JACC VOL. ■, NO. ■, 2025

Effect of ANGPTL3 Inhibition With Solbinsiran in Preclinical and Early Human Studies

Kausik K. Ray, FMEDSCI,[a] Helle Linnebjerg, PHD,[b] Laura F. Michael, PHD,[b] Xi Shen, PHD,[b] Xiaosu Ma, PHD,[b] Shufen Lim, PHD,[b] Eugene Y. Zhen, PHD,[b] Henryk Dudek, PHD,[c] Marc Abrams, PHD,[c,d] Utsav Saxena, PHD,[c] Anton Turanov, PHD,[c] Stephen J. Nicholls, PHD,[e] Giacomo Ruotolo, MD[b]

ABSTRACT

BACKGROUND The residual cardiovascular risk associated with hypertriglyceridemia and remnant particles supports efforts to develop effective novel therapeutic approaches. Angiopoietin-like protein 3 (ANGPTL3) inhibits lipoprotein and endothelial lipases, and Mendelian randomization studies associate lower ANGPTL3 activity with lower triglycerides, and lower cardiovascular risk.

OBJECTIVES The aim of this study was to evaluate the impact of solbinsiran, an N-acetylgalactosamine-conjugated small interfering RNA developed to inhibit hepatic translation of *ANGPTL3* messenger RNA (mRNA), on ANGPTL3 and lipid levels in preclinical models and humans.

METHODS In preclinical studies, the impact of solbinsiran on ANGPTL3 levels was assessed in mouse and nonhuman primate models. The phase 1 clinical study enrolled participants with mixed dyslipidemia. In the single-ascending-dose study, participants received single subcutaneous doses of solbinsiran (24-960 mg) or matching placebo. In the repeat-dose study, subcutaneous solbinsiran (208 or 480 mg) or matching placebo on days 1 and 29 was evaluated. Safety, pharmacokinetics, and effect on levels of ANGPTL3 and lipid parameters were evaluated over 169 days.

RESULTS In mice transiently expressing human *ANGPTL3*, a single dose of solbinsiran reduced hepatocyte *ANGPTL3* mRNA expression by 65% vs vehicle-treated mice. In cynomolgus monkeys, mean ± SEM reductions in hepatic *ANGPTL3* mRNA expression up to 73% ± 2% ($P < 0.0001$) and serum ANGPTL3 protein expression up to 69% ± 4% ($P < 0.001$) were seen vs vehicle-treated monkeys. In humans, a single dose of solbinsiran resulted in dose-dependent mean ± SD percentage reductions from baseline in ANGPTL3 up to 86% ± 4%, triglycerides up to 73% ± 7%, low-density lipoprotein (LDL) cholesterol up to 30% ± 16%, non–high-density lipoprotein cholesterol up to 41% ± 12%, and apolipoprotein B up to 30% ± 11%, with sustained effects at higher doses ($P < 0.0001$ for all). The repeat-dose study demonstrated reductions in ANGPTL3 of 89% ± 6%, triglycerides up to 70% ± 13%, LDL cholesterol up to 42% ± 14%, non–high-density lipoprotein cholesterol up to 46% ± 14%, and apolipoprotein B up to 36% ± 13% ($P < 0.0001$ for all). Nuclear magnetic resonance lipoprotein analysis demonstrated reductions in the total number of triglyceride-rich lipoprotein and LDL particles with solbinsiran. Adverse events were mostly mild in severity, with similar incidence in solbinsiran- and placebo-treated participants.

CONCLUSIONS Solbinsiran inhibits hepatic *ANGPTL3* translation and results in significant reductions in all atherogenic lipoproteins in mixed dyslipidemia. The impact of this approach on cardiovascular outcomes remains to be determined. (A Study of LY3561774 in Participants With Dyslipidemia; NCT04644809) (JACC. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Public Health and Primary Care, Imperial College London, London, United Kingdom; [b]Eli Lilly & Company, Indianapolis, Indiana, USA; [c]Dicerna Pharmaceuticals, Lexington, Massachusetts, USA; [d]Carbon Biosciences, Waltham, Massachusetts, USA; and the [e]Victorian Heart Institute, Monash University, Clayton, Victoria, Australia.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 24, 2025; revised manuscript received February 25, 2025, accepted March 2, 2025.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2025.03.005

ABBREVIATIONS AND ACRONYMS

ABCA1 = adenosine triphosphate-binding cassette transporter A1

ANGPTL3 = angiopoietin-like protein 3

apo = apolipoprotein

AUC = area under the concentration-time curve

C_{max} = maximum observed drug concentration

GalNAc = N-acetylgalactosamine

HDL = high-density lipoprotein

HDL-C = high-density lipoprotein cholesterol

HDL-P = high-density lipoprotein particles

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein cholesterol

LDL-P = low-density lipoprotein particles

mRNA = messenger RNA

NMR = nuclear magnetic resonance

siRNA = small interfering RNA

TEAE = treatment-emergent adverse event

TRL-P = triglyceride-rich lipoprotein particles

Despite widespread use of statins to reduce levels of low-density lipoprotein cholesterol (LDL-C) in high-risk cardiovascular patients, many clinical events continue to occur.[1] This residual risk supports the need to develop additional therapeutic strategies to achieve more effective reduction in cardiovascular risk by targeting additional risk factors. Analyses from cohort studies and randomized clinical trials of lipid-lowering therapies have established that elevated triglyceride levels are associated with residual cardiovascular risk.[2] Genetic studies have demonstrated that mutations in lipoprotein lipase gene are significantly associated with higher triglyceride levels and higher risk for cardiovascular events.[3] These findings implicate the role of triglycerides, or pathways involved in their regulation, in the causal process of atherosclerotic cardiovascular disease. Triglycerides are carried in apolipoprotein (apo) B-containing lipoproteins, and these triglyceride-rich lipoproteins and their remnants also contain cholesterol, commonly known as remnant cholesterol. The importance of remnant cholesterol in cardiovascular disease is further supported by recent data showing that individual triglyceride-rich lipoproteins may be more atherogenic than low-density lipoprotein (LDL) particles.[4-6] On the basis of these observations, there is considerable interest in developing therapies that modulate triglyceride-rich lipoprotein metabolism.

Angiopoietin-like protein 3 (ANGPTL3) is a key regulator of triglyceride-rich lipoprotein metabolism via inhibition of lipoprotein lipase and endothelial lipase.[7] In addition to elevating triglyceride levels, ANGPTL3 regulates the production and clearance of LDL particles (LDL-P) through a mechanism that is independent of the LDL receptor.[7,8] Specifically, ANGPTL3 facilitates the clearance of intermediate-density lipoprotein particles (remnants), upstream of LDL production. Fewer LDL-P are formed (which is likely why it is LDL receptor independent). The observation that genetic variants resulting in less ANGPTL3 are associated with lower levels of triglycerides, LDL-C, and apoB, in addition to lower rates of cardiovascular disease,[9,10] supports interest in the development of ANGPTL3 inhibitors for the treatment of patients with a broad spectrum of lipid disorders from severe hypercholesterolemia to severe hypertriglyceridemia. As the *ANGPTL3* gene is expressed mainly in the liver, RNA interference-based therapeutic approaches that inhibit hepatic translation of *ANGPTL3* messenger RNA (mRNA) have the potential to modulate levels of atherogenic lipid parameters.

Solbinsiran (LY3561774) is a small interfering RNA (siRNA) therapeutic with a nucleotide base sequence selected from an in silico RNA interference prediction algorithm, followed by validation of activity in vitro and in vivo, and is designed to reduce the expression of *ANGPTL3* mRNA, known to be conserved in humans and cynomolgus monkeys. Solbinsiran is N-acetylgalactosamine (GalNAc)-conjugated (Supplemental Figures 1A and 1B).[11] The use of GalNAc conjugation permits selective and targeted delivery of the siRNA to the hepatocyte, with the potential for minimization of adverse effects. The purpose of these studies was to determine the ability of solbinsiran to reduce *ANGPTL3* expression in preclinical models and, subsequently, safety, pharmacokinetics, and lipid efficacy in humans with mixed dyslipidemia.

