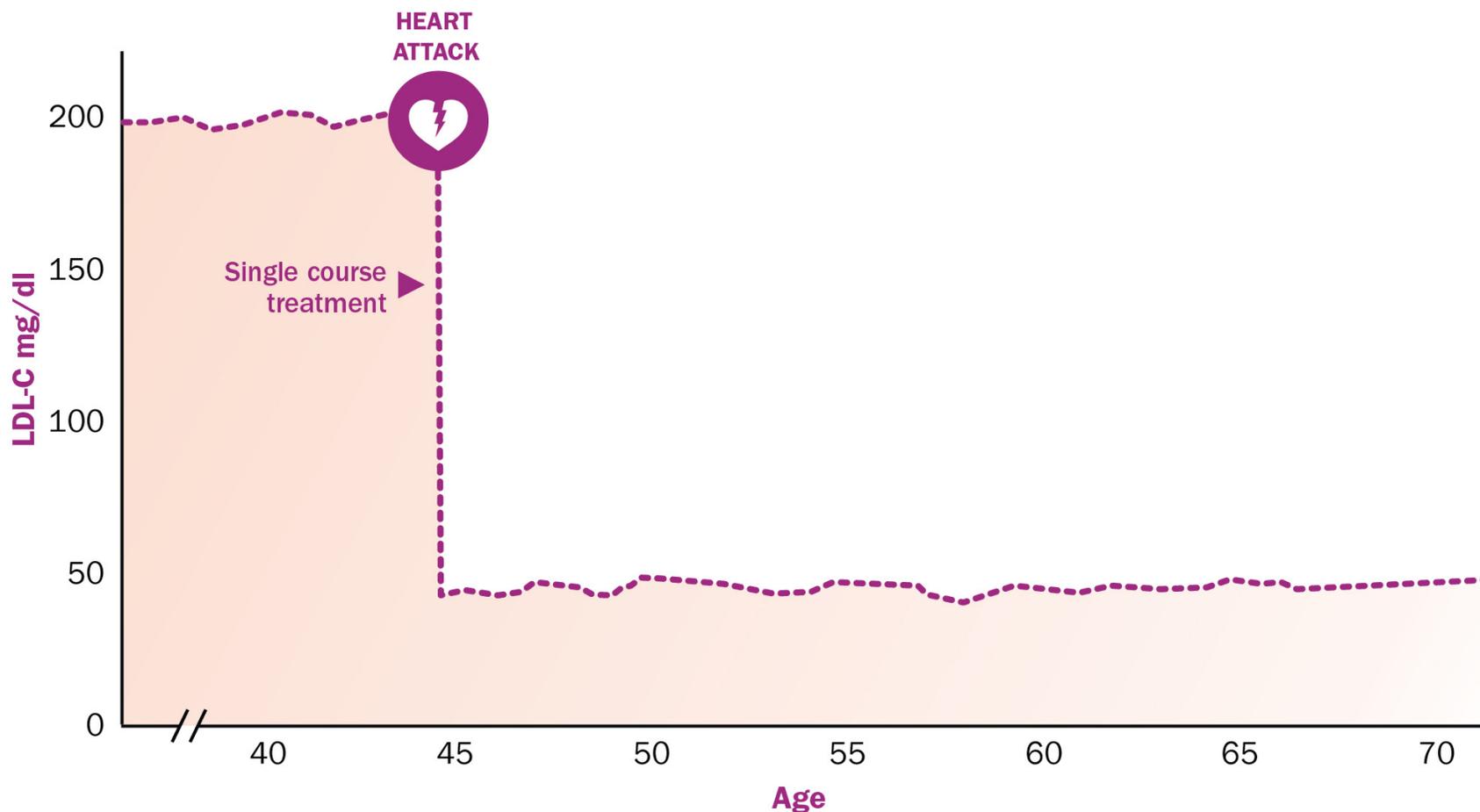


Unmet need: current chronic care model for ASCVD results in poor control of cumulative blood LDL-C exposure



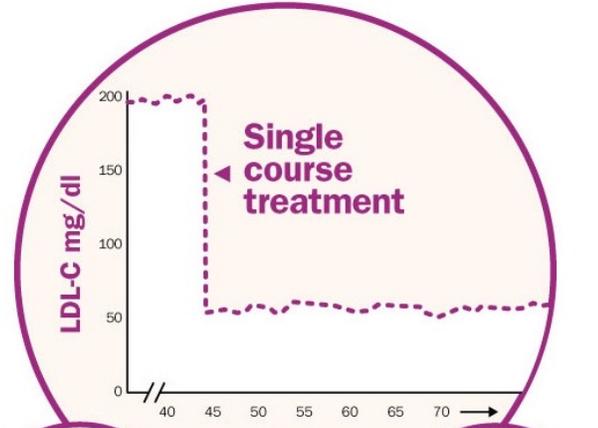
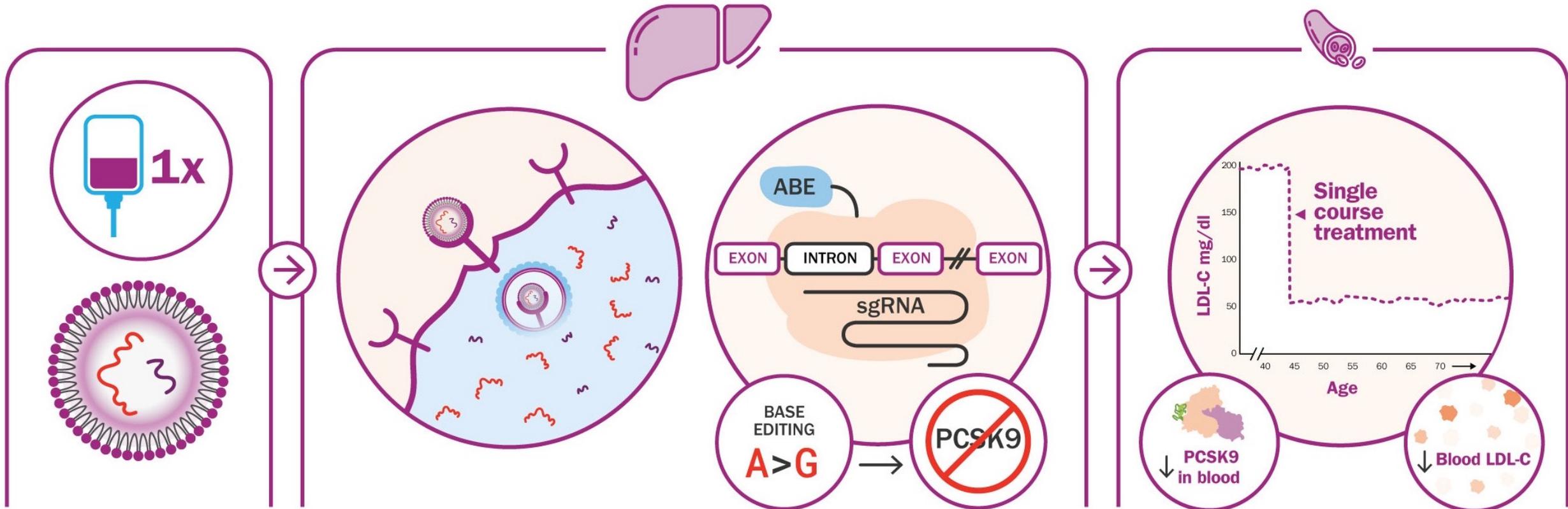
Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

