ORIGINAL ARTICLE

In Vivo Base Editing of *PCSK9* with VERVE-102 for Hypercholesterolemia

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ABSTRACT

BACKGROUND

Persons carrying loss-of-function variants of proprotein convertase subtilisin–kexin type 9 (*PCSK9*) have reduced levels of low-density lipoprotein (LDL) cholesterol and fewer atherosclerotic cardiovascular disease events than persons without such variants. VERVE-102 is an investigational base-editing therapy designed to durably inactivate *PCSK9* in the liver.

METHODS

In this phase 1, open-label, single-ascending-dose study, we administered one intravenous infusion of VERVE-102 at one of six doses (ranging from 0.3 to 1.0 mg of total RNA per kilogram of body weight [mg per kilogram]) to adults with heterozygous familial hypercholesterolemia or premature coronary artery disease. VERVE-102 consists of a messenger RNA encoding an adenine base-editor protein and a guide RNA targeting *PCSK9*, which are encapsulated in a lipid nanoparticle incorporating *N*-acetylgalactosamine. The objectives were to assess safety and changes in blood PCSK9 protein and LDL cholesterol levels.

RESULTS

A total of 35 participants across the six dose cohorts received VERVE-102 and had at least 28 days of follow-up. No dose-limiting toxic effects occurred. Mild-to-moderate infusion-related reactions and transient elevations in alanine aminotransferase levels were observed. Aspiration pneumonitis occurred in a participant with gastroesophageal reflux disease. Dose-dependent mean reductions in the PCSK9 level ranged from 51% at the 0.3-mg-per-kilogram dose to 88% at the 1.0-mg-per-kilogram dose. Corresponding reductions in the LDL cholesterol level ranged from 9% at the 0.3-mg-per-kilogram dose to 62% at the 1.0-mg-per-kilogram dose, with an absolute reduction of 78 mg per deciliter at the highest dose. Reductions appeared to be durable throughout follow-up, which was at least 1 year in 15 participants.

CONCLUSIONS

One dose of VERVE-102 led to dose-dependent, substantial, and sustained reductions in PCSK9 and LDL cholesterol levels. (Funded by Verve Therapeutics; ClinicalTrials.gov number, NCT06164730.)

Twenty years ago, seminal studies of human genetics showed that loss-of-function variants in the gene proprotein convertase subtilisin–kexin type 9 (*PCSK9*) confer lifelong low levels of blood PCSK9 protein and low-density lipoprotein (LDL) cholesterol, without apparent adverse effects.[1-3] These biomarker changes were associated with a markedly reduced incidence of atherosclerotic cardiovascular disease events.[2] Since its discovery, PCSK9 has emerged as one of the most validated therapeutic targets in cardiovascular medicine.[4,5] Multiple PCSK9-targeting therapies have been approved, and several cardiovascular-outcome studies have confirmed the safety and efficacy of PCSK9 inhibition in patients with hypercholesterolemia.[6-9]

Mendelian randomization studies have shown that reduction of cardiovascular risk depends not only on the magnitude of the decrease in LDL cholesterol levels but also on the cumulative duration of exposure to lower levels.[2,10,11] Lowering LDL cholesterol levels by 39 mg per deciliter (1.0 mmol per liter) over a 5-year period with statin treatment reduces the risk of major vascular events by approximately 22%.[12] In contrast, persons who carry *PCSK9* genetic variants that are associated with the same magnitude of reduction of LDL cholesterol levels have up to an 88% lower lifetime risk of coronary artery disease events.[2] These findings suggest that the benefits of lowering LDL cholesterol levels accrue with time and that effective clinical management should prioritize early intervention and a durable therapeutic response.[13-16]

The current treatment model for managing LDL cholesterol, which depends on daily pills or regular injections, has yielded suboptimal results. Inconsistent access to care, side effects, out-of-pocket costs, and other factors drive a high incidence of treatment discontinuation and limit real-world effectiveness.[17-20] For patients at high risk for cardiovascular events, such as those with heterozygous familial hypercholesterolemia or premature coronary artery disease, clinical guidelines recommend long-term reduction of LDL cholesterol levels, potentially over a period of decades.[13,14] However, the real-world incidence of discontinuation of lipid-lowering therapy across therapeutic classes, including PCSK9 inhibitors, ranges from 30 to 50% within 12 months after treatment initiation,[21,22] and a lack of treatment persistence has been associated with worsened cardiovascular outcomes.[23]