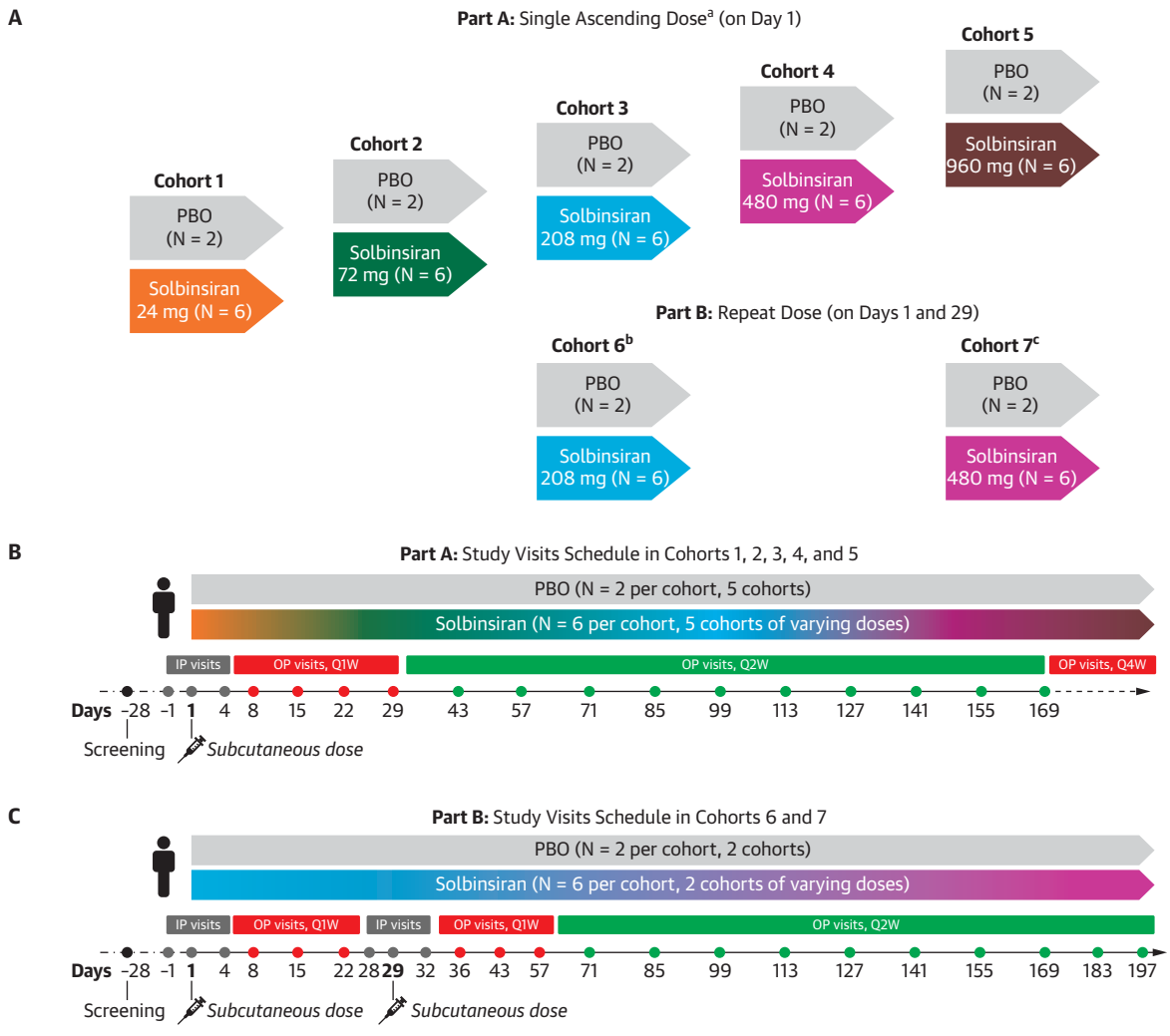
METHODS

PRECLINICAL STUDIES. Details of the preclinical studies are available in the Supplemental Appendix. Briefly, studies were performed in female CD1 mice aged 6 to 8 weeks. Mice received a single subcutaneous injection of solbinsiran or phosphate-buffered saline vehicle and on day 4 received tail-vein injections of 20 μg pcDNA3-hANGPTL3 plasmid in 2 mL phosphate-buffered saline for transient expression of human ANGPTL3. On day 5, the mice were killed, and liver tissue was collected for analysis of *ANGPTL3* mRNA expression.

A nonhuman primate study was conducted in cynomolgus monkeys (3-13 years of age, weight 3.1-7.6 kg). Monkeys were treated with a single subcutaneous injection of 3 mg/kg solbinsiran or phosphate-buffered saline vehicle. On study days −5, 28, 56, 84, and 113, liver tissue samples were collected by percutaneous biopsy for analysis of *ANGPTL3* mRNA expression. Serum ANGPTL3 protein concentrations were measured using enzyme-linked immunosorbent assay.

CLINICAL STUDY DESIGN AND STUDY POPULATION. The full study protocol is available as part of the Supplemental Appendix. Briefly, a phase 1, multicenter, double-blind, placebo-controlled randomized trial was conducted to assess the safety, pharmacokinetics, and effect of solbinsiran on ANGPTL3 and lipid parameters. Inclusion criteria included age 18 to 65 years, body mass index between 18.5 and 40.0 kg/m^2, triglyceride levels between 150 and 499 mg/dL, and LDL-C levels of at least 70 mg/dL. The

FIGURE 1 Clinical Study Design



(A) Dose regimen and cohorts in the single-ascending-dose study and repeat-dose study. Single-ascending-dose study: up to 5 single-ascending-dose levels of solbinsiran in 5 cohorts of 6 individuals. Repeat-dose study: repeat doses administered on days 1 and 29 in 2 cohorts of 6 individuals. (B) Study visit schedule in the single-ascending-dose study. (C) Study visit schedule in the repeat-dose study. [a]Safety and tolerability review included results for adverse events, clinical safety laboratory tests, vital signs, and 12-lead electrocardiography from at least 5 participants who received solbinsiran. [b]The repeat-dose study was initiated after review of the safety, tolerability, pharmacokinetic, and pharmacodynamic data up to day 15 in cohort 3 of the single-ascending-dose study. [c]The second dose level in the repeat-dose study was selected on the basis of the safety, tolerability, pharmacokinetic, and pharmacodynamic data up to day 8 from at least 5 participants in cohort 4 of the single-ascending-dose study. IP = inpatient; OP = outpatient; PBO = placebo; Q1W = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.

use of a statin was not mandatory but allowed, whereas all other lipid-lowering medications were prohibited during the trial.

The study consisted of a single-ascending-dose study and a repeat-dose study (Figure 1). The single-ascending-dose study recruited 40 participants who were randomized to receive a single subcutaneous dose of solbinsiran (n = 30; 24, 72, 208, 480, or 960 mg) or matching placebo (n = 10) on day 1. The repeat-dose study recruited 16 participants who were randomized to receive subcutaneous doses of solbinsiran (n = 12; 208 or 480 mg) or matching placebo (n = 4) on days 1 and 29.

The safety assessment included electrocardiography, vital signs (blood pressure and heart rate), clinical laboratory tests, and the number of reported

adverse events and their severity and potential relationship to study drug during follow-up. Evaluation of injection-site reactions was prespecified and classified by the presence of erythema, induration, pain, pruritus, or edema. For assessment of pharmacokinetics, plasma concentrations were measured at 11 time points after dosing. Pharmacokinetic parameter estimates were calculated using standard noncompartmental methods of analysis using Phoenix WinNonlin version 8.1.1 (Certara). Plasma concentrations of solbinsiran were used to determine the pharmacokinetic parameters, including maximum observed drug concentration (C_{max}), area under the concentration-time curve (AUC) from time 0 to t, where t is time of last quantifiable sample (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$) of solbinsiran.

Fasting blood samples for measurement of lipid profile and ANGPTL3 were obtained on days 1, 2, and 4, then weekly (weeks 2-5) and fortnightly (weeks 7-25), in the single-ascending-dose study and before each dose and weekly (up to week 9), then fortnightly (weeks 11-29), in the repeat-dose study. The following analytes were measured using Roche Cobas 8000 (LabCorp) by either enzymatic (total cholesterol, triglycerides, direct LDL-C, and high-density lipoprotein cholesterol [HDL-C]) or immunoturbidimetric (apoB, apoA-I, and apoC-III) methods. Very low-density lipoprotein cholesterol was calculated as total cholesterol minus HDL-C minus direct LDL-C. Non-HDL-C was calculated as total cholesterol minus HDL-C. ANGPTL3 and ANGPTL3/8 complex were measured using enzyme-linked immunosorbent assay. Lipoprotein particle concentration and average lipoprotein particle size, as well as triglyceride-rich lipoprotein cholesterol were measured using nuclear magnetic resonance (NMR) spectroscopy (LabCorp).[12] The NMR-derived lipoprotein insulin resistance score, a weighted combination of 6 lipoprotein subclass measures (large triglyceride-rich lipoprotein particles [TRL-P], large HDL particles [HDL-P], small LDL-P, and mean sizes of TRL-P, LDL-P, and HDL-P) was also calculated. Cholesterol efflux capacity (a measure of HDL functionality) was assessed by incubation with J774 macrophages after depleting participant serum of apoB particles using polyethylene glycol precipitation (Vascular Strategies). The intra-assay and interassay coefficients of variation were 8% and 10% for global efflux and 9% and 15% for adenosine triphosphate-binding cassette transporter A1 (ABCA1)-mediated efflux, respectively. Non-ABCA1-mediated efflux was calculated as the difference between global and ABCA1-mediated efflux.[13,14]

STATISTICAL ANALYSIS. Safety endpoints were reported as counts and proportions. Pharmacokinetic parameters were listed and summarized by part, treatment, and study day. Dose proportionality was assessed in each part of the study. In the single-ascending-dose study, log-transformed pharmacokinetic parameters of solbinsiran were evaluated using a power model, in which log dose acts as an explanatory variable. Estimate ratios of dose-normalized geometric mean and 90% CIs were calculated, and the ratios between the highest and lowest doses were assessed; time to C_{max} was analyzed using a Kruskal-Wallis test. In the repeat-dose study, log-transformed pharmacokinetic parameters were dose normalized and analyzed using a linear mixed effects model for repeated measures. The treatment differences were back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs; time to C_{max} was analyzed using a Wilcoxon rank sum test.

The pharmacodynamic endpoints were the percentage change from baseline for ANGPTL3, ANGPTL3/8, triglycerides, LDL-C, HDL-C, non-HDL-C, apoA-I, apoB, apoC-III, and very low-density lipoprotein cholesterol, which were analyzed using a mixed-effects model for repeated measures. The percentage changes from baseline for pharmacodynamic parameters in the single-ascending-dose study were analyzed using a mixed-effects model for repeated measures. The estimated mean percentage change from baseline for each treatment and respective 90% CIs, and the difference in estimated mean percentage change from baseline, comparing solbinsiran and placebo, along with the 90% CI for the differences, were reported. Data analyses were performed using SAS version 9.4 (SAS Institute).

ETHICS. The study was sponsored and designed by Eli Lilly & Company, and the study protocol was approved by an independent ethics committee and was carried out in accordance with the Declaration of Helsinki and in compliance with current regulations and standards of Good Clinical Practice. All participants provided written informed consent.