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 began standard-of-care treatment after suffering a heart attack at age 44

VERVE-101 designed to turn off *PCSK9* gene with base editing to durably lower LDL-C and treat ASCVD

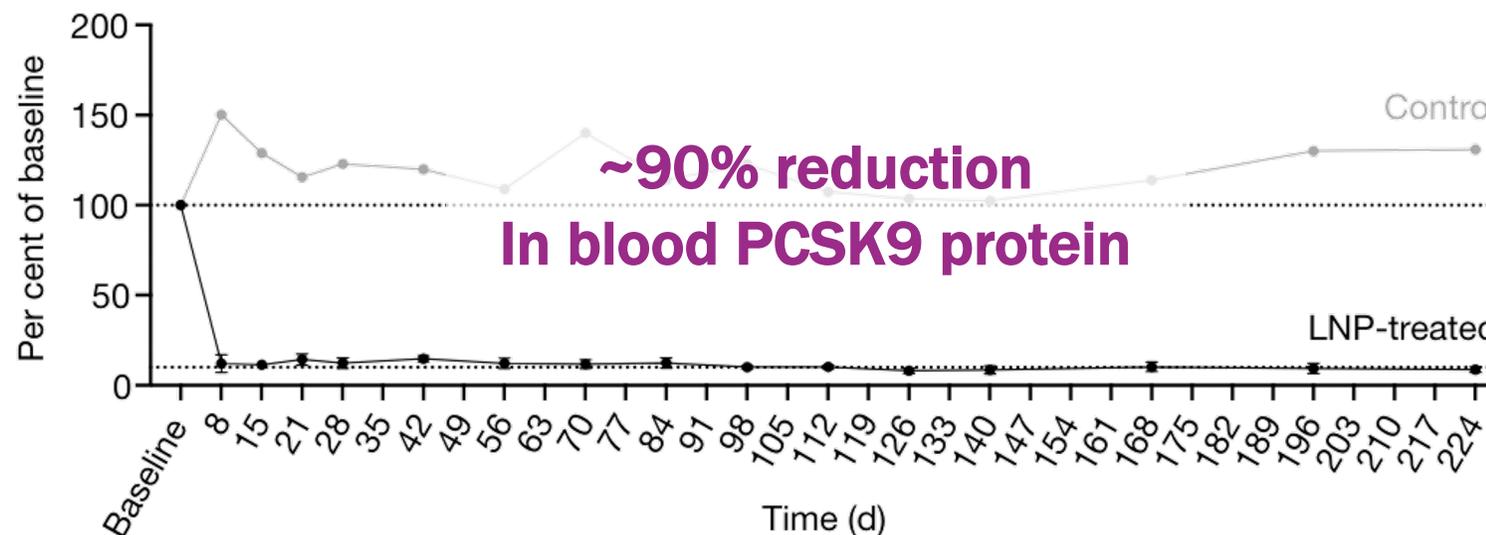


mRNA gRNA

Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

4 non-human primates treated with 3.0 mg/kg of VERVE-101 precursor



Having demonstrated proof-of-concept in non-human primates, 4 key questions prior to initiation of a clinical trial

A purple circular icon containing a white line graph with three data points and an upward trend, representing potency or efficacy.

Potency: what degree of liver *PCSK9* editing can be achieved?

A purple circular icon containing a white hourglass, representing durability or long-term effects.

Durability: what evidence supports potential for permanent effect?

A purple circular icon containing a white clipboard with a checklist and a line graph, representing tolerability or safety.

Tolerability: what is the safety profile of VERVE-101 in nonclinical studies?

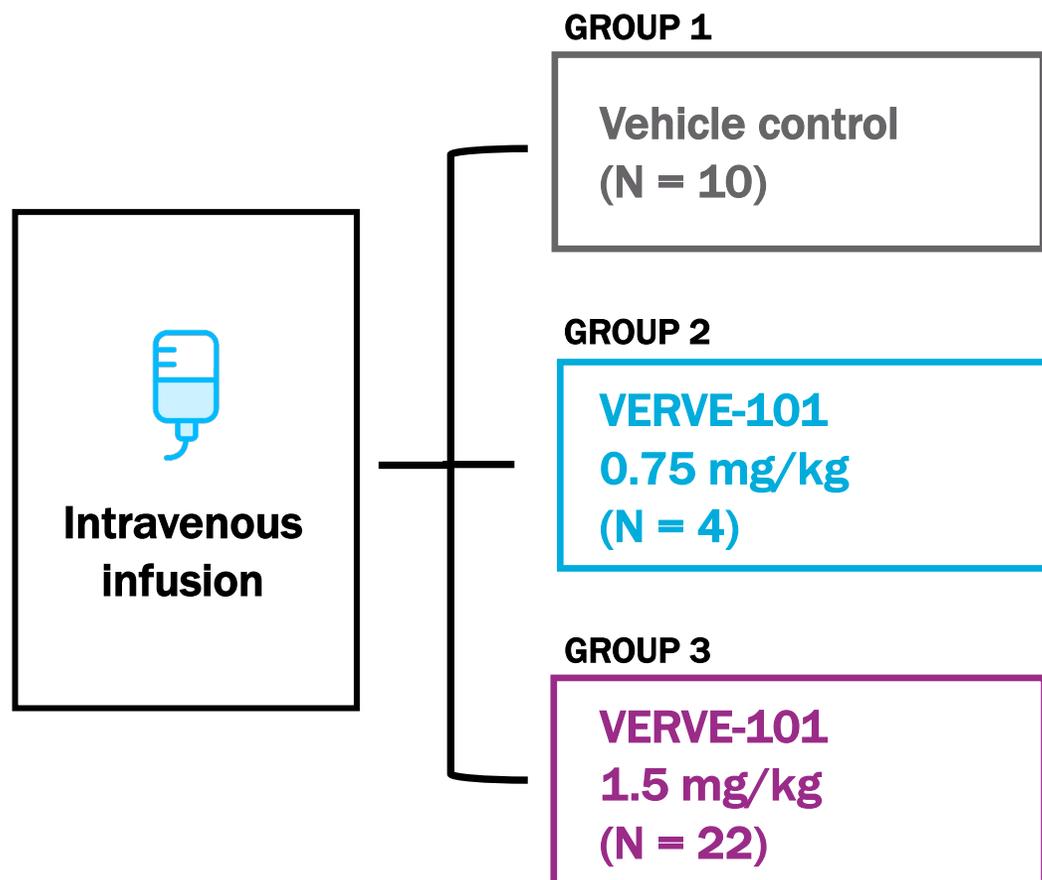
A purple circular icon containing a white family tree diagram with three generations, representing biodistribution or inheritance.