To overcome the limitations of the current treatment model, we developed an in vivo base-editing medicine — VERVE-102 — which was designed to mimic the effects of naturally occurring cardioprotective *PCSK9* variants and durably lower the LDL cholesterol level after a single infusion. VERVE-102 consists of two drug substances — a messenger RNA (mRNA) encoding an adenine base-editor protein and a guide RNA targeting *PCSK9*. These two drug substances are encapsulated in a lipid nanoparticle delivery system that incorporates an *N*-acetylgalactosamine (GalNAc)–targeting ligand to enhance delivery to hepatocytes. The guide RNA targets a splice site at the 5′ end of intron 1 of *PCSK9*. Altering the splice site with a single DNA base-pair substitution enables read-through to a stop codon that prevents translation and expression of PCSK9 protein in the liver (Fig. 1).[24] Here we report the results from an interim analysis of a phase 1, ongoing, single-ascending-dose study (Heart-2) conducted to evaluate the safety and efficacy of VERVE-102 in adults with heterozygous familial hypercholesterolemia or premature coronary artery disease.

METHODS

VERVE-102 Description and Preclinical Data

VERVE-102 consists of an mRNA encoding an adenine base-editor protein (version 8.8) and a guide RNA targeting *PCSK9*, which are encapsulated by a GalNAc-lipid nanoparticle.[25] The GalNAc moiety enables hepatocyte uptake through the asialoglycoprotein receptor, which supplements apolipoprotein E–mediated uptake through the LDL receptor.[26] The adenine base editor combines an engineered adenosine deaminase domain with a modified clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9) domain that has been catalytically inactivated so that it nicks one strand of DNA instead of making a double-strand break.[25]

Editing with VERVE-102 was specific for the target site in *PCSK9* in off-target screening experiments involving primary human hepatocytes in vitro (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In nonhuman primates that received an infusion of VERVE-102, the biodistribution of *PCSK9* editing across 26 tissues supported high levels of editing activity in the liver and low levels of editing in the adrenal glands and spleen

(Fig. S2). Assessment of the offspring of mice that had been given an orthologous mouse equivalent of VERVE-102, with a guide RNA targeting mouse *Pcsk9*, showed no transmission of the *Pcsk9* edit, which is consistent with an absence of editing of the parental germline (i.e., sperm or egg cells). Additional details are provided in the Supplementary Appendix.

STUDY OVERSIGHT

The Heart-2 study was sponsored by Verve Therapeutics, a wholly owned subsidiary of Eli Lilly, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The study was approved by the relevant regulatory authorities, institutional review boards, and ethics committees at the participating trial sites. All the participants provided written informed consent. Safety oversight was carried out by a study monitoring committee and an independent data and safety monitoring board.

The study was designed by employees of the sponsor. The study-site investigators advised on the conduct of the study. Study data were collected by clinical investigators and staff from participating study sites in Australia, Canada, New Zealand, and the United Kingdom. Authors who are employees of the sponsor analyzed the data and wrote the first draft of the manuscript with subsequent input from the other authors. All the authors critically reviewed and approved the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. The protocol and statistical analysis plan are available at NEJM.org.