RESULTS

PRECLINICAL STUDIES. In CD1 mice, a single subcutaneous dose of solbinsiran 1 mg/kg resulted in a 65% reduction in human *ANGPTL3* mRNA levels compared with vehicle-treated mice ($P < 0.001$) (Supplemental Figure 2A). In the studies of cynomolgus monkeys, a single subcutaneous dose of 3 mg/kg dose solbinsiran resulted in mean ± SEM

TABLE 1 Baseline Demographic Characteristics

		Single-Ascending-Dose Study					Repeat-Dose Study	
	Pooled PBO (n = 14)	Solbinsiran 24 mg (n = 6)	Solbinsiran 72 mg (n = 6)	Solbinsiran 208 mg (n = 6)	Solbinsiran 480 mg (n = 6)	Solbinsiran 960 mg (n = 6)	Solbinsiran 208 mg (n = 6)	Solbinsiran 480 mg (n = 6)
Age, y	52.0 (39.0-59.0)	46.5 (41.0-64.0)	52.0 (46.0-60.0)	47.5 (44.0-65.0)	41.5 (28.0-63.0)	54.5 (39.0-59.0)	54.0 (51.0-59.0)	55.0 (49.0-64.0)
Male	9 (64)	6 (100)	3 (50)	4 (67)	5 (83)	6 (100)	5 (83)	1 (17)
BMI, kg/m^2	33.0 (27.0-39.0)	31.0 (26.0-33.0)	33.0 (26.0-40.0)	29.0 (22.0-31.0)	35.0 (32.0-36.0)	32.0 (27.1-39.0)	36.0 (24.0-39.0)	30.0 (21.0-31.0)
ANGPTL3, μg/L	180 (127-302)	178 (135-198)	218 (160-322)	215 (142-255)	160 (199-359)	201 (96-153)	225 (131-294)	202 (163-278)
ANGPTL3/8, μg/L	30 (9-79)	24 (21-40)	33 (25-48)	24 (18-58)	26 (19-40)	23 (17-45)	36 (16-47)	27 (17-36)
TG, mg/dL	189 (123-406)	196 (161-247)	242 (131-357)	244 (180-393)	195 (161-283)	242 (58-399)	203 (119-310)	178 (121-363)
Non-HDL-C, mg/dL	179 (110-226)	183 (146-214)	203 (126-290)	189 (131-234)	185 (119-213)	173 (103-192)	201 (115-229)	164 (157-225)
LDL-C, mg/dL	141 (91-180)	142 (107-180)	161 (98-235)	150 (74-190)	133 (81-166)	114 (87-152)	162 (96-184)	143 (119-193)
HDL-C, mg/dL	46 (24-68)	38 (33-45)	44 (30-58)	37 (29-49)	35 (31-60)	39 (30-52)	36 (30-47)	44 (27-55)
ApoA-I, mg/L	152 (93-190)	128 (123-141)	149 (120-195)	136 (115-178)	126 (112-150)	145 (118-168)	134 (102-140)	147 (107-181)
ApoB, mg/L	130 (78-167)	137 (113-144)	150 (93-192)	147 (99-190)	122 (79-145)	116 (89-138)	144 (87-156)	126 (104-176)
ApoC-III, mg/dL	17 (10-27)	15 (14-18)	17 (12-27)	18 (14-24)	14 (12-18)	18 (8-31)	15 (12-22)	15 (11-23)
Statin use	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)

Values are median (range) or n (%).

ANGPTL3 = angiopoietin-like protein 3; ANGPTL3/8 = angiopoietin-like protein 3/8; apo = apolipoprotein; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PBO = placebo; TG = triglyceride.

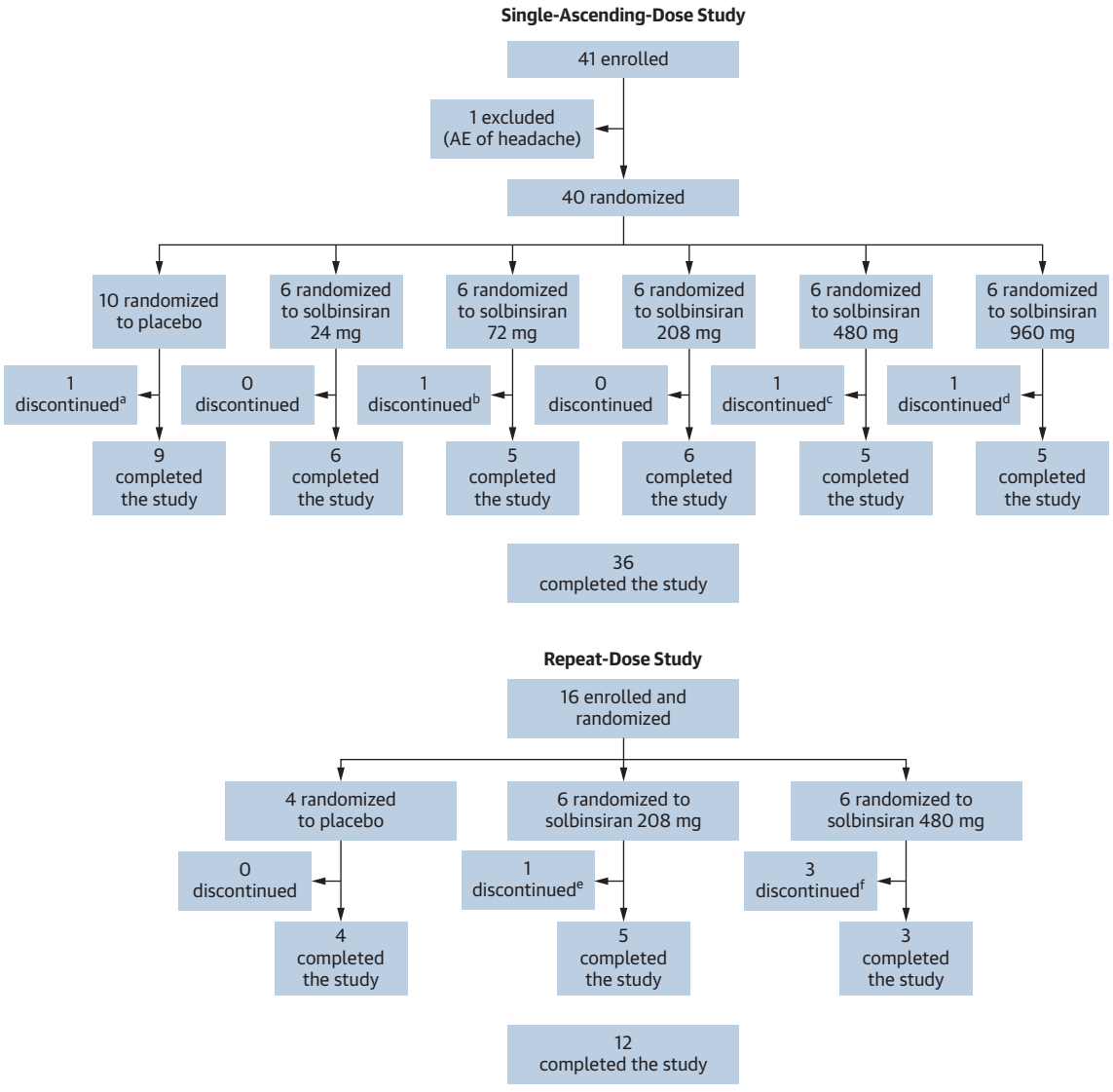
reductions in hepatic *ANGPTL3* mRNA expression of up to 72.9% ± 2.4% ($P < 0.0001$) and serum ANGPTL3 levels of up to 68.6% ± 4.4% ($P < 0.001$) at day 28 after dosing compared with vehicle-treated animals. Hepatic mRNA knockdown remained >50% 12 weeks after the single dose of solbinsiran (Supplemental Figure 2B).

PHASE 1 CLINICAL STUDY. Baseline demographic characteristics. The demographics and flow of participants in the study are illustrated in Table 1 and Figure 2. In the single-ascending-dose study, participants (n = 40) had a mean age of 50.2 years, and 75% were men. In the repeat-dose study, participants (n = 16) had a mean age of 53.6 years, and 56.3% were men. The median triglyceride and LDL-C levels were 204 and 141 mg/dL, respectively, in the single-ascending-dose study and 180 and 147 mg/dL, respectively, in the repeat-dose study.

Safety and tolerability. Treatment-emergent adverse events (TEAEs) were reported by 20% to 50% of participants who received placebo and 17% to 67% of those who received solbinsiran (Table 2). Most TEAEs (32 of 34) were mild in severity (Table 2). Headache, increased blood creatine kinase, and rash were reported in more than 1 participant in the single-ascending-dose study, whereas headache, increased hepatic enzyme, and rash were reported in more than 1 participant in the repeat-dose study. One serious adverse event of visual impairment, which was not considered related to study treatment, was reported by a participant who received 72 mg solbinsiran in the single-ascending-dose study. Investigations showed severe intracranial arterial stenoses, and the participant underwent stent placement. One participant who received 960 mg solbinsiran in the single-ascending-dose study and 2 participants (1 received 208 mg and 1 received 480 mg) in the repeat-dose study reported TEAEs of mild abnormal liver enzymes. Two additional participants (1 received 208 mg and 1 received 960 mg) in the single-ascending-dose study had abnormal liver function test results that were not recorded as TEAEs (Table 2). No TEAEs related to vital signs or electrocardiographic findings were reported following single or repeat doses of solbinsiran. Overall, 14 participants reported injection-site reactions in the study. In the single-ascending-dose study, most injection-site reactions were of mild to moderate pain and reported in the solbinsiran treatment groups at the 0-hour time point. In the repeat-dose study, pain and erythema were the most frequently reported injection-site reactions, with pain (mild or moderate in severity) reported most frequently at the 0-hour time point on day 1. Overall, the frequency of injection-site reactions was not higher after the second injection compared with the first injection.

Pharmacokinetic analysis. In the single-ascending-dose study, the half-life ranged from 5.5 to 12.9 hours, and C_{max} ranged from 66 to 2,360 ng/mL. In the repeat-dose study, the half-life was 6.8 to 7.5 hours and C_{max} was 487 to 1,620 ng/mL. Time to C_{max} ranged from 7.5 to 12.5 hours in the single-ascending-dose study and from 9 to 16 hours in the repeat-dose study (Supplemental Table 1). The plasma concentration-time profiles for solbinsiran following

FIGURE 2 Consolidated Standards of Reporting Trials Diagram



[a]1 participant withdrew on day 225 because of a house move. [b]1 participant was withdrawn from the study on day 15 because of a treatment-emergent adverse event (AE) of visual impairment. [c]1 participant withdrew after day 113 because of a scheduling conflict. [d]1 participant withdrew after day 124 because of a scheduling conflict. [e]1 participant received 208 mg on days 1 and 29 and was withdrawn by the physician after day 113 because of participation in another study. [f]1 participant received 408 mg on days 1 and 29 and withdrew after day 155 because of a scheduling conflict, and 2 participants received 408 mg on days 1 and 29 and were withdrawn by the physician after day 85 because of participation in another study.

single subcutaneous doses on day 1 or repeat doses on days 1 and 29 in participants with mixed dyslipidemia showed no accumulation.

