

No benefit of HDL mimetic CER-001 on carotid atherosclerosis in patients with genetically determined very low HDL levels

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ABSTRACT

Background and aims: Infusion of high-density lipoprotein (HDL) mimetics failed to induce regression of atherosclerosis in recent randomized clinical trials. However, patients in these previous trials had normal levels of HDL-cholesterol, which potentially limited efficacy. Patients with very low levels of HDL-cholesterol and impaired cholesterol efflux capacity can be expected to derive the most potential benefit from infusion of HDL mimetics. This randomized clinical trial evaluated the efficacy of infusions of the HDL mimetic CER-001 in patients with genetically determined very low levels of HDL cholesterol.

Methods: In this multicenter, randomized clinical trial, we recruited patients with familial hypoalphalipoproteinemia (due to ABCA1 and/or APOA1 loss-of-function variants). Participants were randomized to intravenous infusions of 8 mg/kg CER-001 or placebo (2:1 ratio), comprising 9 weekly infusions followed by infusions every two weeks. Patients underwent repeated 3T-MRI to assess mean vessel wall area and ¹⁸F-FDG PET/CT to quantify arterial wall inflammation.

Results: A total of 30 patients with a mean age of 52.7 ± 7.4 years and HDL-cholesterol of 0.35 ± 0.25 mmol/L were recruited. After 24 weeks, the absolute change in mean vessel wall area was not significantly different in the CER-001 group compared with placebo (n = 27; treatment difference: 0.77 mm², p = 0.21). Furthermore, there was no significant difference in carotid arterial wall inflammation (n = 24, treatment difference: 0.10 target-to-background ratio of the most diseased segment, p = 0.33) after 24 weeks.

Conclusion: In patients with genetically determined very low HDL-cholesterol, 24 weeks of treatment with HDL mimetic CER-001 did not reduce carotid vessel wall dimensions or arterial wall inflammation, compared with placebo.

1. Introduction

High-density lipoprotein (HDL) cholesterol is inversely correlated

with atherosclerotic cardiovascular disease (ASCVD) risk in population studies [1] and remains an important predictor in ASCVD risk assessment algorithms [2]. However, several drugs that significantly raised

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HDL-cholesterol levels were unable to reduce ASCVD risk in clinical trials, while human genetic studies further challenged the causal role of HDL-cholesterol in atherosclerosis [3]. Based on these findings, the strategy of targeting the cholesterol concentration carried in the HDL fraction has largely been abandoned.

HDL particles are highly heterogeneous in composition and have been ascribed various biological functions [4,5], which are not captured by the static measurement of HDL-cholesterol levels. One of the putative atheroprotective effects of HDLs is attributed to their role in mediating reverse cholesterol transport from peripheral tissues, including macrophages in the atherosclerotic vessel wall, to the liver for elimination [6]. This property of HDL can be probed by measuring cholesterol efflux capacity – an independent biomarker for cardiovascular events [7]. Infusion of HDL mimetics directly increases the number of functional HDL particles in the circulation and therefore cholesterol efflux capacity [8]. Although results from older proof-of-principle studies were

encouraging [9], infusion of HDL mimetics did not regress coronary atherosclerosis in recent randomized clinical trials [10,11]. However, the patients in these trials received contemporary treatment for ASCVD and were characterized by normal HDL-cholesterol levels, potentially limiting any detectable effects. Whether infusion of HDL mimetics is effective in settings of strongly reduced levels of HDL-cholesterol and impaired cholesterol efflux capacity is unknown.

Patients with familial hypoalphalipoproteinemia (FHA) are characterized by loss-of-function variants in genes involved in HDL metabolism, such as *ABCA1* and *APOA1*, resulting in life-long reduced numbers of circulating HDL particles and diminished cholesterol efflux capacity [12]. These patients have genetically determined very low levels of HDL-cholesterol and can be hypothesized to have the most benefit from an increase in cholesterol efflux capacity following infusion of an exogenous HDL mimetic. Previously, in a small open-label study of patients with FHA, infusion of the HDL mimetic CER-001 resulted in increased cholesterol mobilization and reduced carotid artery wall dimensions and inflammation [13]. Following these findings, the current study was designed as a randomized clinical trial to evaluate the effects of 24 weeks of CER-001 infusions in patients with FHA on established imaging endpoints [14]: carotid artery dimensions and vessel wall inflammation, as measured with 3T-MRI and ^{18}F -FDG PET/CT respectively.