Biodistribution: Does VERVE-101 edit get transmitted to offspring?

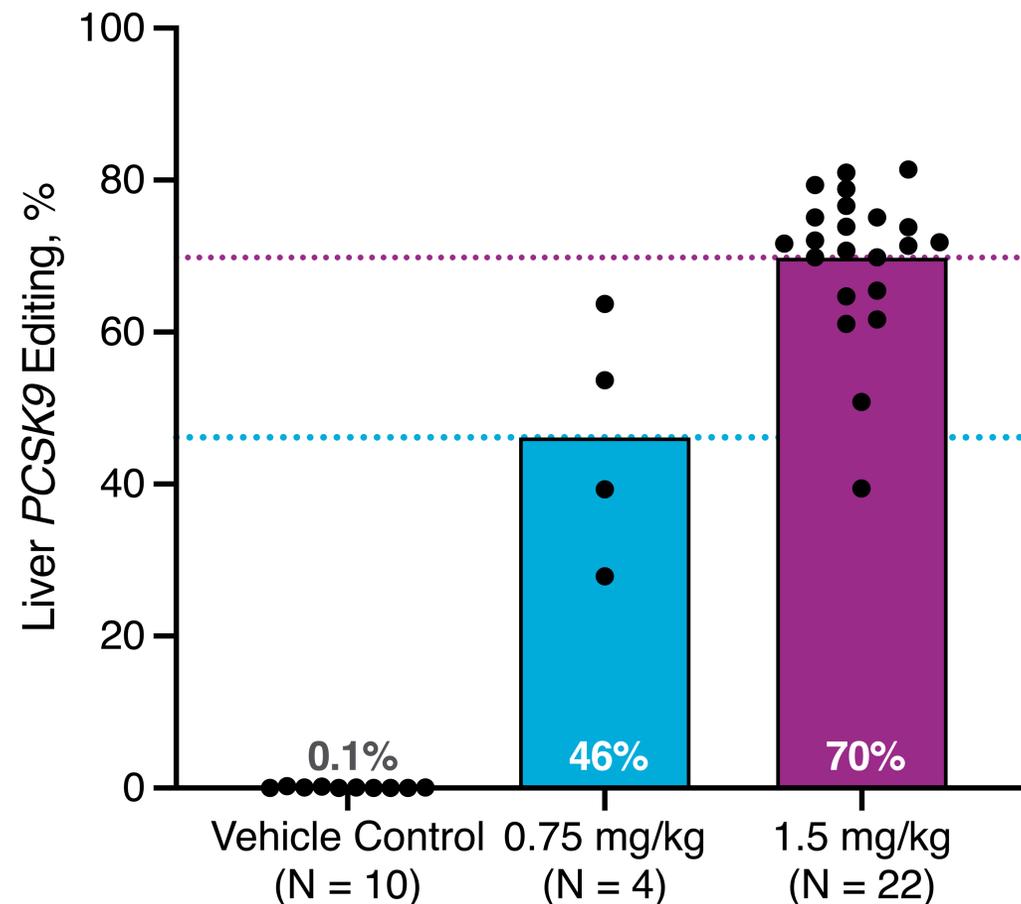
In non-human primates, a single infusion of VERVE-101 achieved mean liver *PCSK9* editing of 70% at higher dose