Pharmacodynamics analysis. In the single-ascending-dose study, administration of solbinsiran was associated with dose-dependent reductions from baseline in ANGPTL3. The mean ± SD percentage reduction from baseline was up to 85.7% ± 4.4% (960 mg solbinsiran, day 29) (Figure 3). Waterfall plots of change in ANGPTL3 from baseline for placebo (pooled) and single and repeat doses of solbinsiran are shown at days 29 and 85. Changes in ANGPTL3 from baseline in the placebo group were matched in number and magnitude of change (Figure 4). In

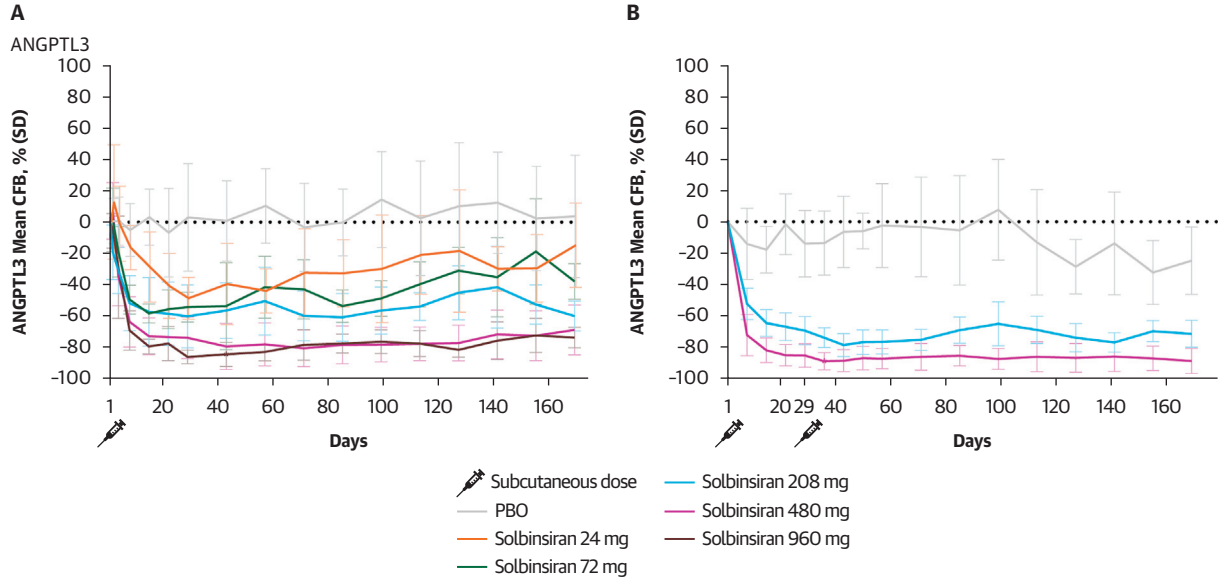
TABLE 2 Safety of Solbinsiran in Participants With Mixed Dyslipidemia

	Single-Ascending-Dose Study						Repeat-Dose Study		
	PBO (n = 10)	Solbinsiran 24 mg (n = 6)	Solbinsiran 72 mg (n = 6)	Solbinsiran 208 mg (n = 6)	Solbinsiran 480 mg (n = 6)	Solbinsiran 960 mg (n = 6)	PBO (n = 4)	Solbinsiran 208 mg (n = 6)	Solbinsiran 480 mg (n = 6)
Participants experiencing AEs, all causalities	2 (20.0)	1 (16.7)	4 (66.7)	3 (50.0)	3 (50.0)	3 (50.0)	2 (50.0)	2 (33.3)	4 (66.7)
Number of AEs and severity	2	1	7	4	3	5	3	2	7
Mild	2	1	5	4	3	5	3	2	7
Moderate	0	0	1	0	0	0	0	0	0
Severe	0	0	1[a]	0	0	0	0	0	0
Participants experiencing AEs related to study treatment[b]	0	0	1 (16.7)	2 (33.3)	0	0	1 (25.0)	0	1 (16.7)
Number of AEs related to study treatment[b] and severity	0	0	3	2	0	0	1	0	1
Mild	0	0	3	2	0	0	1	0	1
Moderate	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0
Participants reporting injection-site reactions[c]	0	0	2 (33.3)	2 (33.3)	0	1 (16.7)	0	2 (33.3)	3 (50.0)
Participants with abnormal liver enzymes levels	0	0	0	1 (16.7)[d]	0	2 (33.3)[e]	0	1 (16.7)[f]	1 (16.7)[f]

Values are n (%) or n. The investigator and any qualified designees were responsible for detecting, documenting, and recording events that met the definition of an AE or serious AE and remained responsible for following up on AEs that were serious and considered related to the study intervention or study procedures. [a]One severe treatment-emergent AE of visual impairment was reported by a participant who received 72 mg solbinsiran in part A; this treatment-emergent AE was considered a serious AE and was not considered related to solbinsiran treatment. This participant discontinued the study because of this serious AE. [b]As judged by the investigator. [c]Assessed prospectively at times defined in the protocol and when spontaneously reported by a participant or an investigator for erythema, edema, pain, induration, and pruritus. [d]This participant had elevated aspartate aminotransferase of 4.5 times the upper limit of normal that returned to the reference range within 14 days. [e]One participant had elevated alanine aminotransferase at baseline and a peak alanine aminotransferase of 3.7 times the upper limit of normal that returned to below baseline within 6 days; the other participant had maximum laboratory values less than 2 times the upper limit of normal of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase for a duration of approximately 90 days. [f]Maximum values for alanine aminotransferase and aspartate aminotransferase did not exceed 2 times the upper limit of normal.

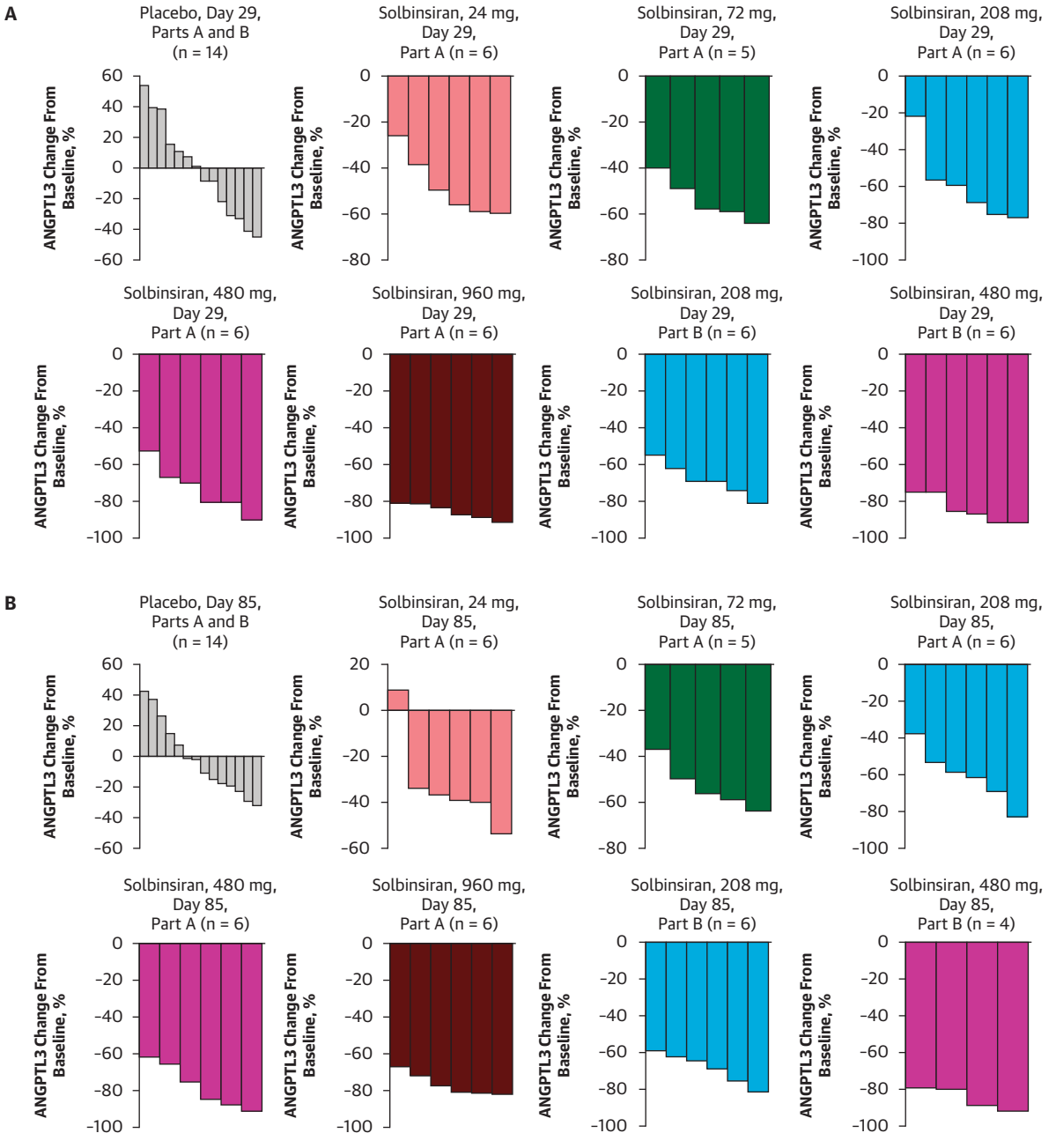
AE = adverse event; PBO = placebo.

FIGURE 3 Effect of Solbinsiran on Percentage Change From Baseline in ANGPTL3



(A) Single-ascending-dose study. (B) Repeat-dose study. ANGPTL3 = angiopoietin-like protein 3; CFB = change from baseline; PBO = placebo.