2. Materials and methods

2.1. Study design

This phase 3 study was conducted in accordance with the Declaration of Helsinki and in compliance with current Good Clinical Practices (ICH E6) and the requirements of the US Food and Drug Administration (21 CFR 312). The study (TANGO) was designed jointly by the academic investigators and the sponsor (Cerenis™ Therapeutics, France). The protocol was approved by the local institutional review board of all participating sites. All participants provided written informed consent prior to enrollment. In brief, we recruited patients ≥ 18 years of age with an HDL-cholesterol (≤ 0.9 mmol/L) or apolipoprotein (apo) A-I (≤ 1.1 g/L) deficiency due to homozygous or heterozygous variants in the *ABCA1* and/or *APOA1* genes confirmed by genetic testing. Patients were required to either have a history of symptomatic cardiovascular disease, defined as cardiovascular events, peripheral artery disease or previous arterial revascularization, or subclinical atherosclerosis, diagnosed using ultrasound, CT or MRI. Exclusion criteria included a variant in the *LCAT* gene, recent cardiovascular event (< 6 months prior to screening) or stroke (< 1 year prior to screening), hypertriglyceridemia (> 500 mg/dL), body mass index (BMI) < 17 kg/m 2 or > 40 kg/m 2 , or contraindications to MRI-scanning. After meeting the inclusion- and exclusion criteria, study participants were randomized in a 2:1 ratio to either CER-001 (8 mg/kg) or placebo treatment. The study was divided into three phases: an induction phase, in which drug was administered weekly through the first 8 weeks (9 doses), followed by a maintenance phase with infusions every two weeks during 16 weeks (8 doses), and an extension phase with infusions every two weeks for an additional 24 weeks (12 doses) (see Fig. 1). Patients completing the study were offered treatment with CER-001 for an additional 24 weeks (12 doses) in an open-label safety extension. Participants had a safety follow-up visit 4 weeks after the last dose administration.

2.2. Study assessments

At baseline, study participants underwent a physical examination with measurements of vital signs and electrocardiography, as well as collection of blood and urine for clinical laboratory determinations. During each dosing visit of CER-001 or placebo, participants had an evaluation of adverse events (AEs) and changes in medication use. Every four visits, a physical examination was performed and blood withdrawal