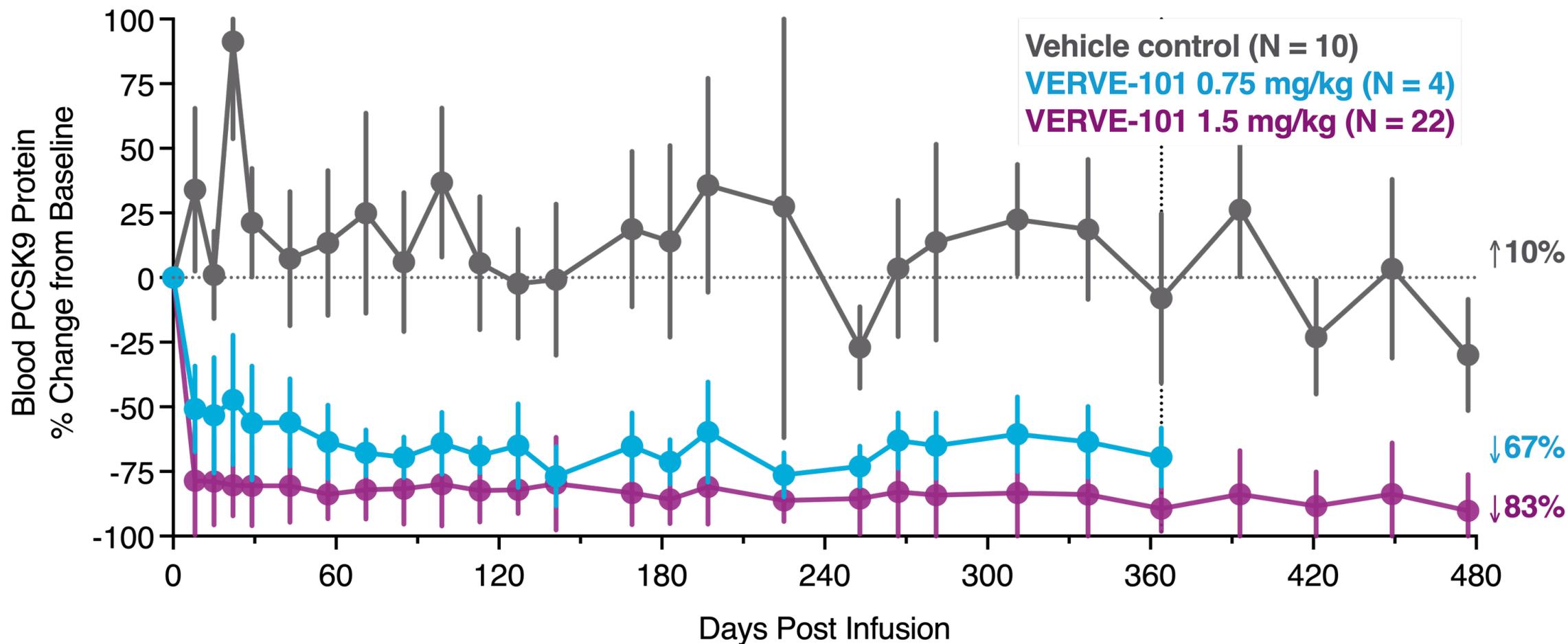
Study of 36 Non-human Primates



Efficient Liver *PCSK9* editing



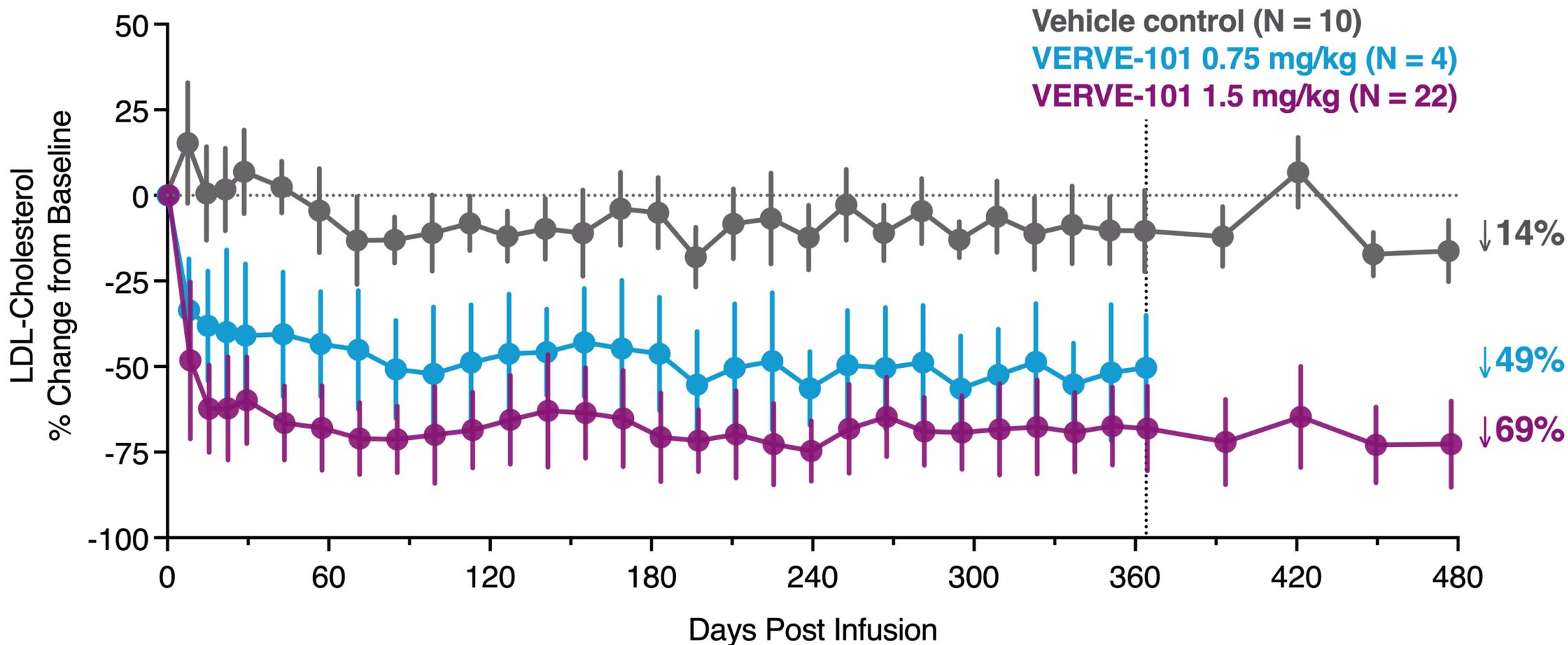
In non-human primates, a single infusion of VERVE-101 achieved blood PCSK9 reduced up to 83%*, durable out to 476 days



A subset of animals underwent scheduled necropsy 1 year following dosing

* Measured as time-weighted average % change from baseline from days 28 and up to 476 days following dosing.

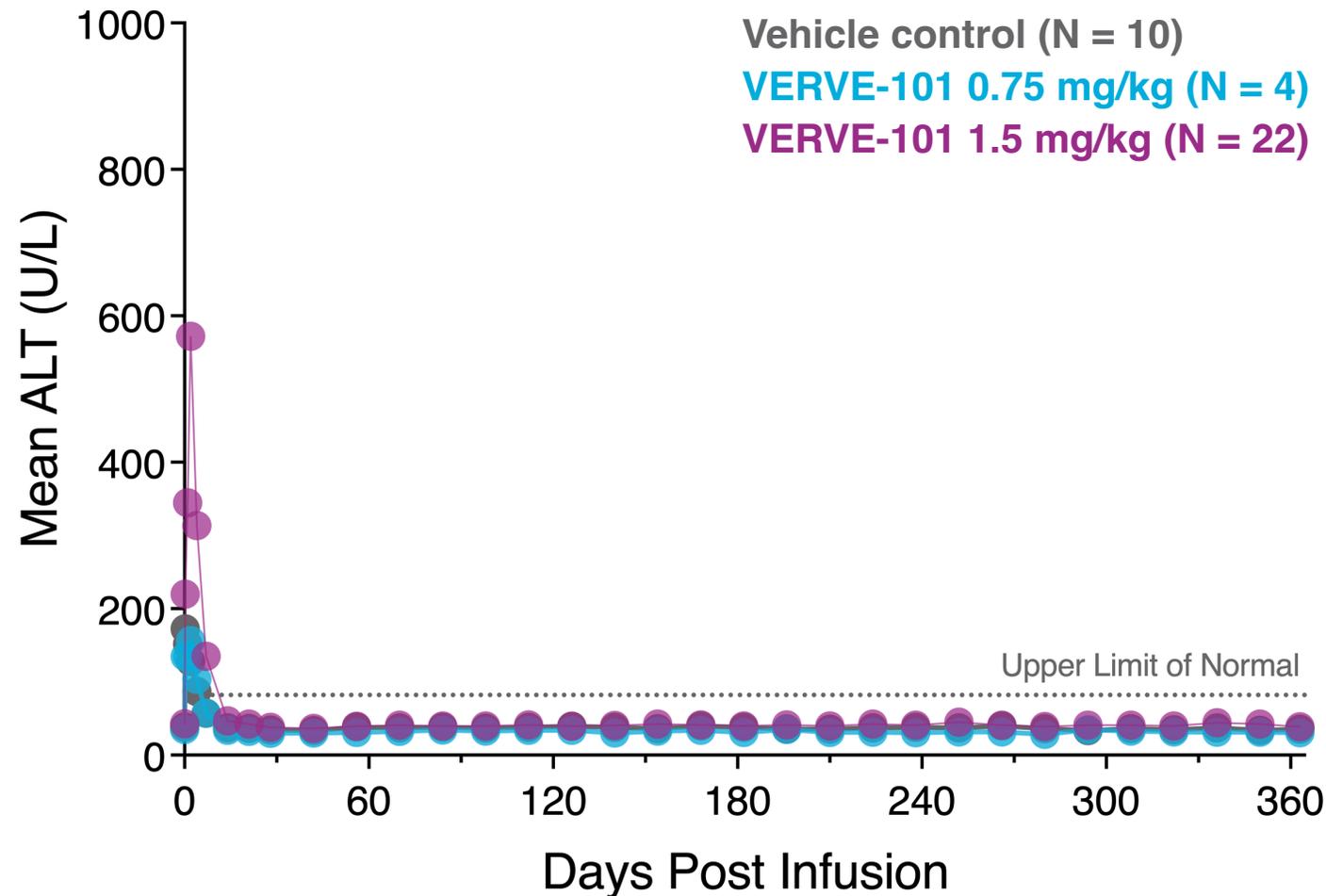
In non-human primates, a single infusion of VERVE-101 achieved blood LDL-C reduced up to 69%*, durable out to 476 days