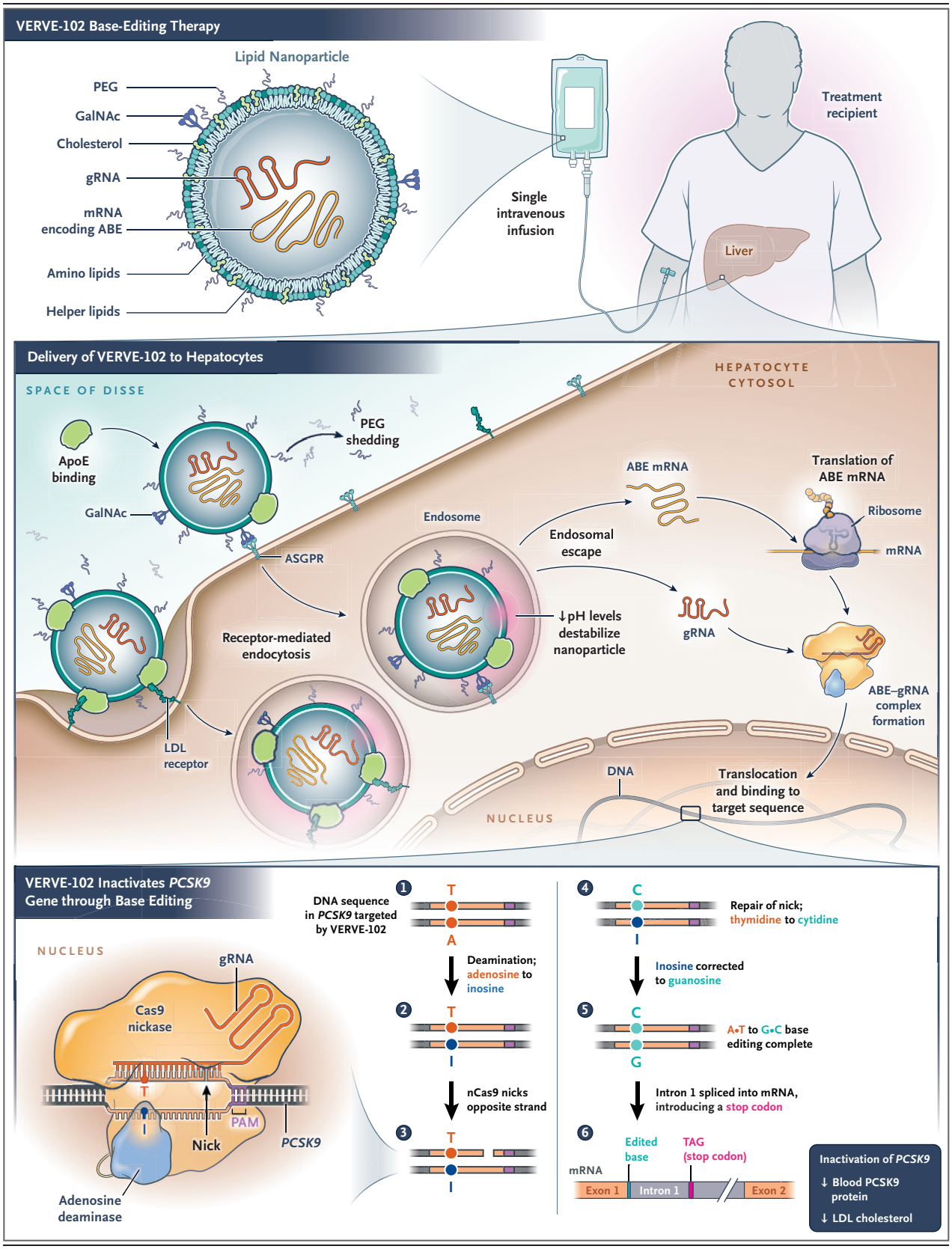
PARTICIPANT ELIGIBILITY AND STUDY PROCEDURE

Adults 18 to 70 years of age were eligible for inclusion if they had a diagnosis of heterozygous familial hypercholesterolemia or premature coronary artery disease (defined as disease occurrence at ≤55 years of age in men or at ≤65 years of age in women). Participants had to have a fasting LDL cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter) while receiving the maximum tolerated dose of oral lipid-lowering therapy (a statin with or without ezetimibe). Exclusion criteria included uncontrolled hypertension, inadequately controlled type 2 diabetes mellitus, and ongoing use of a PCSK9 inhibitor treatment. Complete eligibility criteria are provided in the Supplementary Appendix.

Participants received a single intravenous infusion of VERVE-102 at one of six weight-based doses (0.3, 0.45, 0.6, 0.7, 0.8, or 1.0 mg of total RNA per kilogram of body weight [mg per kilogram]) over a period of up to approximately 4 hours. Premedication was administered to all the participants to reduce the risk of infusion-related reactions and consisted of dexamethasone on the day before VERVE-102 infusion and dexamethasone plus a histamine H_1–receptor antagonist and histamine H_2–receptor antagonist on the day of infusion. Participants underwent inpatient observation for at least 2 days and daily clinical and laboratory assessments through day 4. Subsequent follow-up was weekly through day 28,

Figure 1 (facing page). In Vivo Gene Editing of Hepatocyte *PCSK9* with VERVE-102.

VERVE-102 consists of a messenger RNA (mRNA) encoding an adenine base-editor (ABE) protein and a guide RNA (gRNA) targeting *PCSK9*, which are encapsulated within an *N*-acetylgalactosamine (GalNAc)–lipid nanoparticle. VERVE-102 is administered by a single intravenous infusion with the dose based on milligrams of total RNA administered per kilogram of body weight. After infusion, the GalNAc-lipid nanoparticle binds to apolipoprotein E (ApoE) in the bloodstream. The ApoE-bound lipid nanoparticle then enters hepatocytes through low-density lipoprotein (LDL) receptor–mediated endocytosis or through GalNAc binding to asialoglycoprotein receptor (ASGPR). Inside the cell, pH changes in the endosome destabilize the GalNAc-lipid nanoparticle and the mRNA and guide RNA escape to the cytosol, where the mRNA is translated into the adenine base-editor protein that pairs with the guide RNA. The adenine base-editor complex then localizes to the nucleus and aligns with the target location at the 5′ end of intron 1 of the gene *PCSK9* that is complementary to the unique guide RNA sequence. The DNA strands are separated to form the R-loop. In this conformation, the adenosine deaminase domain chemically converts adenosine to inosine. The adenine base editor nicks the opposite strand of DNA to trigger the process of DNA repair. During the repair, which is based on the intact strand, the inosine is read as guanosine, which leads to placement of a cytidine on the repaired strand. Finally, endogenous DNA-repair mechanisms complete the A·T to G·C single base-pair substitution. Altering the splice site enables read-through to a stop codon that prevents translation and expression of PCSK9 protein. PAM denotes protospacer adjacent motif, and PEG polyethylene glycol.