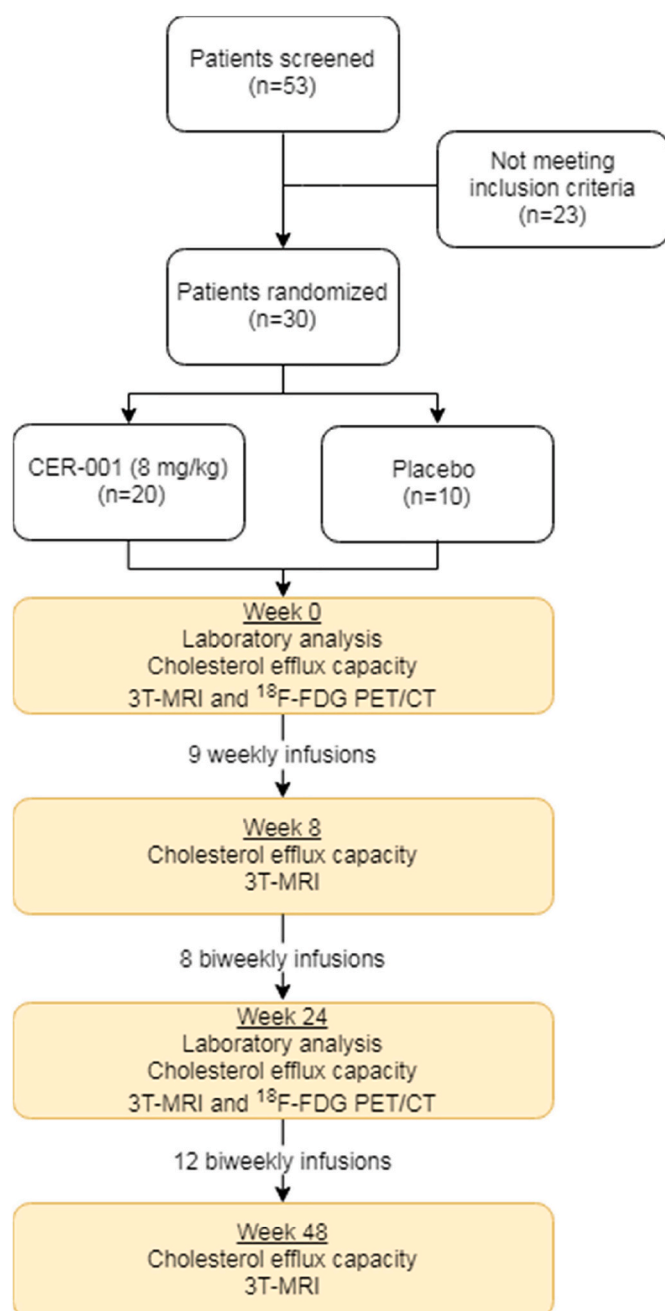


Fig. 1. Flow diagram of TANGO study.

Table 1
Baseline characteristics.

	CER-001 N = 20	Placebo N = 10	Total N = 30
Age, years	52.4 ± 8.1	53.1 ± 6.1	52.7 ± 7.4
Male sex, n (%)	13 (65.0)	6 (60.0)	19 (63.3)
APOA1 variant	9 (45.0)	4 (40.0)	13 (43.3)
ABCA1 variant	10 (50.0)	5 (50.0)	15 (50.0)
APOA1 and ABCA1 variant	1 (5.0)	1 (10.0)	2 (6.7)
BMI, kg/m ²	28.3 ± 5.1	30.4 ± 5.2	29.0 ± 5.1
Smoking status			
Former smoker	7 (35.0)	5 (50.0)	12 (40.0)
Non-smoker	9 (45.0)	4 (40.0)	13 (43.3)
Active smoker	4 (20.0)	1 (10.0)	5 (16.7)
Systolic blood pressure, mmHg	126 ± 13	135 ± 16	129 ± 14
Diastolic blood pressure, mmHg	79 ± 9	80 ± 13	79 ± 10
Glucose, mmol/l	5.5 ± 1.1	5.2 ± 0.6	5.4 ± 0.9
C-reactive protein, mg/l	1.40 [0.83–2.65]	2.10 [1.38–3.80]	1.65 [0.95–2.80]
Total cholesterol, mmol/l	3.27 ± 1.52	2.99 ± 0.68	3.17 ± 1.28
HDL-c, mmol/l	0.35 ± 0.29	0.35 ± 0.19	0.35 ± 0.25
LDL-c, mmol/l	2.23 ± 1.14	1.74 ± 0.56	2.06 ± 1.00
Triglycerides, mmol/l	1.50 [1.18–2.40]	1.76 [1.47–2.73]	1.59 [1.23–2.55]
Apolipoprotein A-I, g/l	0.50 ± 0.43	0.58 ± 0.30	0.53 ± 0.38
Lipid-lowering therapy	13 (65)	7 (70)	20 (66.7)
Cardiovascular disease	20 (100)	10 (100)	30 (100)
Subclinical atherosclerosis	6 (30.0)	7 (70.0)	13 (43.3)
Coronary artery disease	12 (60.0)	2 (20.0)	4 (13.3)
Myocardial revascularization	8 (40.0)	2 (20.0)	10 (33.3)
Stroke	1 (5.0)	1 (10.0)	1 (3.3)
Peripheral arterial disease	1 (5.0)	0 (0.0)	1 (3.3)

Values are listed as mean ± standard deviation, median [interquartile range] or number (percent).

and urine collection took place for the analysis of safety parameters. In addition, blood withdrawal at baseline and week 24 was used for analysis of plasma lipids and inflammatory markers at a dedicated core laboratory. Cholesterol efflux capacity was quantified from plasma samples obtained during the screening visit and 2 h after infusion at weeks 8, 24 and 48 using previously validated methods [15]. Patients had an additional safety follow-up visit four weeks after the last dose.