A subset of animals underwent scheduled necropsy 1 year following dosing

* Measured as time-weighted average % change from baseline from days 28 and up to 476 days following dosing.

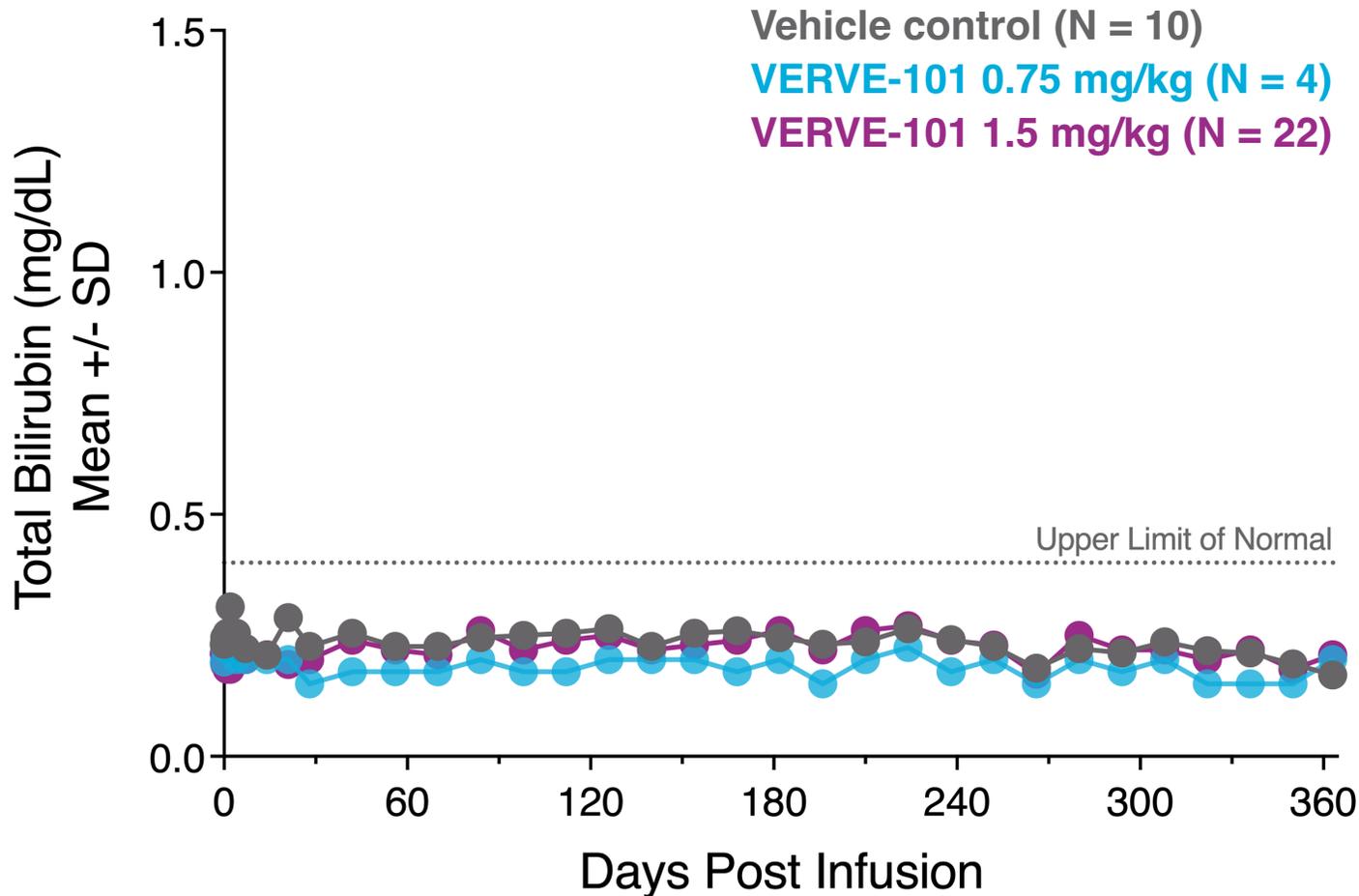
In non-human primates dosed with single infusion of VERVE-101, transient impact on alanine aminotransferase (ALT) observed



Liver safety monitoring

- Maximal ALT and AST concentrations noted within 48 hours after dosing, with normalization by day 14.
- Normal ALT and AST noted in each of 26 NHPs treated with VERVE-101 one year after dosing.
- Normal total bilirubin observed with no change from baseline.
- Normal liver histopathology one year after dosing in subset of 10 treated NHPs who underwent scheduled necropsy