FIGURE 4 Waterfall Plots of Change in ANGPTL3 From Baseline in the Single-Ascending-Dose Study (Part A) and the Repeat-Dose Study (Part B) for Placebo (Pooled Data From Part A and B) and Single and Repeat Doses of Solbinsiran at Day 29 and Day 85



(A) Day 29 and (B) day 85. ANGPTL3 = angiopoietin-like protein 3.

contrast, increasing and repeat dosing reduced between-person variability (eg, 960 mg vs 480 mg at day 29, 480 mg at day 85 vs day 29) (Figure 4). Solbinsiran was also associated with dose-dependent mean ± SD percentage reductions in triglycerides of up to 73.2% ± 7.0% (960 mg, day 22), LDL-C up to 29.5% ± 16.3% (960 mg, day 22), HDL-C up to 26.5% ± 19.8% (480 mg, day 141), non-HDL-C up to

41.1% ± 11.6% (960 mg, day 22), and apoB up to 29.8% ± 10.9% (960 mg, day 22) (**Figure 5**).

In the repeat-dose study, solbinsiran administration was associated with dose-dependent reductions in ANGPTL3 of up to 88.8% ± 5.5% (480 mg solbinsiran, day 36) (**Figure 3**), as well as dose-dependent reductions in triglycerides up to 69.6% ± 12.5% (480 mg, day 85), LDL-C up to 42.3% ± 14.0% (480 mg, day 85), HDL-C up to 37.7% ± 6.6% (480 mg, day 57), non-HDL-C up to 45.6% ± 13.5% (480 mg, day 85), and apoB up to 36.0% ± 13.3% (480 mg, day 85) (**Figure 5**). These reductions were sustained for up to 169 days at the higher doses. Across the single-ascending-dose and repeat-dose studies, the between-treatment *P* values for the reduction achieved for each parameter were as follows: ANGPTL3 and triglycerides, $P < 0.001$; LDL-C, $P = 0.023$; HDL-C, $P = 0.020$; non-HDL-C, $P = 0.003$; and apoB, $P = 0.014$. Dose-dependent reductions in very low-density lipoprotein cholesterol, apoA-I, and apoC-III were also observed (Supplemental Figure 3).

NMR spectroscopy. Administration of solbinsiran was associated with reduced numbers of total, very large, large, medium, and small TRL-P in both the single-ascending-dose and repeat-dose studies at days 29 and 85 (Supplemental Table 2). Across the 2 studies, the least squares mean ± SE percentage reduction from baseline for total TRL-P was up to 69.5% ± 7.3% ($P < 0.001$) (480-mg dose, day 85, repeat-dose study). Similarly, the proportion of very large and large TRL-P decreased by up to 86.3% ± 12.4% from baseline ($P < 0.001$) (480-mg dose, day 29, single-ascending-dose study), whereas the proportion of medium TRL-P decreased from baseline up to 87.9% ± 7.1% ($P = 0.02$) (480-mg dose, day 85, repeat-dose study). The proportion of small and very small TRL-P decreased from baseline up to 67.8% ± 7.7% ($P < 0.001$) (480-mg dose, day 85, repeat-dose study). As the greatest reductions were observed for larger TRL-P, administration of solbinsiran resulted in TRL-P of smaller average size, with least squares mean ± SE percentage reductions from baseline of up to 21.7% ± 5.0% (480-mg dose, day 85, repeat-dose study; $P = 0.02$) (Supplemental Table 2). Administration of solbinsiran also resulted in dose-dependent least squares mean ± SE percentage reductions from baseline in NMR-estimated triglyceride-rich lipoprotein cholesterol up to 60.3% ± 7.3% (480-mg dose, day 29, single-ascending-dose study; $P < 0.001$) and up to 71.7% ± 6.4% (480-mg dose, day 85, repeat-dose study; $P < 0.001$) (Supplemental Figure 4).

In the single-ascending-dose study, solbinsiran 960 mg was associated with a least squares mean ± SE percentage reduction from baseline in the total number of LDL-P up to 30.5% ± 10.5% ($P = 0.002$) and large LDL-P up to 46.4% ± 24.0% ($P = 0.004$) on day 29 compared with placebo (Supplemental Table 3). Solbinsiran 960 mg in the single-ascending-dose study also resulted in a reduction up to 27.7% ± 9.9% in total HDL-P on day 29 ($P = 0.004$), up to 42.0% ± 14.2% in large HDL-P on day 85 ($P = 0.03$), and up to 29.2% ± 7.9% in small HDL-P on day 29 ($P < 0.001$) compared with placebo (Supplemental Table 4). Administration of solbinsiran did not significantly affect the average size of LDL-P and HDL-P compared with placebo, except for the 960-mg single dose at day 29 (reduction in LDL-P size by 1.9% ± 0.9%; $P = 0.04$) (Supplemental Table 3). Solbinsiran produced dose-dependent decreases from baseline in lipoprotein insulin resistance score up to 26.3% ± 3.0% (repeat-dose study, 480-mg dose, day 29; $P < 0.001$) compared with placebo (Supplemental Figure 5).

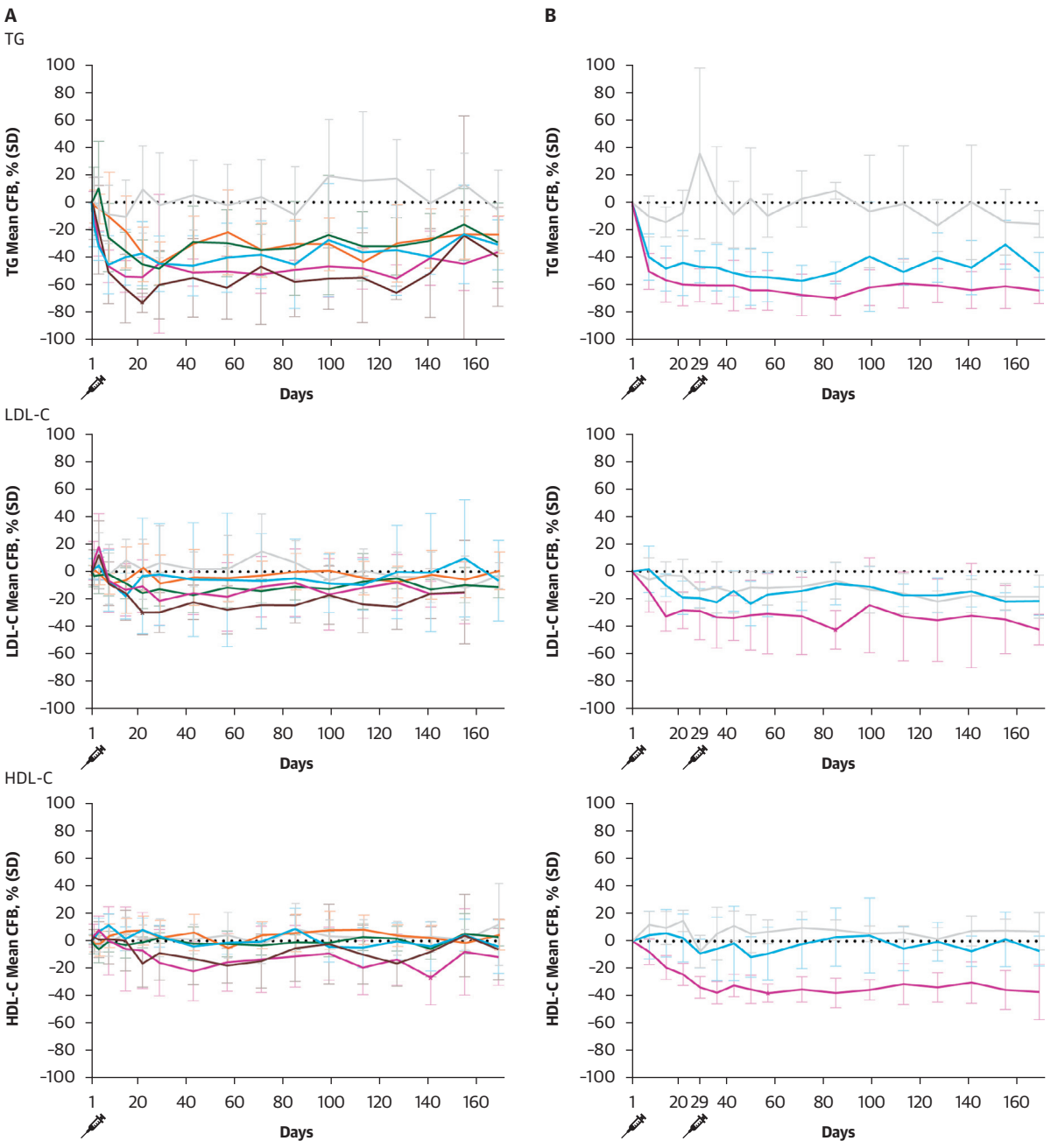
Cholesterol efflux capacity. In the single-ascending-dose study, cholesterol efflux did not significantly change with different doses of solbinsiran. However, at day 85 in the repeat-dose study, solbinsiran 480 mg produced a least squares mean ± SE percentage reduction from baseline in global cholesterol efflux of 9.6% ± 9.1% ($P = 0.047$) and ABCA1-mediated cholesterol efflux of 42.3% ± 10.7% ($P = 0.002$) compared with placebo (Supplemental Table 5).

DISCUSSION

Solbinsiran reduced human *ANGPTL3* mRNA expression in hepatocytes of mice transiently expressing human *ANGPTL3*, and a single dose reduced hepatic cynomolgus monkey *ANGPTL3* mRNA expression by 72.9% at 28 days, with durable knockdown of more than 50% at 12 weeks, which was accompanied by a decrease in circulating serum ANGPTL3 level of up to 68.6%. Taken together, these data demonstrate that solbinsiran can effectively lower circulating ANGPTL3 by inhibiting the translation of hepatic mRNA for *ANGPTL3* with a durable effect. These preclinical findings provided the rationale for the first-in-human clinical evaluation of solbinsiran (**Central Illustration**).