2.3. Imaging procedures

Patients underwent 3T-MRI at baseline, weeks 8, 24 and 48 for carotid mean vessel wall area (MVWA) measurements. 3T-MRI scans were performed with a dedicated carotid phased array coil of at least 4 channels for carotid imaging. For the carotid arteries, after initial scout scans, axial T1-weighted and T2-weighted turbo-spin echo images were acquired, centred at the right carotid artery, with double inversion recovery preparation for black blood. MRI sequence parameters are listed in [Supplementary Tables S1 and S2](#). Analysis of MVWA of the right carotid artery were performed by a blinded reader of the imaging core lab using dedicated software. ¹⁸F-FDG PET/CT was performed at baseline and after 24 weeks of treatment. ¹⁸F-FDG uptake in the common carotid arteries, quantified as standardized uptake value (SUV), was assessed by a blinded reader from the imaging core lab according to previously described methods [16]. The carotid artery with the highest baseline ¹⁸F-FDG uptake was defined as the index vessel. The obtained arterial SUV was corrected for the background blood activity in the venous blood pool to derive the target-to-background ratio of the most diseased segment (TBR_{MDS}).

2.4. Statistical analysis

The primary efficacy parameter of this study was the absolute change in the carotid artery MVWA on 3T-MRI after 24 week treatment with CER-001 as compared with placebo. Secondary efficacy parameters were changes after 8 and 48 weeks of treatment with CER-001 on carotid MVWA compared with placebo, and change after 24 weeks in the TBR_{MDS}. Power calculations are provided in Supplementary Materials. For safety evaluations, all randomized patients who received at least one

dose of study medication were included. The primary efficacy endpoint, the difference in the change from baseline in carotid MVWA at 24 weeks in patients treated with CER-001 compared with placebo, was analysed using a linear mixed model which included treatment group, baseline MVWA and the genetic variant (*ABCA1* and/or *APOA1*) as a covariate. Secondary endpoints were analysed using the same linear mixed model as for the primary endpoint. Descriptive statistics are provided for all safety parameters.

3. Results

3.1. Baseline characteristics of patients

Between December 4th, 2015 and October 2nd, 2017, a total of 53 patients at 16 centers in the Netherlands, Belgium, France, Italy, Israel, Canada and US were screened, of whom 30 were randomized to receive either CER-001 or placebo. A total of 28 (93%) participants completed the first 8 weeks of treatment, 27 (90%) participants completed 24 weeks of treatment, and all these participants also completed the extension period up to week 48. Baseline characteristics are listed in [Table 1](#). The mean age of the patients was 52.7 ± 7.4 years and 19 (63%) were male.

Of the randomized patients, 15 had variants in *ABCA1* (7 had a homozygous variant), 13 had variants in *APOA1* (2 had a homozygous variant), and 2 participants had heterozygous variants in both genes ([Supplementary Table S3](#)). Accordingly, all patients were characterized by low levels of HDL-cholesterol (mean 0.35 ± 0.25 mmol/L) and apoA-I (mean 0.53 ± 0.38 g/L). Patients in the CER-001 treatment group were well balanced compared with the placebo group with respect to traditional ASCVD risk factors, baseline HDL-cholesterol and apoA-I levels. Furthermore, all patients were characterized by the presence of ASCVD, with a diagnosis of subclinical atherosclerosis in 6 (30%) participants in the CER-001 treatment group and 7 (70%) in the placebo group.

3.2. Effects on plasma lipid and inflammatory biomarkers

After 24 weeks of treatment, comprising 9 weekly infusions followed by 8 infusions every two weeks, there was no difference in HDL-

Table 2
Cholesterol efflux capacity.