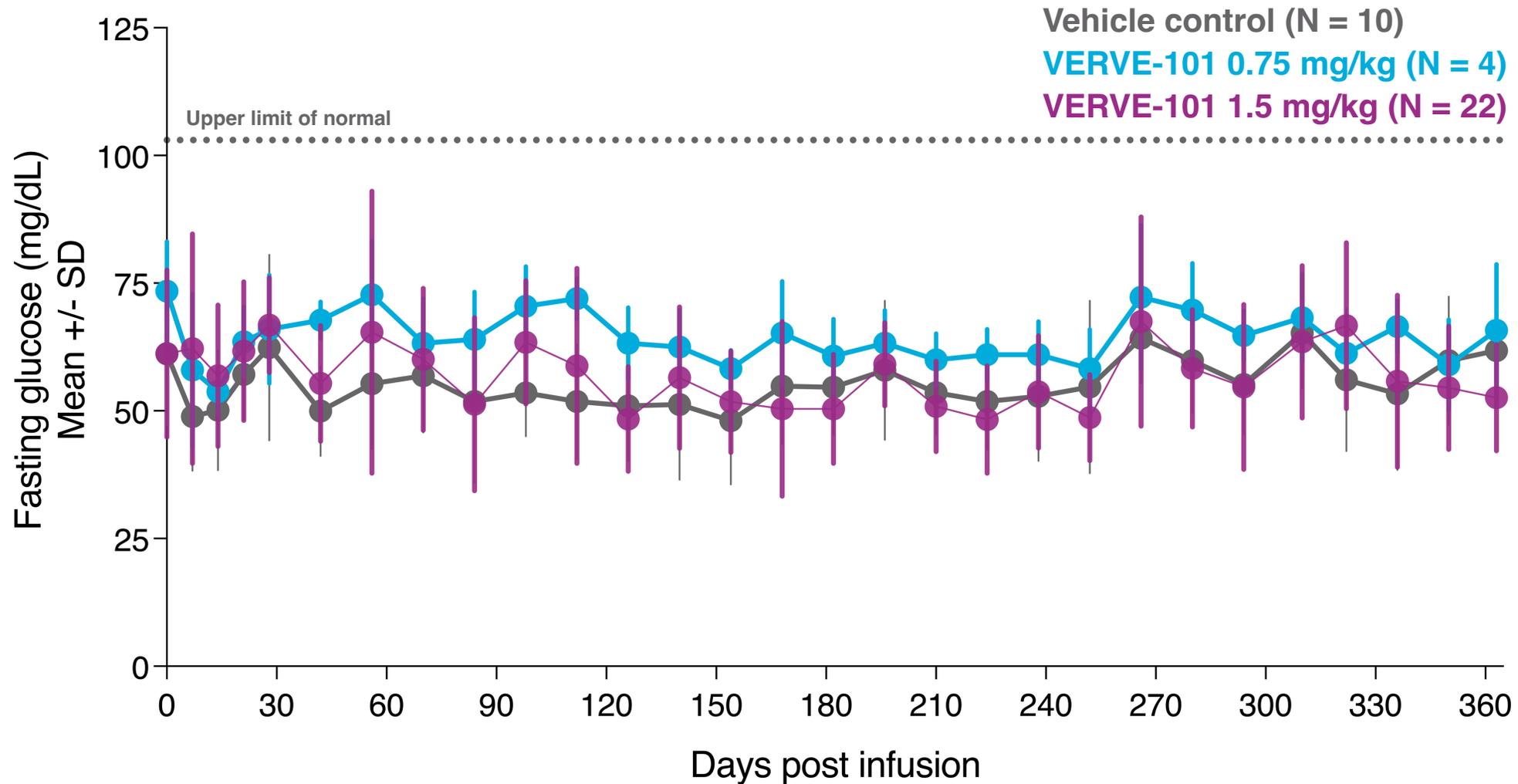
In non-human primates dosed with single infusion of VERVE-101, no impact on total bilirubin observed



Liver safety monitoring

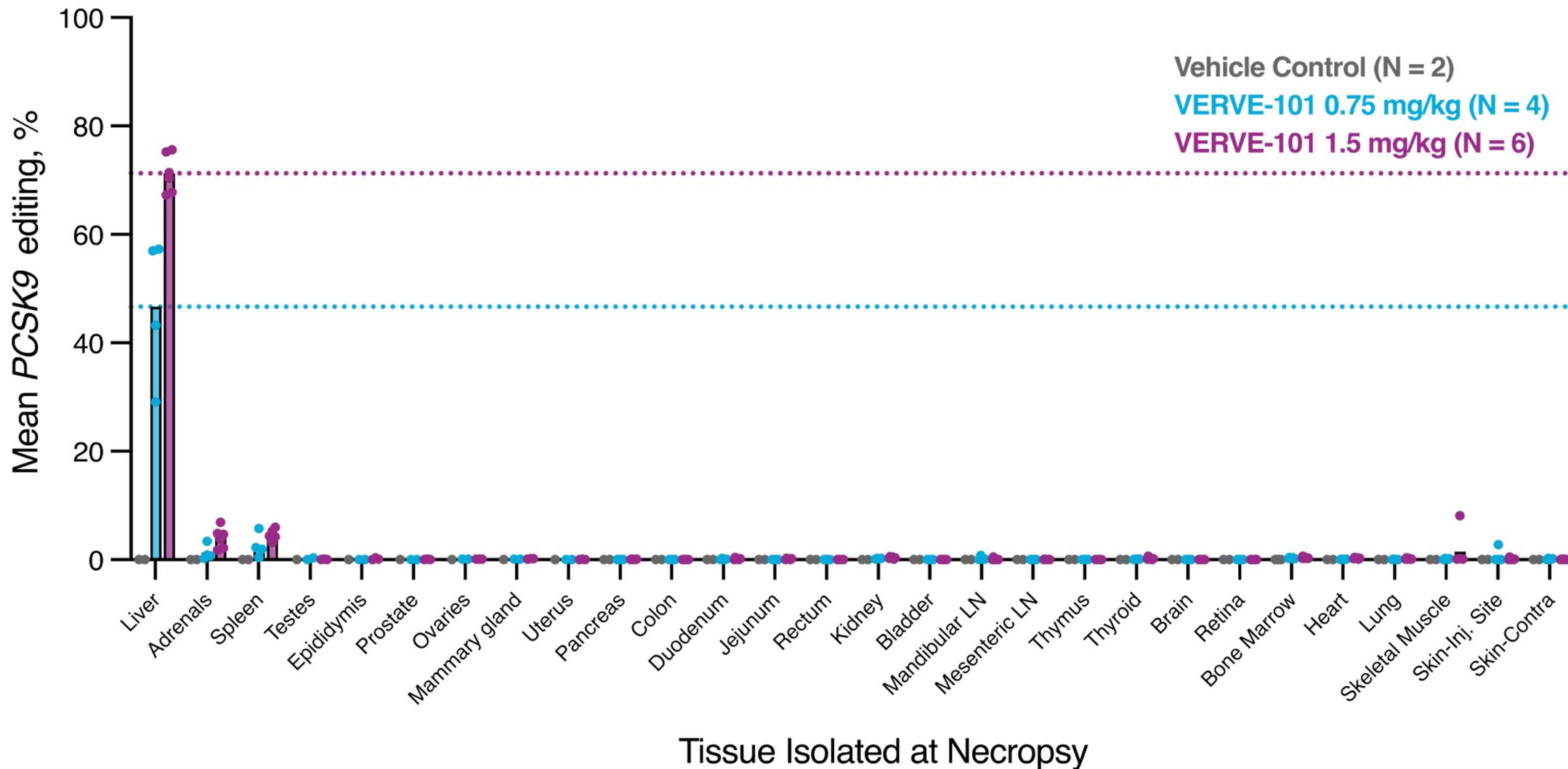
- Maximal ALT and AST concentrations noted within 48 hours after dosing, with normalization by day 14.
- Normal ALT and AST noted in each of 26 NHPs treated with VERVE-101 one year after dosing.
- **Normal total bilirubin observed with no change from baseline.**
- Normal liver histopathology one year after dosing in subset of 10 treated NHPs who underwent scheduled necropsy

In non-human primates dosed with single infusion of VERVE-101, no impact on fasting glucose observed*



* No impact of VERVE-101 was observed on additional biomarkers of glucose homeostasis, including fasting insulin and hemoglobin A1c.