with additional scheduled visits on days 60, 90, 180, 270, and 365. Data were reviewed by the independent data and safety monitoring board before dose escalation. Participants who complete their visit on day 365 are expected to transition to a long-term follow-up study.

CLINICAL-OUTCOME ASSESSMENTS

The primary objective was to assess the safety of VERVE-102 in participants with heterozygous familial hypercholesterolemia or premature coronary artery disease. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Secondary objectives were to characterize the pharmacokinetics of VERVE-102 and to evaluate pharmacodynamic effects, which were measured as the percent change and the absolute change from baseline in plasma PCSK9 and fasting LDL cholesterol levels. To capture the effects of VERVE-102 for the full duration of follow-up for each participant, pharmacodynamic data, where indicated, are reported as the time-averaged values of the variable from day 28 through the participant's last follow-up visit on the basis of an area-under-the-curve analysis performed with the trapezoidal rule. Details on data handling and assessments are available in the protocol and statistical analysis plan.

EXPLORATORY ANALYSIS

Two approaches to analyzing dose response were explored — response to weight-based dose and response to dose based on total milligrams of RNA. The total RNA administered is the product of the dose (in milligrams per kilogram) times the participant's weight. We explored the relationship between the total RNA dose administered to each participant and pharmacodynamic response.

STATISTICAL ANALYSIS

The study is designed to enroll up to 85 participants to enable characterization of VERVE-102 across a range of doses. This nonprespecified interim analysis was completed to update the scientific community regarding a potential new therapeutic approach for the treatment of hypercholesterolemia, but no formal statistical testing was performed.

RESULTS

PARTICIPANTS

In this interim analysis, 35 participants had received an intravenous infusion of VERVE-102 and had undergone at least 28 days of follow-up as of the data-cutoff date of February 27, 2026 (4 participants had received 0.3 mg per kilogram, 6 had received 0.45 mg per kilogram, 4 had received 0.6 mg per kilogram, 8 had received 0.7 mg per kilogram, 6 had received 0.8 mg per kilogram, and 7 had received 1.0 mg per kilogram) (Fig. S3). The characteristics of the participants at baseline are shown in Table 1; the representativeness of the sample with respect to the broader population of persons with heterozygous familial hypercholesterolemia or premature coronary artery disease is shown in Table S1. The mean age of the participants was 52 years, and 24 were men (69%). A total of 29 participants (83%) had heterozygous familial hypercholesterolemia, of whom 9 also had premature coronary artery disease; 6 participants (17%) had premature coronary artery disease alone. The mean LDL cholesterol level at baseline was 129 mg per deciliter (3.3 mmol per liter). A total of 32 participants (91%) were receiving statin therapy at baseline, including 25 (71%) who were receiving a high-intensity statin. The median follow-up duration among all the participants was approximately 9 months, with the last study visit occurring at 28 days to 18 months as of the data-cutoff date.

SAFETY

Details on adverse events are shown in Table 2 and Table S2. All the participants received the full planned dose of VERVE-102. No participants withdrew from the study, and no dose-limiting toxic effects or deaths occurred.

Transient infusion-related reactions, all of grade 1 or 2, occurred in seven participants (20%). Five participants (two participants in the 0.7-mg-per-kilogram dose cohort, two in the 1.0-mg-per-kilogram cohort, and one in the 0.8-mg-per-kilogram cohort) had grade 1 infusion-related reactions that resolved without medical treatment, and two participants (one in the 0.6-mg-per-kilogram cohort and one in the 0.7-mg-per-kilogram cohort) had grade 2 reactions that were treated with

paracetamol or antihistamines. One grade 1 infusion-related reaction in a participant who received a dose of 0.7 mg per kilogram led to a temporary interruption of infusion of approximately 40 minutes.