Timepoint	Cholesterol efflux capacity, %		Treatment difference (CER-001 minus placebo)	p-value
	CER-001	Placebo		
Baseline (W0)	4.73 [1.84–7.88]	5.84 [3.42–8.70]	–	–
Week 8	5.62 [3.68–9.71]	5.47 [4.68–8.11]	2.40 [1.04–3.77]	<0.001
Week 24	5.45 [3.46–9.84]	5.00 [2.58–7.26]	2.53 [1.19–3.86]	<0.001
Week 48	6.91 [3.62–8.54]	5.89 [3.81–6.97]	1.68 [0.35–3.01]	0.0141

Cholesterol efflux capacity was quantified from whole plasma samples obtained during the baseline visit and 2 h after infusion at week 8, week 24 and week 48. A linear mixed model with repeated measures was used to assess the change in cholesterol efflux capacity from baseline to week 8, week 24 and week 48. Values are listed as median [interquartile range].

Table 3
Carotid mean vessel wall area (3T-MRI).

Timepoint	Carotid MVWA, mm ²		Treatment difference (CER-001 minus placebo)	p-value
	CER-001	Placebo		
Baseline (W0)	22.92 ± 4.89	27.13 ± 11.28	–	–
Week 8	22.83 ± 4.91	26.41 ± 10.48	0.69 [–0.54–1.93]	0.27
Week 24	22.69 ± 4.86	27.46 ± 10.71	–0.77 [–2.00–0.45]	0.21
Week 48	22.62 ± 4.36	27.45 ± 11.79	–0.20 [–1.48–1.08]	0.76

A linear mixed model with repeated measures was used to assess the change in carotid artery mean vessel wall area from baseline to week 8, week 24 and week 48. MVWA = mean vessel wall area. Values are listed as mean ± standard deviation or median [interquartile range].

cholesterol and apoA-I levels compared to baseline in both treatment groups, as expected due to the plasma half-life of CER-001. Other plasma lipid and inflammatory biomarkers were also unaffected after 24 weeks of treatment, as depicted in [Supplementary Table S3](#).

3.3. Cholesterol efflux capacity increases significantly after CER-001 infusion

Plasma-mediated cholesterol efflux capacity was measured during the screening visit, and study visits on week 8 and 24, at 2 h post-infusion. At baseline, there was no significant difference in absolute cholesterol efflux capacity between patients randomized to CER-001 and placebo (4.73 [1.84–7.88] % vs. 5.84 [3.42–8.70] %) ([Table 2](#)). At the week 8 visit, infusion of CER-001 resulted in a significant upregulation of cholesterol efflux capacity with an absolute treatment difference of 2.40 [1.04–3.77]% compared with placebo ($p < 0.001$). This increase of cholesterol efflux capacity by CER-001 infusion persisted after 24 and 48 weeks of treatment, with an absolute treatment difference of 2.53 [1.19–3.86]% ($p \leq 0.001$) and 1.68 [0.35–3.01]% ($p = 0.0141$) respectively, compared with placebo.

3.4. Carotid artery imaging efficacy endpoints

The imaging end points of change in carotid MVWA as measured by 3T-MRI are summarized in [Table 3](#). The mean carotid MVWA at baseline was 22.92 ± 4.89 mm² in the CER-001 treatment group versus 27.13 ± 11.28 mm² in the placebo group. At the week 8 MRI scan, performed after 9 weekly infusions, we did not observe a difference in carotid MVWA between patients treated with CER-001 and placebo (treatment difference 0.69 [–0.54–1.93] mm², $p = 0.27$). After 24 weeks of treatment (9 weekly infusions followed by 8 infusions every two weeks),

carotid MVWA in the CER-001 treatment decreased numerically to 22.69 ± 4.86 mm², but we observed no significant differences compared with placebo (treatment difference –0.77 [–2.00–0.45] mm², $p = 0.21$). Finally, there was also no significant effect of CER-001 compared with placebo at the week 48 visit (treatment difference –0.20 [–1.48; 1.08] mm², $p = 0.76$).

In an exploratory sensitivity analysis, the effect of CER-001 compared with placebo on carotid MVWA after 24 weeks was consistent across the subgroups of patients with a loss-of-function variant in *ABCA1* (treatment difference: 0.84 [–2.52; 0.85] mm²; $p = 0.32$) and those with only a loss-of-function variant in *APOA1* (treatment difference: 0.59 [–2.18; 1.00] mm², $p = 0.45$).