In non-human primates dosed with a single infusion of VERVE-101, on-target *PCSK9* editing occurred mostly in the liver*

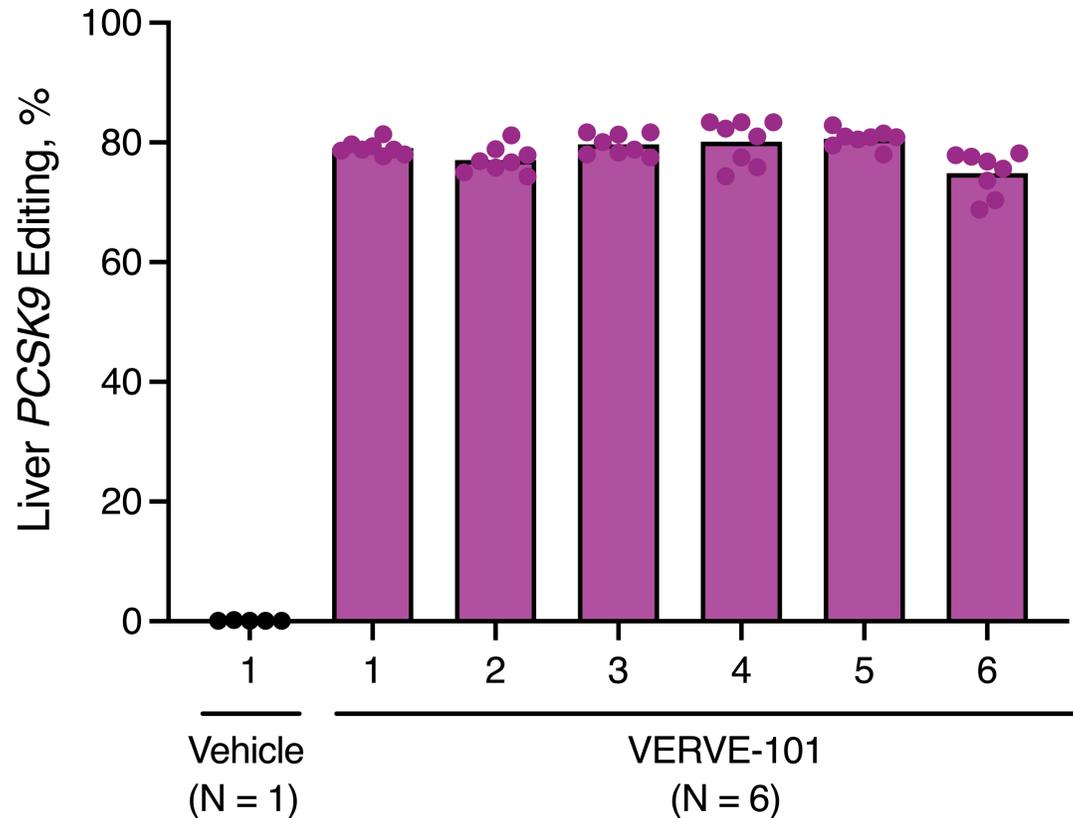


* *PCSK9* editing assessed using targeted amplicon sequencing in tissues isolated at scheduled necropsy 1 year after dosing

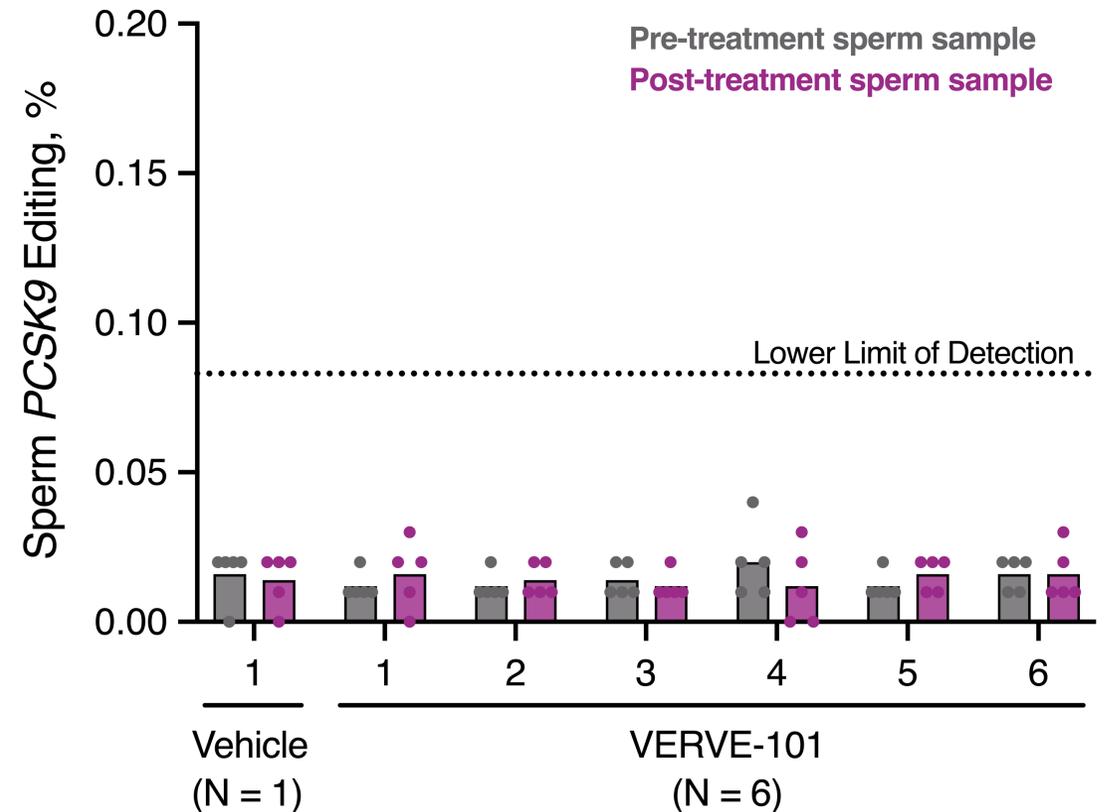
In sexually mature male NHPs treated with VERVE-101, No evidence of *PCSK9* editing in sperm