Transient, asymptomatic elevations in alanine aminotransferase levels were observed in the early postdose period (Fig. S4). Among the 35 participants, 3 had increased alanine aminotransferase levels that met or exceeded two times the upper limit of the normal range, with levels reaching 2.0, 2.2, and 2.4 times the upper limit of the normal range at their peak. In all 3 participants (1 in the 0.7-mg-per-kilogram dose cohort and 2 in the 1.0-mg-per-kilogram cohort), alanine aminotransferase levels peaked on day 3 or 4 and decreased below two times the upper limit of the normal range by day 8. Additional laboratory values are shown in Figure S5.

One serious adverse event of grade 3 aspiration pneumonitis was reported approximately 2 weeks after the infusion in a participant who received a dose of 0.45 mg per kilogram. The participant had a history of gastroesophageal reflux disease and sliding hiatal hernia. The participant was hospitalized for evaluation and was discharged the next day. The adverse event was assessed by the site investigator as being unrelated to VERVE-102 treatment. Additional details are reported in the Supplementary Appendix. No adverse events higher than grade 3 occurred during the study.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Participants (N=35)
Mean age (range) — yr	52 (27–66)
Male sex — no. (%)	24 (69)
Race — no. (%)†	
Asian	6 (17)
Black	1 (3)
White	30 (86)
Mean weight — kg	79±14
Mean body-mass index‡	27±4
Mean PCSK9 level — μg/liter	455±98
Mean LDL cholesterol level — mg/dl	129±42
Clinical status — no. (%)	
Heterozygous familial hypercholesterolemia only	20 (57)
Heterozygous familial hypercholesterolemia and premature coronary artery disease	9 (26)
Premature coronary artery disease only	6 (17)
Concomitant statin use — no. (%)	
High intensity	25 (71)
Moderate or low intensity	7 (20)
None	3 (9)
Concomitant ezetimibe use — no. (%)	15 (43)

* Plus–minus values are means ±SD. To convert values for low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586.
† Race was reported by the participant. Participants could report more than one race and were counted in each category.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic analyses of lipid nanoparticle components of VERVE-102 indicated rapid clearance from the circulation after infusion. The mean terminal half-life for the primary lipid component of VERVE-102 was less than 20 hours (Fig. S6).

Reductions in plasma PCSK9 levels were observed after treatment with VERVE-102 across all dose cohorts by day 28 (Table 3 and Fig. 2). Changes from baseline in time-averaged PCSK9 levels were dose-dependent and substantial at the higher doses. The mean percent change in PCSK9 level was –51% (range, –73 to –30) in the 0.3-mg-per-kilogram dose cohort, –59% (range, –92 to –34) in the 0.45-mg-per-kilogram cohort, –61% (range, –84 to –38) in the 0.6-mg-per-kilogram cohort, –64% (range, –93 to –34) in the 0.7-mg-per-kilogram cohort, –77% (range, –87 to –66) in the 0.8-mg-per-kilogram cohort, and –88% (range, –94 to –78) in the 1.0-mg-per-kilogram cohort.

We also observed dose-dependent changes from baseline in time-averaged LDL cholesterol levels, which corresponded to reductions in the PCSK9 levels (Table 3 and Fig. 2). The mean percent change in the LDL cholesterol level was –9% (range, –26 to 26) in the 0.3-mg-per-kilogram dose cohort, –44% (range, –57 to –30) in the 0.45-mg-per-kilogram cohort, –45% (range, –54 to –34) in the 0.6-mg-per-kilogram cohort, –33% (range, –70 to –14) in the 0.7-mg-per-kilogram cohort, –51% (range, –86 to –16) in the

Table 2. Adverse Events.

Event	Participants (N=35)
	no. (%)
Any adverse event	26 (74)
Any adverse event of grade 3 or higher*	1 (3)
Any serious adverse event*	1 (3)
Any treatment-related adverse event	11 (31)
Treatment-related adverse events occurring in >1 participant	
Infusion-related reaction	7 (20)
Fatigue	2 (6)

* Aspiration pneumonitis occurred in one participant with a history of gastroesophageal reflux disease and sliding hiatal hernia and was assessed by the site investigator as being unrelated to VERVE-102 treatment.

0.8-mg-per-kilogram cohort, and −62% (range, −79 to −45) in the 1.0-mg-per-kilogram cohort. In the 1.0-mg-per-kilogram cohort, the mean LDL cholesterol level decreased from 128 mg per deciliter (3.3 mmol per liter) at baseline to a time-averaged level of 51 mg per deciliter (1.3 mmol per liter), which represented an absolute reduction of 78 mg per deciliter (2.0 mmol per liter) (Table 3). Changes in additional fasting lipid laboratory measures and remnant cholesterol levels are provided in Table S3.