The secondary imaging endpoint of changes in carotid arterial wall inflammation as measured by ¹⁸F-FDG PET/CT are listed in [Table 4](#). At baseline, carotid ¹⁸F-FDG uptake was comparable between treatment groups (CER-001 TBR_{MDS} 1.38 ± 0.14 versus placebo TBR_{MDS} 1.45 ± 0.26). No significant changes were observed between groups after 24 weeks of treatment ($n = 24$), treatment difference 0.10 [–0.13–0.33], $p = 0.37$).

3.5. Safety

Study infusions were generally well tolerated in this study. In total, 3 patients had adverse events leading to permanent discontinuation of the study medication before 48 weeks, all of whom were in the CER-001 group. These adverse events consisted of one case of unstable angina during the first infusion visit (W0), one anaphylactic reaction with angioedema during the first infusion visit (W0), and one subject who developed a skin rash after infusion (W6). Furthermore, one participant discontinued CER-001 at week 56 during the open-label safety extension due to a skin rash. We did not observe any clinically significant changes

Table 4
Carotid ¹⁸F-FDG uptake.

Timepoint	Carotid mean TBR _{MDS}		Treatment difference (CER-001 minus placebo)	p-value
	CER-001	Placebo		
Baseline (W0)	1.38 ± 0.14	1.45 ± 0.26		
Week 24	1.49 ± 0.30	1.45 ± 0.23	0.10 [–0.13–0.33]	0.37

A linear mixed model was used to assess the change in carotid mean TBR_{MDS} from baseline to week 24. TBR_{MDS} = target-to-background ratio of the most diseased segment. Values are listed as mean ± standard deviation or median [interquartile range].

in the differential white blood cell counts. Clinical and biochemical adverse events are listed in [Supplementary Table S4](#).

4. Discussion

In patients with genetically determined very low HDL-cholesterol levels, infusion of the HDL mimetic CER-001 did not demonstrate beneficial effects on carotid atherosclerosis after 24 weeks of treatment, compared with placebo. While CER-001 increases cholesterol efflux capacity upon infusion, this did not result in a reduction of carotid vessel wall dimensions as measured by 3T-MRI, nor in a reduction of arterial wall inflammation, as measured by ^{18}F -FDG PET/CT. These findings do not support clinical use of HDL mimetic CER-001 to regress atherosclerosis in the setting of familial hypoalphalipoproteinemia.

The concept of HDL targeted therapy is strongly rooted in numerous experimental studies, which established that promoting the RCT pathway reduces atherosclerosis in animal models, irrespective of whether this was achieved by transgenic expression of apoA-I, hepatic transfection of apoA-I or infusion of apoA-I containing HDL particles [3]. In humans, the most analogous intervention to promote RCT is intravenous infusion of HDL mimetics. Nonetheless, previous randomized clinical trials investigating the effect of HDL mimetics MDCO-21 [10], CSL111 [17] and CER-001 [18] all failed to regress coronary plaques on intravascular ultrasound in patients after recent acute coronary syndrome. In this study, we included patients with severe loss-of-function variants in the *ABCA1* and *APOA1* genes, causing very low HDL-cholesterol levels and increased risk of ASCVD [12], since these patients can be hypothesized to have the greatest benefit from HDL infusion aimed at restoring cholesterol efflux capacity [13]. Our finding that CER-001 does not regress carotid atherosclerosis despite increasing cholesterol efflux capacity in patients with genetically determined very low HDL-c levels is another lead suggesting infusion of HDL mimetics is ineffective to induce regression of atherosclerosis in contemporary patients.

There are several possible explanations for the lack of a beneficial effect on carotid atherosclerosis in the present study. First, in order to demonstrate regression of atherosclerosis, sufficient plaque burden should ideally be present at baseline [19]. While the current study recruited FHA patients with signs of macrovascular atherosclerosis, reflected by the increased MVWA of thickened carotid arteries [20], the presence of overt carotid plaques was relatively minor, potentially limiting the detection of effects. Nevertheless, mean vessel wall area of participants in the present study ($22.9 \pm 4.9 \text{ mm}^2$ in the CER-001 group and $27.1 \pm 11.3 \text{ mm}^2$ in the placebo group) were significantly increased compared to those previously observed with 3T-MRI in younger healthy subjects, as well as older healthy subjects ($10.1 \pm 1.5 \text{ mm}^2$ and $16.1 \pm 3.8 \text{ mm}^2$ respectively) [21]. In fact, MVWA was comparable to patients with established cardiovascular disease ($22.0 \pm 6.8 \text{ mm}^2$). However, the CARAT trial, which prospectively recruited patients with acute coronary syndrome and >30% percent atheroma volume on intravascular ultrasound, was also unable to demonstrate plaque regression by serial low-dose (3 mg/kg) CER-001 infusions despite preselection for marked baseline plaque burden [11].