6 NHPs treated with VERVE-101
Mean liver *PCSK9* editing 79%



Sequencing of sperm noted
no detectable *PCSK9* editing



F1 progeny study of VERVE-101mu treated female mice

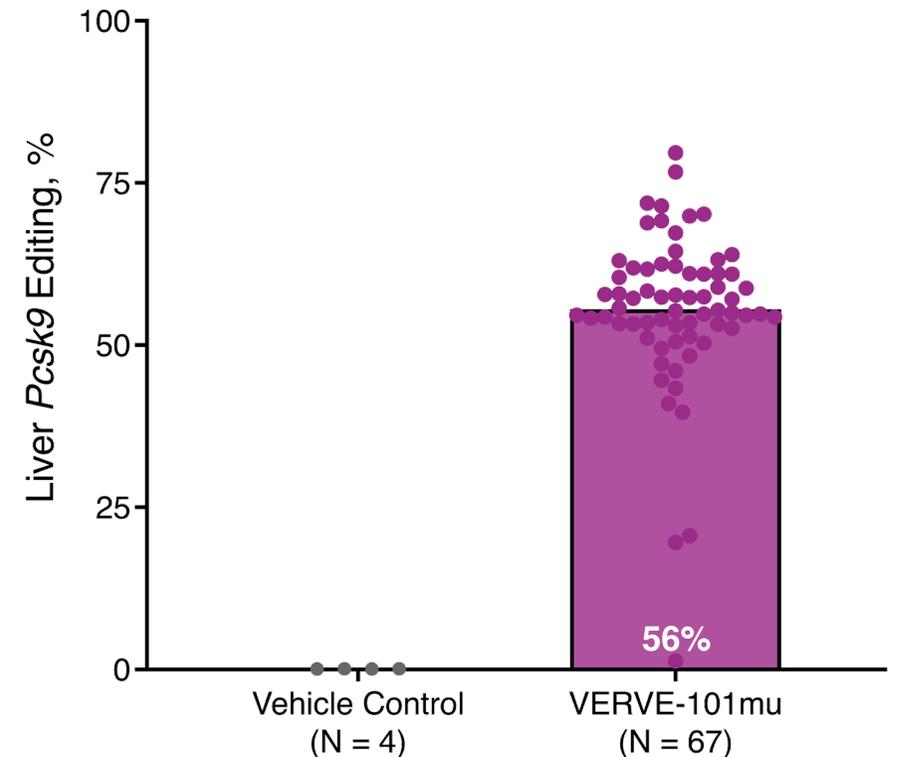
Problem

Not technically feasible to reliably dissect oocytes from ovarian tissue to assess for germline editing

Solution

Assess editing in offspring of 90 female mice treated with 0.1 mg/kg VERVE-101mu saturating dose

Liver PCSK9 editing confirmed in VERVE-101mu treated female dams

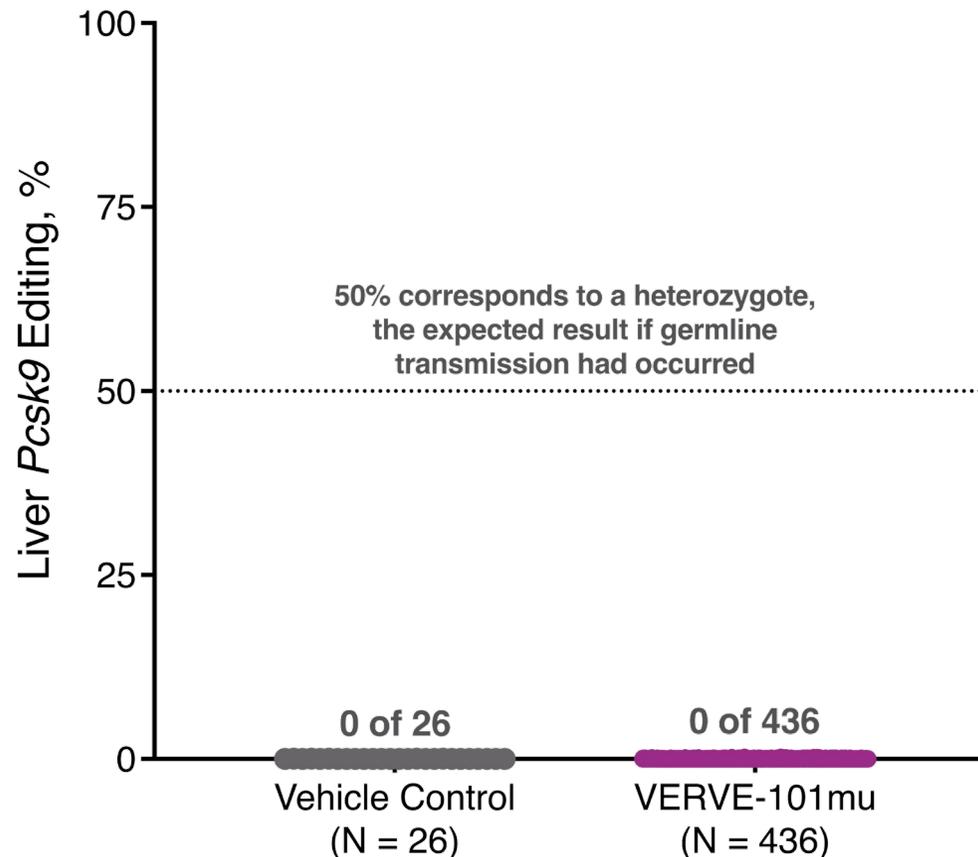


Data from 67 out of 90 treated females who became pregnant.

F1 progeny study of VERVE-101mu treated female mice observes no evidence of germline transmission of the *PCSK9* edit



436 offspring of treated females No detectable transmission



0 of 436 translates into upper bound of the 95% CI of 0.8%.

VERVE-101: base editing medicine designed to inactivate PCSK9; Phase 1 clinical trial underway, interim data expected in 2023



- Mean 83% reduction in blood PCSK9 protein and 69% reduction in LDL-C was observed in NHPs treated with 1.5 mg/kg of VERVE-101, durable out to 476 days
- VERVE-101 was well-tolerated in NHPs, with normal liver function tests and histopathology 1 year following dosing and no detectable impact on glucose homeostasis
- No detectable evidence of germline transmission of *PCSK9* edit to offspring in study of NHPs and a F1 progeny mouse mouse study
- The ongoing **heart-1** clinical trial is studying VERVE-101 in patients with heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease

Additional details available in
publication online in

Circulation

<https://doi.org/10.1161/CIRCULATIONAHA.122.062132>

Efficacy and safety of an investigational single-course CRISPR base editing therapy targeting *PCSK9* in non-human primate and mouse models

Richard G. Lee, PhD; Anne Marie Mazzola, MS; Maurine C. Braun, MS;
Colin Platt, PhD; Scott B. Vafai, MD; Sekar Kathiresan, MD; Ellen Rohde, PhD;
Andrew M. Bellinger, MD PhD; Amit V. Khera, MD MSc