DURABILITY OF PCSK9 AND LDL CHOLESTEROL REDUCTIONS

Among the 35 participants, follow-up of pharmacodynamic variables extended to a maximum of 18 months. Given the dose-escalation design, participants in the lowest dose cohort had the longest available follow-up, whereas those in the highest dose cohort had the shortest. Of the 35 participants, 15 had follow-up extending 1 year or longer. Overall, reductions in PCSK9 protein and LDL cholesterol levels appeared to be durable (Fig. 2). PCSK9 and LDL cholesterol levels at day 28 were consistent with the time-averaged values over the duration of follow-up, reflecting a stable pharmacodynamic response (Table 3).

EXPLORATORY ANALYSIS

Results of the analysis of the relationship between the total RNA dose administered to each participant and pharmacodynamic response are shown in Figure S7. Among the 35 participants, the total RNA dose correlated with reduction of the LDL cholesterol level (Pearson correlation coefficient, −0.68).

DISCUSSION

In this phase 1 study, a single infusion of VERVE-102 produced dose-dependent and sustained reductions in PCSK9 and LDL cholesterol levels, with a mean reduction of 88% and 62%, respectively, at the highest dose. Mild-to-moderate infusion-related reactions and transient elevations in alanine aminotransferase levels (<2.5 times the upper limit of normal) were observed.

These results from an interim analysis support four key insights. First, the GalNAc-lipid nanoparticle used in VERVE-102 to deliver the base editor was not associated with the adverse events observed with our previous in vivo base-editing therapy, VERVE-101.[27] Emerging data from the field of in vivo gene editing indicate that the lipid nanoparticle is the primary driver of acute adverse events. Other gene-editing studies, including the previous study of VERVE-101, have noted infusion-related reactions as well as increased liver aminotransferase levels and decreased platelet counts, with varying severity.[27-33] Our current results support the concept that changes to the formulation and lipid components of the base-editing therapy and the addition of a GalNAc ligand may result in a relatively safe means of delivering the cargo RNAs to the liver. Because our results are preliminary, this interpretation must be considered with caution. The same GalNAc-lipid nanoparticle is being used to develop a second investigational medicine — VERVE-201 — which delivers an adenine base editor and guide RNA designed to inactivate *ANGPTL3*, with the aim of reducing both LDL cholesterol and triglyceride levels (ClinicalTrials.gov number, NCT06451770).

Second, at a VERVE-102 dose of 1.0 mg per kilogram, base editing at *PCSK9* appears to have been achieved in a large proportion of hepatocytes, as shown by the observed reductions in circulating PCSK9 protein and LDL cholesterol levels. The mean reduction in PCSK9 levels of 88% (range, 78 to 94) from baseline in the 1.0-mg-per-kilogram dose cohort is consistent with near-complete suppression of hepatically produced PCSK9, given that the liver is the principal source of circulating PCSK9 protein.[34] The

Table 3. Changes in PCSK9 and LDL Cholesterol Levels According to VERVE-102 Dose Cohort.*

Variable	0.3 mg/kg (N=4)	0.45 mg/kg (N=6)	0.6 mg/kg (N=4)	0.7 mg/kg (N=8)	0.8 mg/kg (N=6)	1.0 mg/kg (N=7)
Total RNA dose (range) — mg	20 (18 to 23)	37 (27 to 45)	51 (40 to 58)	55 (34 to 70)	62 (48 to 80)	80 (57 to 95)
Mean PCSK9 level (range) — μg/liter						
At baseline	448 (264 to 591)	482 (351 to 599)	451 (420 to 489)	474 (340 to 578)	421 (283 to 604)	447 (317 to 740)
At day 28	201 (82 to 288)	251 (45 to 535)	181 (57 to 273)	193 (32 to 416)	101 (56 to 202)	58 (30 to 118)
Time-averaged PCSK9 level during follow-up (range) — μg/liter	220 (97 to 316)	199 (39 to 306)	173 (71 to 260)	176 (34 to 317)	98 (49 to 204)	53 (28 to 99)
Mean percent change from baseline in time-averaged PCSK9 level (range) — %	−51 (−73 to −30)	−59 (−92 to −34)	−61 (−84 to −38)	−64 (−93 to −34)	−77 (−87 to −66)	−88 (−94 to −78)
Mean LDL cholesterol level (range) — mg/dl						
At baseline	154 (61 to 200)	140 (89 to 205)	124 (111 to 159)	105 (90 to 129)	139 (82 to 203)	128 (82 to 230)
At day 28	114 (47 to 147)	82 (46 to 124)	67 (53 to 102)	65 (20 to 94)	73 (26 to 156)	51 (20 to 127)
Time-averaged LDL cholesterol level during follow-up (range) — mg/dl	143 (50 to 234)	77 (55 to 107)	69 (51 to 105)	70 (32 to 95)	68 (26 to 171)	51 (20 to 118)
Mean change from baseline in LDL cholesterol level (range) — mg/dl	−11 (−51 to 48)	−64 (−97 to −34)	−55 (−60 to −49)	−35 (−74 to −15)	−71 (−163 to −31)	−78 (−117 to −54)
Mean percent change from baseline in time-averaged LDL cholesterol level (range) — %	−9 (−26 to 26)	−44 (−57 to −30)	−45 (−54 to −34)	−33 (−70 to −14)	−51 (−86 to −16)	−62 (−79 to −45)