Second, it can be speculated that the current infused dose of 8 mg/kg of CER-001 is insufficient to achieve a significant reduction in plaque size. Cholesterol efflux capacity was previously found to be 11% on average in a cohort of healthy volunteers [22]. In the current study, CER-001 significantly increased cholesterol efflux capacity to 5.5% (at 24 weeks), which is known to return to pre-infusion levels after approximately 24 h [13]. Although infusions were performed on a (bi) weekly basis, these observations suggest that the magnitude and period of time of increased *in vivo* cholesterol efflux capacity may have been insufficient. Previous studies administered other HDL-mimetics, MDCO-216 (20 mg/kg) and CSL111 (~80 mg/kg), at several-fold higher doses, leading to profound increases in *ex vivo* cholesterol efflux capacity [23,24]. Yet, at higher concentrations these compounds

also failed to reduce coronary plaque size, regardless of stronger up-regulation of cholesterol efflux capacity compared with the current study. In fact, it has been suggested that higher dosing of HDL mimetics may even result in downregulation of the ABCA1 transporter, potentially impairing efficient RCT by infused HDL [25]. The apparent disconnect between increased cholesterol efflux capacity and absence of effect on arterial wall dimensions is further complicated by a discordant study that challenged whether this biomarker captures HDL functionality and predicts risk of cardiovascular events [26].

Third, HDL infusion may not provide incremental benefit when levels of low-density lipoprotein cholesterol and other apoB-containing lipoproteins are managed using statin therapy. It is known that statin therapy regresses carotid atherosclerosis predominantly in the first 6 months in patients with familial hypercholesterolemia, indicating that a marked atherogenic lipoprotein burden is required to demonstrate regression of atherosclerosis [27]. In the ENHANCE study, the failure of ezetimibe to reduce carotid intima-media thickness was in part attributed to the prior treatment with statins [28], leading to delipidation of carotid plaques [29]. Conversely, two pilot studies suggested CER-001 [30] and autologous delipidated HDL (NCT03135184) do reverse atherosclerosis in patients with homozygous familial hypercholesterolemia, who are burdened by extremely high residual ASCVD risk due to uncontrolled hypercholesterolemia in spite of intensive statin therapy. Therefore, we cannot exclude whether prior treatment with lipid-lowering drugs may have obscured an effect of CER-001 on carotid MVWA in the current study.

What have we learned from interventional studies evaluating the effects of HDL mimetic infusion in patients with ASCVD? To date, all HDL mimetic compounds failed to regress atherosclerosis across a range of patient demographics, doses, treatment regimens and formulations, when subjected to the rigor of a randomized trial design [31]. HDL mimetic therapy has primarily been envisaged as a short-term intervention due to the invasive nature of repetitive intravenous infusions. Therefore, one aspect common to these trials was the measurement of atheroma dimensions as surrogate endpoint after a relatively short treatment duration: 4–10 weeks for post-acute coronary syndrome trials and 24–48 weeks in the current study. In patients taking medium-to-high intensity statin therapy, this period may be insufficient to detect plaque regression. Indeed, contemporary imaging studies demonstrate that strong intensification of lipid-lowering therapy, entailing PCSK9-inhibition on top of high intensity statin therapy, results in changes in coronary plaque size after 18 months [32], although changes in plaque composition can be observed at an earlier stage [33]. Whether HDL infusion therapies reduce ASCVD risk through mechanisms other than plaque regression cannot be determined from available human data. The only HDL mimetic still under investigation is CSL112, which has progressed to a large phase 3 outcomes trial (AEGIS-II; NCT03473223) and will provide a definitive answer to whether infusion of HDL mimetics reduces ASCVD event risk in patients.