In the present phase 1 clinical study of solbinsiran in participants with elevated triglycerides and LDL-C, solbinsiran was well tolerated with increasing doses or upon repeat dosing, with no evidence of accumulation in pharmacokinetic studies. Solbinsiran reduced ANGPTL3 levels, which produced the expected reductions in atherogenic lipid parameters. At an individual level, there was little in the way of between-person variability in ANGPTL3 levels at higher doses or upon repeat dosing at intermediate

FIGURE 5 Effect of Solbinsiran on Percentage Change From Baseline in TG, LDL-C, HDL-C, Non-HDL-C, and ApoB

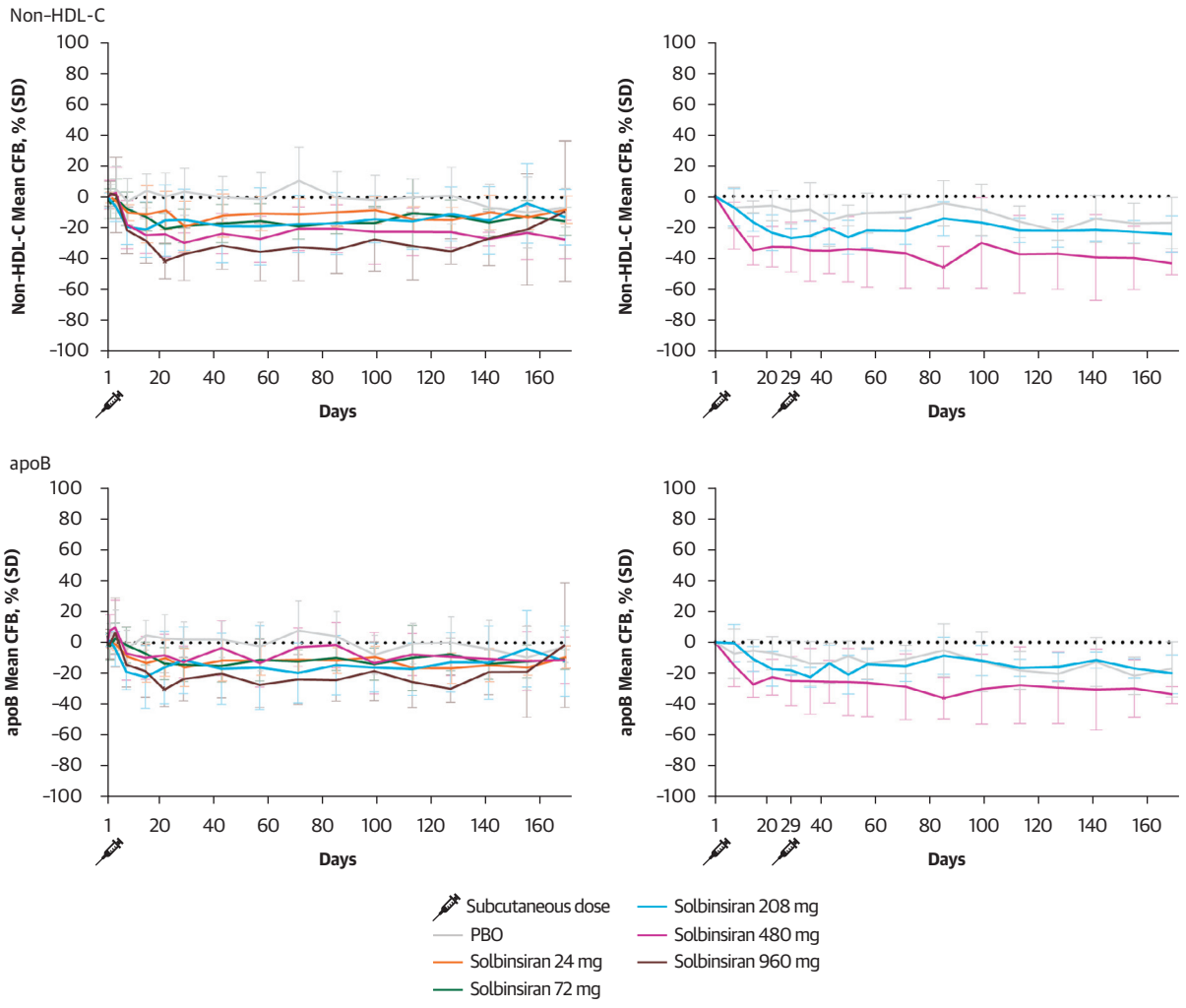


(A) Single-ascending-dose study. (B) Repeat-dose study. apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; other abbreviations as in Figures 2 and 3.

Continued on the next page

doses. Although larger and longer studies are needed, the present study does offer insight into potential efficacy. Specifically, mean percentage reductions from baseline were recorded up to 73.2% for triglycerides in the single-ascending-dose study and for non-HDL-C, LDL-C, and apoB up to 45.6%, 42.3%, and 36.0%, respectively, in the repeat-dose study. The NMR lipoprotein profile showed that the dose-

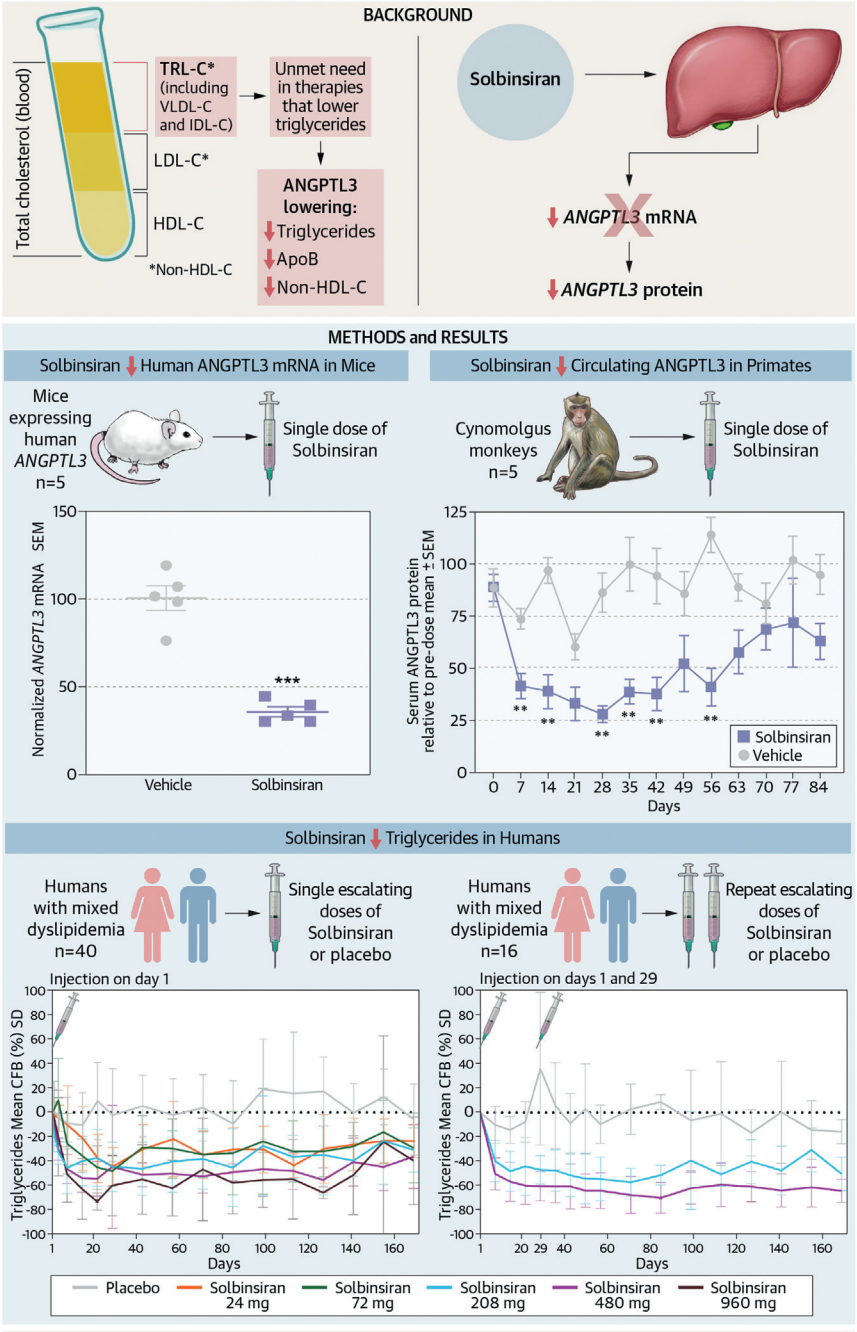
FIGURE 5 Continued



dependent reduction of the total number of TRL-P with solbinsiran treatment was due to the reduction of TRL-P of all sizes. Besides LDL-C, the total number of LDL-P was also significantly reduced with solbinsiran treatment. Although the overall LDL phenotype appears to improve, data from the Women's Health Study have shown that cardiovascular disease risk prediction associated with lipoprotein profiles evaluated by NMR was comparable with but not superior to that of standard lipids or apolipoproteins.[15] The reduction in LDL-P number with solbinsiran is consistent with the biological effects of ANGPTL3, whereby lowering ANGPTL3 increases lipoprotein lipase and endothelial lipase-mediated clearance of intermediate-density lipoprotein particles, through LDL receptor independent mechanisms, and as a consequence, fewer LDL-P are formed and LDL-C levels are decreased.[8] As expected, solbinsiran also reduced the total number of HDL-P, including both large and especially small HDL-P. Finally, the sustained reduction in ANGPTL3 and lipid parameters suggest that solbinsiran could be dosed infrequently.

The effects of solbinsiran on lipid parameters should be considered in the context of other ANGPTL3-directed therapies. Evinacumab is a monoclonal antibody that binds circulating ANGPTL3 and is currently approved for homozygous familial hypercholesterolemia. In patients with little or no LDL receptor activity, the effects of ANGPTL3 inhibition, which enhances non-LDL receptor-mediated clearances, reduces LDL-C by approximately 50% and apoB by approximately 40% in adults and adolescents

CENTRAL ILLUSTRATION **Solbinsiran Inhibits Hepatic ANGPTL3 Production in Preclinical and Clinical Studies**



Solbinsiran, a GalNAc-conjugated siRNA to ANGPTL3, reduces hepatic ANGPTL3 mRNA in mice, reduces circulating ANGPTL3 in non-human primates, reduces ANGPTL3 and triglycerides in humans, and is under investigation to treat a wide range of hyperlipidemias.