* Time-averaged values are calculated with the trapezoidal rule and are based on all available values from day 28 throughout follow-up. Day 28 values were substituted for the time-averaged value if day 28 was the last follow-up visit. The changes from baseline compare the time-averaged value of the variable with the baseline value.

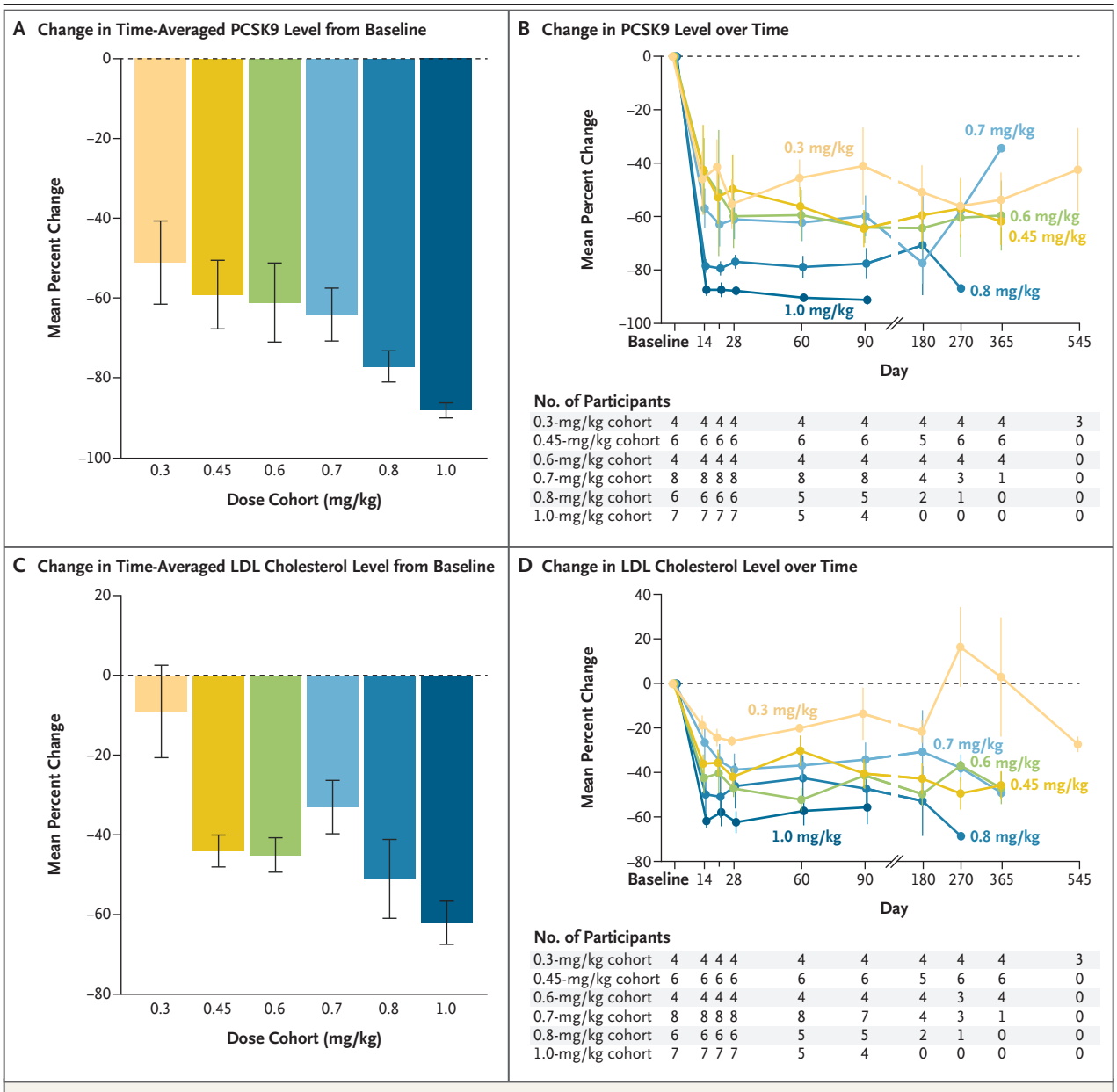


Figure 2. Mean Changes from Baseline in PCSK9 and LDL Cholesterol Levels According to Dose Cohort.