4.1. Limitations

While the cholesterol efflux mediated by pre-beta HDL is considered to be dependent upon the ABCA1 transporter, previous work indicates significant contributions of other efflux pathway mediators, including ABCG1, SRB1 and passive diffusion [34]. In support, residual cholesterol efflux capacity in patients with loss-of-function variants in ABCA1 was associated with the degree of arterial wall thickening. Furthermore, beneficial effects of HDL infusion in patients with loss-of-function variants in ABCA1 were observed in pilot studies [13,35]. Therefore, we hypothesized that patients with FHA, including those with *ABCA1* loss-of-function variants, would benefit from infusion of CER-001 to increase the number of circulating cholesterol acceptors. Although this study was not powered for an accurate analysis of genetic subsets, an exploratory sensitivity analysis did not indicate a different therapeutic response in patients with an *ABCA1* variant. Because prior results

demonstrated that CER-001 mobilized cholesterol in patients with FHA, we did not repeat serial lipid profiling in the current study.

Considering that FHA is a rare genetic disorder, it was not feasible to perform a large imaging trial or to assess hard clinical endpoints over a period of several years, but the current study had sufficient power to detect a similar reduction of carotid MVWA previously observed in the open-label SAMBA study in patients with FHA [13]. We standardized the scanning protocols across different 3T-MRI equipment brands, but we cannot exclude that inherent variation across multiple centers introduced variability in MRI measurements, although previous studies have shown that 3T-MRI measurements of carotid atherosclerosis are highly reproducible, with an interscan variability of 0.99 (0.98–0.99) and inter- and intraobserver variability of 0.99 (0.98–0.99) and 0.97 (0.95–0.98), respectively [21,36]. Thus, we performed serial imaging with 3T-MRI to assess changes in atherosclerotic burden as primary endpoint. However, there was no observable trend toward efficacy of CER-001 compared with placebo. Furthermore, we cannot exclude any beneficial effects of CER-001 on plaque composition, although this is unlikely given the lack of a favorable signal by ¹⁸F-FDG PET/CT imaging, a secondary endpoint of the study.

4.2. Conclusion

In patients with genetically determined very low HDL-cholesterol levels based on FHA, we did not observe a reduction of atherosclerotic plaque size, nor arterial wall inflammation after 24 weeks of treatment with CER-001 infusions compared with placebo, despite an increase in cholesterol efflux capacity. These results are in line with contemporary randomized clinical trials, which failed to demonstrate benefit of HDL infusion on imaging endpoints in atherosclerosis.

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CRediT authorship contribution statement

Kang H. Zheng: Investigation, Writing - original draft, Formal analysis. **Yannick Kaiser:** Writing - original draft, Formal analysis. **Casper C. van Olden:** Investigation, Writing - review & editing. **Raul D. Santos:** Investigation, Writing - review & editing. **Jean-Louis Dasseux:** Conceptualization, Resources, Project administration, Funding acquisition, Writing - review & editing. **Jacques Genest:** Investigation, Resources, Writing - review & editing. **Daniel Gaudet:** Investigation, Writing - review & editing. **Jan Westerink:** Investigation, Writing - review & editing. **Constance Keyserling:** Conceptualization, Resources, Data curation, Project administration, Funding acquisition, Writing - review & editing. **Hein J. Verberne:** Investigation, Writing - review & editing. **Eran Leitersdorf:** Investigation, Writing - review & editing. **Robert A. Hegele:** Investigation, Writing - review & editing. **Olivier S. Descamps:** Investigation, Writing - review & editing. **Paul Hopkins:** Investigation, Writing - review & editing. **Aart J. Nederveen:** Investigation, Writing - review & editing. **Erik S.G. Stroes:** Project administration, Supervision, Methodology, Funding acquisition, Conceptualization, Writing - review & editing.

Declaration of competing interest

R.D.S. has received honoraria related to consulting, research and/or speaker activities from Akcea, Amgen, Astra Zeneca, Esperion, Kowa, Novo-Nordisk, Merck, MSD, Pfizer, PTC and Sanofi/Regeneron; and he is recipient of a scholarship from the Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico (CNPq), Brazil #303734/2018–3. O.S.D.

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Appendix A. Supplementary data

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