Ray KK, et al. JACC. 2025;■(■):■-■.

*Non-HDL-C = *TRL-C + *LDL-C. ANGPTL3 = angiopoietin-like protein 3; apo = apolipoprotein; CFB = change from baseline; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; mRNA = messenger RNA; TRL-C = Triglyceride-rich lipoprotein cholesterol; VLDL = very-low-density lipoprotein.

with homozygous familial hypercholesterolemia.[16,17] Despite the efficacy of evinacumab, its monthly dosing regimen, the requirement for a 1-hour infusion often in the hospital, and variable effects in mixed dyslipidemia[18] mean that it is not likely to be a therapeutic option for common conditions such as mixed dyslipidemia.

There are other RNA-based therapies that target translation of *ANGPTL3* mRNA. Vupanorsen, an antisense oligonucleotide that inhibits mRNA translation in the nucleus, dosed subcutaneously fortnightly or monthly, was observed to result in dose-dependent increases in transaminases and hepatic fat. As a result, the development of vupanorsen has been terminated.[19] Whether this was an on-target effect of ANGPTL3 inhibition or an off-target effect of the drug is not known for certain.[20] In a phase 2 study, zodasiran, which is a GalNAc-conjugated siRNA dosed subcutaneously once every 12 weeks, reduced mean triglyceride levels (difference in change vs placebo up to 63.1%) and mean LDL-C levels (difference in change vs placebo up to 19.9%) at week 24 in participants with mixed dyslipidemia.[21] In the same study in a subgroup of patients who had liver steatosis (magnetic resonance imaging proton density fat fraction ≥8%), dose-dependent reductions in hepatic fat content were observed up to 28% (vs 2% reduction with placebo).[21] Although we did not assess liver fat in this phase 1 study, we saw improvements in insulin resistance index, which would be expected to show favorable effects on hepatic steatosis. This requires formal assessment in later-phase studies of solbinsiran. Notably, the safety of solbinsiran in this phase 1 study was similar to other siRNA therapies targeting ANGPTL3 at the same stage of development and base-editing approaches in nonhuman primates. This suggests that ANGPTL3 itself, as well as blocking hepatic ANGPTL3 production, is likely to be a biologically safe approach in the long term.

Although the effects of solbinsiran on triglycerides and TRL-P number appear large, the effects on other atherogenic lipid parameters appear more modest compared with therapies directed against proprotein convertase subtilisin/kexin type 9, and it should be remembered that these are not like-for-like comparisons. For instance, TRL-P have a plasma residence time of 6 hours vs 3 to 5 days for LDL-P; therefore, at any given time, approximately 90% of circulating apoB particles consist of LDL-P. Furthermore, recent data suggest that TRL-P are approximately 2-fold more atherogenic than LDL per particle.[4,6] The NMR data suggest that TRL-P number, which may contribute a large part of the atherogenic burden in patients with mixed dyslipidemia, is significantly attenuated by solbinsiran. Therefore, if recent data suggesting that TRL-P are approximately 2-fold more atherogenic than LDL per particle are confirmed, considering the reductions in apoB with solbinsiran as the only lipoprotein biomarker predicting major adverse cardiovascular events might underestimate the potential cardiovascular benefit of reducing hepatic ANGPTL3 production with solbinsiran, as total apoB reflects apoB on TRL-P and on LDL-P.

There are 4 key questions left for therapeutic inhibition of ANGPTL3 in mixed dyslipidemia. First, is there a need? Second, might the efficacy vary by LDL-C and triglyceride levels? Third, are there other alternatives to triglyceride lowering that might reduce cardiovascular events? Finally, might there be harm from HDL-C lowering through this approach? These key points merit further discussion.

The increased incidence of obesity and diabetes are considered in part responsible for attenuating the beneficial gains in lower cardiovascular morbidity and mortality of the previous 2 decades. Key components of these traits are insulin resistance and the overproduction of very low density lipoprotein particles from the liver, resulting in high circulating triglycerides and remnant cholesterol. This suggests that there is a need.

Recently, a large comparison of recently completed trials in patients who are well treated with statins and typically recruit patients with triglyceride levels in the 200 to 499 mg/dL range observed a modest gradient of risk for cardiovascular disease with increasing triglyceride levels. In comparison, the gradient of risk for cardiovascular risk was more marked when extended to triglyceride levels of up 1,000 mg/dL in the same research when studying the Copenhagen general population. This led the investigators to speculate that future trials should recruit patients with a higher upper limit for triglyceride as an inclusion criterion, to enroll subjects more likely to derive benefit from triglyceride lowering.[22] The effect of ANGPTL3 inhibition may be dependent on triglyceride levels and LDL-C. For instance, in studies of a monoclonal antibody to ANGPTL3 in populations with higher triglyceride baseline levels, less LDL-C and apoB reduction was observed following ANGPTL3 inhibition.[23] In comparison, in a homozygous familial hypercholesterolemia population with low triglycerides but high LDL-C, much larger reductions in LDL-C and apoB (approximately 40%-45%) were observed, including individuals with no LDL receptor activity. Currently, evinacumab is used only in homozygous familial hypercholesterolemia[16] or severe refractory heterozygous familial hypercholesterolemia.[24] The

present study (albeit with small numbers) had a relatively high LDL-C level and less triglyceride elevation, which can be expected to show a higher (more familial hypercholesterolemia-like) apoB reduction of 32% than, for instance, the phase 2 trial of zodasiran, which had lower LDL-C and higher triglycerides and demonstrated approximately 20% apoB lowering.

The current and future landscape of triglyceride-lowering therapies in which solbinsiran is being developed merits consideration. Fibrates appear to remodel TRL-P-reducing triglyceride content without materially affecting the clearance of atherogenic lipoproteins, thereby increasing both LDL-C and apoB.[25] This approach, however, has not translated into reductions in cardiovascular events, and hence this therapy is reserved for pancreatitis. Although high-dose icosapent ethyl reduces cardiovascular events in individuals with high triglycerides, it is likely that benefits are not related to lipid changes, as the changes in lipids are modest in comparison with the large clinical benefits.[26] Both icosapent ethyl and fibrates are oral therapies that require daily dosing and are thus more prone to the vagaries of adherence. However, triglyceride reductions of about 20% to 30% and 30% to 50% are achievable with these approaches, respectively. RNA-based therapies require infrequent dosing, target regulators of lipoprotein lipase, specifically ANGPTL3 or apoC-III mRNA, have been shown to reduce triglycerides by 50% to 70% or >70%, respectively. ApoC-III inhibitors do not require endogenous lipoprotein lipase activity to lower triglyceride, and both an antisense oligonucleotide (olezarsen),[27] requiring monthly dosing, and a siRNA (plozasiran),[28] dosed every 3 months, have been approved for use in familial chylomicronemia syndrome.[29,30] Mendelian randomization supports apoC-III as a causal target for cardiovascular events, and plozasiran is being considered for a cardiovascular outcomes trial. One of the broader challenges is the concept of what is important for cardiovascular risk reduction. As the Mendelian randomization analyses point to apoB, the argument could be made that the apoB reduction with ANGPT3 inhibition alone will be sufficient. However, the question is whether it is reasonable to expect (or hope) for additional benefit with lowering of either triglyceride-rich lipoprotein cholesterol or remnant cholesterol. That is the forward-looking question that the field is asking.

Finally, the apoA-I and HDL-C lowering observed with solbinsiran is consistent with the reduction of endogenous ANGPTL3-mediated repression of endothelial lipase activity. Mendelian randomization studies using genetic variants as proxies to study the effects of causal estimates of HDL-C increases have not shown that higher HDL-C levels due to genotype lead to a lower risk for cardiovascular events.[31,32] In Mendelian randomization studies, genetic variants in ANGPTL3 were associated with a near-identical pattern of lipid changes to those seen with solbinsiran and a lower risk for cardiovascular events.[9] The clinical implications of the HDL-C reduction are unknown. The number of total HDL-P and small HDL-P also decreased with solbinsiran, and this was reflected in the reduction of global and ABCA1-mediated cholesterol efflux capacities, respectively. Although better cholesterol efflux has been associated with lower cardiovascular risk,[33] different therapeutic approaches that raise HDL-C and increase cholesterol efflux capacity have not demonstrated cardiovascular benefits in clinical trials or been associated with reduced plaque volume in imaging studies.[34-37] Whether this reduction in total cholesterol efflux capacity and ABCA1-mediated cholesterol efflux results in an attenuation of clinical benefits from atherogenic lipid changes on atherosclerosis and cardiovascular outcomes can be answered only through further investigation, including imaging and outcomes trials.

STUDY LIMITATIONS. As with all phase 1 clinical trials, only a small number of participants were enrolled, and demographic characteristics in terms of sex and ethnicity were not broad, thereby limiting generalizability. The short duration of the study does not allow a full evaluation of long-term safety with repeat exposure or in uncommon, rare events that require larger, longer studies.

CONCLUSIONS

In this phase 1 study, solbinsiran was well tolerated and produced dose-dependent and durable reductions in ANGPTL3 and triglycerides and atherogenic lipid parameters in participants with mixed dyslipidemia. This supports the further evaluation of solbinsiran to potentially address the unmet residual atherogenic risk in patients with mixed dyslipidemia with the convenience of infrequent dosing. This is currently being evaluated in a phase 2 clinical trial (PROLONG-ANG3 [A Study of LY3561774 in Participants With Mixed Dyslipidemia]; NCT05256654).