Panel A shows the mean percent change from baseline in time-averaged PCSK9 levels. Panel B shows the change from baseline in PCSK9 levels over time. Panel C shows the mean percent change from baseline in time-averaged LDL cholesterol levels. Panel D shows the change from baseline in LDL cholesterol levels over time. PCSK9 and LDL cholesterol levels at baseline were derived as the average value of all available central laboratory results collected before administration of premedications on day –1 (the day before administration of VERVE-102). In Panels A and C, time-averaged values are calculated with the trapezoidal rule and are based on all visits from day 28 onward throughout follow-up. Day 28 values were substituted for the time-averaged value if day 28 was the last follow-up visit. In Panels B and D, the number of participants supporting each data point is provided below the x axis. The axis scale changes after day 90 to allow greater resolution for visits that occurred early in the study. The apparent increase in PCSK9 levels occurring after day 180 in the 0.7-mg-per-kilogram cohort in Panel B reflects variable duration of follow-up across participants rather than an upward trend in individual participants. The error bars indicate standard errors.

associated mean reduction in LDL cholesterol levels of 62% (range, 45 to 79) is similar to that achieved with long-term administration of PCSK9 inhibitors, which reduce LDL cholesterol levels by approximately 40 to 60%.[35-38] The reduction in LDL cholesterol with VERVE-102 was achieved with a single infusion rather than with ongoing treatment. Of note, we have observed a relationship between total RNA dose and pharmacodynamic measures that may warrant additional study.

Third, the results support a durable effect of VERVE-102 on PCSK9 and LDL cholesterol levels in the blood. Gene-editing therapies have the potential to generate permanent therapeutic responses because they act at the DNA level. Here, we report the appearance of a durable reduction in both PCSK9 and LDL cholesterol levels up to 12 months. Because mature hepatocytes have an average lifespan of 200 to 300 days,[39] these results suggest that the edited gene and resultant pharmacodynamic effect persist through hepatocyte turnover. Stable inactivation of hepatic genes in humans through 3 years of follow-up has been documented with another in vivo gene-editing medicine, with no waning of effect.[40] That said, we report here the results of an interim analysis, and the appearance of a durable effect, as with the safety results, must be regarded with caution.

Fourth, participants who received 1 mg per kilogram of VERVE-102 had a mean absolute reduction in LDL cholesterol level of 78 mg per deciliter (range, 54 to 117). A reduction of this magnitude, if maintained over 20 years, is predicted to reduce the risk of atherosclerotic cardiovascular disease by more than 50% for most patients with hypercholesterolemia,[15] but larger and much longer studies are warranted to determine whether the decrease in LDL cholesterol levels observed in this study is durable over the course of decades.

Our study has several limitations. Heart-2 is a phase 1 study intended to assess the safety profile of VERVE-102. The safety profile of VERVE-102 was evaluated in a selected population of participants with stable disease who were given premedication and observed in an inpatient setting for at least 2 days after infusion. The study is not powered to determine the statistical effect size of the pharmacodynamic response, never mind an effect on cardiovascular disease. Moreover, the relatively short duration of follow-up in this nonprespecified interim analysis precludes an assessment of the long-term safety (including potential risks of off-target editing) and efficacy of VERVE-102. In accordance with regulatory guidance, all participants in Heart-2 are expected to enroll in a long-term follow-up study for a total period of 15 years. Finally, because of the geographic footprint of this study, the majority of the participants were White. Work involving nonclinical off-target screening has also been performed largely in cells isolated from White donors.

Treatment with VERVE-102 led to dose-dependent, substantial, and sustained reductions in PCSK9 and LDL cholesterol levels. Together with the safety data, these results support continued development of VERVE-102 as a treatment for hypercholesterolemia. Twenty years after the observation that lifelong inactivation of *PCSK9* protects against atherosclerotic cardiovascular disease,[2] these data provide early clinical evidence that a single infusion of a base-editing therapy can mimic the LDL cholesterol–lowering effects of *PCSK9* cardioprotective variants.

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