ACKNOWLEDGMENTS The authors are thankful to the participants and their families for participating in this study. The authors thank the study personnel and coworkers at clinical sites for the provision of the data for the analyses.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

These studies were funded by Eli Lilly & Company, manufacturer and licensee of LY3561774. Eli Lilly was involved in the study design, data collection, data analysis, and preparation of the manuscript. Dr Ray is supported by the National Institute for Health and Care Research Imperial Biomedical Research Centre. As per Good Publication Practice 2022, all sources of financial support (including disclosure of funding for medical writing services), roles of the funding source or sponsor, roles of the contributors, and conflicts of interest should be disclosed appropriately, even if this information is not requested by the journal. Medical writing assistance was provided by Charlie Bellinger, BSc, and Clare Weston, MSc, of ProScribe-Envision Pharma Group and was funded Eli Lilly & Company. ProScribe's services complied with international guidelines for Good Publication Practice. Dr Ray has received research grants from Amarin, Amgen, Daiichi-Sankyo, Merck Sharp & Dohme, Pfizer, Regeneron, and Sanofi; and is a consultant for Abbott, Amarin, Amgen, AstraZeneca, Bayer, Biologix Pharma, Boehringer Ingelheim, Cargene Therapeutics, CRISPR, CSL Behring, Eli Lilly & Company, Esperion Therapeutics, Kowa Pharmaceuticals, NewAmsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, Scribe Therapeutics, Silence Therapeutics, Vaxxinity, and Viatris; has received honoraria for lectures from Amarin, Amgen, AstraZeneca, Biologix Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Esperion, Macleod, Novartis, Novo Nordisk, Sanofi, and Viatris; and has stock options from NewAmsterdam Pharma, Pemi 31, and Scribe Therapeutics. Drs Linnebjerg, Michael, Shen, Ma, Lim, Zhen, and Ruotolo are employees and shareholders of Eli Lilly & Company. Drs Dudek, Saxena, and Turanov are employees and shareholders of Novo Nordisk and former employees of Dicerna. Dr Abrams is a former employee of Dicerna. Dr Nicholls has received research support from Amgen, Anthera Pharmaceuticals, AstraZeneca, Cerenis Therapeutics, CSL Behring, Eli Lilly & Company, Esperion Therapeutics, Infraredx, NewAmsterdam Pharma, Novartis, Resverlogix, and Sanofi Regeneron; and is a consultant for Akcea Therapeutics, Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Daiichi-Sankyo, Eli Lilly & Company, Esperion Therapeutics, Kowa Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sanofi Regeneron, and Takeda.

ADDRESS FOR CORRESPONDENCE: Dr Kausik K. Ray, Department of Public Health and Primary Care, Imperial College, White City Campus, 90 Wood Lane, London, United Kingdom. E-mail: k.ray@imperial.ac.uk. X handle: @profKausikRay OR Dr Giacomo Ruotolo, Clinical Research in Diabetes, Obesity, and Complications, Eli Lilly & Company, Lilly Corporate Center, Indianapolis, Indiana 46285, USA. E-mail: ruotolo_giacomo@lilly.com. X handle: @Giacomo_Ruotolo.

REFERENCES

1. Mach F, Visseren FLJ, Cater NB, et al. Addressing residual risk beyond statin therapy: New targets in the management of dyslipidaemias—a report from the European Society of Cardiology Cardiovascular Round Table. *J Clin Lipidol*. 2024;18:e685–e700. https://doi.org/10.1016/j.jacl.2024.07.001

2. Vallejo-Vaz AJ, Corral P, Schreier L, Ray KK. Triglycerides and residual risk. *Curr Opin Endocrinol Diabetes Obes*. 2020;27:95–103. https://doi.org/10.1097/MED.0000000000000530

3. Khera AV, Won HH, Peloso GM, et al. Association of rare and common variation in the lipoprotein lipase gene with coronary artery disease. *JAMA*. 2017;317:937–946. https://doi.org/10.1001/jama.2017.0972

4. Bjornson E, Adiels M, Taskinen MR, et al. Triglyceride-rich lipoprotein remnants, low-density lipoproteins, and risk of coronary heart disease: a UK Biobank study. *Eur Heart J*. 2023;44:4186–4195. https://doi.org/10.1093/eurheartj/ehad337

5. Ginsberg HN, Packard CJ, Chapman MJ, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur Heart J*. 2021;42:4791–4806. https://doi.org/10.1093/eurheartj/ehab551

6. Tybjaerg-Hansen A, Nordestgaard BG, Christoffersen M. Triglyceride-rich remnant lipoproteins are more atherogenic than LDL per particle: is this important? *Eur Heart J*. 2023;44:4196–4198. https://doi.org/10.1093/eurheartj/ehad419

7. Ginsberg HN, Goldberg IJ. Broadening the scope of dyslipidemia therapy by targeting APOC3 (apolipoprotein C3) and ANGPTL3 (angiopoietin-like protein 3). *Arterioscler Thromb Vasc Biol*. 2023;43:388–398. https://doi.org/10.1161/ATVBAHA.122.317966

8. Adam RC, Mintah IJ, Alexa-Braun CA, et al. Angiopoietin-like protein 3 governs LDL-cholesterol levels through endothelial lipase-dependent VLDL clearance. *J Lipid Res*. 2020;61:1271–1286. https://doi.org/10.1194/jlr.RA120000888

9. Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med*. 2017;377:211–221. https://doi.org/10.1056/NEJMoa1612790

10. Stitziel NO, Khera AV, Wang X, et al. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol*. 2017;69:2054–2063. https://doi.org/10.1016/j.jacc.2017.02.030

11. Dudek H, Abrams M, Saxena U, et al. Abstract 12705: Identification and characterization of solbinsiran, a GalNAc conjugated siRNA targeting angiopoietin-like 3. *Circulation*. 2023;148:A12705.

12. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med*. 2006;26:847–870. https://doi.org/10.1016/j.cll.2006.07.006

13. de la Llera-Moya M, Drazul-Schrader D, Asztalos BF, Cuchel M, Rader DJ, Rothblat GH. The ability to promote efflux via ABCA1 determines the capacity of serum specimens with similar high-density lipoprotein cholesterol to remove cholesterol from macrophages. *Arterioscler Thromb Vasc Biol*. 2010;30:796–801. https://doi.org/10.1161/ATVBAHA.109.199158

14. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med*. 2011;364:127–135. https://doi.org/10.1056/NEJMoa1001689

15. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939. https://doi.org/10.1161/CIRCULATIONAHA.108.816181

16. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383:711–720. https://doi.org/10.1056/NEJMoa2004215

17. Wiegman A, Greber-Platzer S, Ali S, et al. Evinacumab for pediatric patients with homozygous familial hypercholesterolemia. *Circulation*. 2024;149:343–353. https://doi.org/10.1161/CIRCULATIONAHA.123.065529

18. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Longer-term efficacy and safety of evinacumab in patients with refractory hypercholesterolemia. *JAMA Cardiol*. 2023;8:1070–1076. https://doi.org/10.1001/jamacardio.2023.2921

19. Pfizer. Pfizer and Ionis announce discontinuation of vupanorsen clinical development program. Accessed February 16, 2025. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-ionis-announce-discontinuation-vupanorsen

20. Bergmark BA, Marston NA, Bramson CR, et al. Effect of vupanorsen on non-high-density lipoprotein cholesterol levels in statin-treated patients with elevated cholesterol: TRANSLATE-TIMI 70. *Circulation*. 2022;145:1377–1386. https://doi.org/10.1161/CIRCULATIONAHA.122.059266

21. Rosenson RS, Gaudet D, Hegele RA, et al. Zodasiran, an RNAi therapeutic targeting

ANGPTL3, for mixed hyperlipidemia. *N Engl J Med*. 2024;391:913-925. https://doi.org/10.1056/NEJMoa2404147

22. Nordestgaard AT, Pradhan AD, Everett BM, et al. Expanding the triglyceride range in clinical trials: therapeutic opportunities. *Eur Heart J*. https://doi.org/10.1093/eurheartj/ehaf074

23. Rosenson RS, Gaudet D, Ballantyne CM, et al. Evinacumab in severe hypertriglyceridemia with or without lipoprotein lipase pathway mutations: a phase 2 randomized trial. *Nat Med*. 2023;29:729-737. https://doi.org/10.1038/s41591-023-02222-w

24. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med*. 2020;383:2307-2319. https://doi.org/10.1056/NEJMoa2031049

25. Das Pradhan A, Glynn RJ, Fruchart JC, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med*. 2022;387:1923-1934. https://doi.org/10.1056/NEJMoa2210645

26. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11-22. https://doi.org/10.1056/NEJMoa1812792

27. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Engl J Med*. 2024;390:1781-1792. https://doi.org/10.1056/NEJMoa2400201

28. Watts GF, Rosenson RS, Hegele RA, et al. Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N Engl J Med*. 2025;392:127-137. https://doi.org/10.1056/NEJMoa2409368

29. U.S. Food and Drug Administration. Tryngolza (olezarsen). U.S. FDA prescribing information. Accessed February 21, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218614s000lbl.pdf

30. Arrowhead Pharmaceuticals. Arrowhead Pharmaceuticals announces acceptance of new drug application by U.S. FDA of plozasiran for the treatment of familial chylomicronemia syndrome. Accessed February 21, 2025. https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-announces-acceptance-new-drug

31. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36:539-550. https://doi.org/10.1093/eurheartj/eht571

32. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572-580. https://doi.org/10.1016/S0140-6736(12)60312-2

33. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383-2393. https://doi.org/10.1056/NEJMoa1409065

34. Gibson CM, Duffy D, Korjian S, et al. Apolipoprotein A1 infusions and cardiovascular outcomes after acute myocardial infarction. *N Engl J Med*. 2024;390:1560-1571. https://doi.org/10.1056/NEJMoa2400969

35. Nicholls SJ, Andrews J, Kastelein JJP, et al. Effect of serial infusions of CER-001, a pre-β high-density lipoprotein mimetic, on coronary atherosclerosis in patients following acute coronary syndromes in the CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial: a randomized clinical trial. *JAMA Cardiol*. 2018;3:815-822. https://doi.org/10.1001/jamacardio.2018.2121

36. Ray KK, Ditmarsch M, Kallend D, et al. The effect of cholesteryl ester transfer protein inhibition on lipids, lipoproteins, and markers of HDL function after an acute coronary syndrome: the dal-ACUTE randomized trial. *Eur Heart J*. 2014;35:1792-1800. https://doi.org/10.1093/eurheartj/ehu105

37. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089-2099. https://doi.org/10.1056/NEJMoa1206797

KEY WORDS ANGPTL3, dyslipidemia, LDL-C, solbinsiran, triglycerides

APPENDIX For supplemental methods, tables, and figures, as well as the clinical protocol and the statistical analysis plan, please see the online version of this paper.