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Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. xx, No. x, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.03.007

Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolemia Receiving Ongoing Stable Atorvastatin Therapy

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Objectives The primary objective of this study was to evaluate the low-density lipoprotein cholesterol (LDL-C)–lowering efficacy of 5 REGN727/SAR236553 (SAR236553) dosing regimens versus placebo at week 12 in patients with LDL-C ≥100 mg/dl on stable atorvastatin therapy. Secondary objectives included evaluation of effects on other lipid parameters and the attainment of LDL-C treatment goals of <100 mg/dl (2.59 mmol/l) and <70 mg/dl (1.81 mmol/l).

Background Serum proprotein convertase subtilisin kexin 9 (PCSK9) binds to low-density lipoprotein receptors, increasing serum LDL-C. SAR236553 is a fully human monoclonal antibody to PCSK9.

Methods This double-blind, parallel-group, placebo-controlled trial randomized 183 patients with LDL-C ≥100 mg/dl (2.59 mmol/l) on stable-dose atorvastatin 10, 20, or 40 mg for ≥6 weeks to subcutaneous placebo every 2 weeks (Q2W); SAR236553 50, 100, or 150 mg Q2W; or SAR236553 200 or 300 mg every 4 weeks (Q4W), alternating with placebo for a total treatment period of 12 weeks.

Results SAR236553 demonstrated a clear dose-response relationship with respect to percentage LDL-C lowering for both Q2W and Q4W administration: 40%, 64%, and 72% with 50, 100, and 150 mg Q2W, respectively, and 43% and 48% with 200 and 300 mg Q4W. LDL-C reduction with placebo at week 12 was 5%. SAR236553 also substantially reduced non–high-dose lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a). SAR236553 was generally well tolerated. One patient on SAR236553 experienced a serious adverse event of leukocytoclastic vasculitis.

Conclusions When added to atorvastatin, PCSK9 inhibition with SAR236553 further reduces LDL-C by 40% to 72%. These additional reductions are both dose- and dosing frequency–dependent. (Efficacy and Safety Evaluation of SAR236553 [REGN727] in Patients With Primary Hypercholesterolemia and LDL-cholesterol on Stable Atorvastatin Therapy; NCT01288443) (J Am Coll Cardiol 2012;xx:xxx) © 2012 by the American College of Cardiology Foundation

Cardiovascular disease remains the leading cause of death in most Western nations, and is increasing rapidly in the developing world. Reduction of low-density lipoprotein cholesterol (LDL-C), especially with statins, is widely recognized as the single most effective intervention to reduce cardiovascular risk (1–4), and clinical trial evidence

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Manuscript received February 6, 2012; revised manuscript received March 7, 2012, accepted March 13, 2012.

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Abbreviations and Acronyms

AE = adverse event
Apo = apolipoprotein
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
LDLR = low-density lipoprotein receptor
Lp(a) = lipoprotein a
mITT = modified intent-to-treat
PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease
Q2W = every 2 weeks
Q4W = every 4 weeks
ULN = upper limit of normal

strongly supports a positive correlation between greater levels of LDL-C lowering and cardioprotective benefits (5–9). Accordingly, current US, Canadian, and European treatment guidelines advocate decreasing LDL-C to <70 mg/dl in patients at very high risk (2–4). Within-trial analyses indicate that greater risk reduction may be achieved with even lower LDL-C levels, and indicate no association of these lower LDL-C levels with increased incidences of adverse events (AEs) (10–13).

Despite the proven cardioprotective effects of statins, many patients fail to reach recommended LDL-C targets in clinical practice, even with the addition of cholesterol absorption inhibitors, niacin, or bile acid resins to a statin (14,15).

Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) plays a pivotal role in low-density lipoprotein receptor (LDLR) degradation. Gain-of-function mutations of PCSK9 in humans result in hypercholesterolemia (16,17), whereas loss-of-function mutations are associated with low LDL-C and significantly reduced cardiovascular risk (18).

REGN727/SAR236553 (SAR236553) is a highly specific, fully human monoclonal antibody to PCSK9 that, in proof-of-concept trials in familial and non-familial hypercholesterolemia, dose-dependently reduced LDL-C by up to 62% from baseline, either with or without atorvastatin (19–21). The current phase 2 trial assessed 5 different SAR236553 dose regimens in patients with LDL-C ≥100 mg/dl while receiving stable 10-, 20-, or 40-mg atorvastatin doses.

Methods

This double-blind, parallel-group, placebo-controlled, US multicenter trial included patients with LDL-C ≥100 mg/dl (2.59 mmol/l) on stable-dose atorvastatin 10 mg, 20 mg, or 40 mg for ≥6 weeks. All patients reviewed and signed an informed consent form approved by a local or central institutional review board prior to any study-related procedures. Study procedures complied with International Conference on Harmonization Good Clinical Practice guidelines. An independent data monitoring committee monitored patient safety.

The primary objective was to evaluate the effect of 12 weeks treatment with SAR236553 versus placebo on LDL-C. Other objectives reported here are measurement of: absolute and/or percentage changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, non–HDL-C, apolipoprotein (Apo)-B, Apo-A1, and lipoprotein a (Lp(a)); and the proportion of patients achieving LDL-C treatment goals of <100 mg/dl (2.59 mmol/l) and <70 mg/dl (1.81 mmol/l).

Study population. Eligible subjects were men and nonpregnant, nonlactating women aged 18 to 75 years (inclusive), with LDL-C ≥100 mg/dl (2.59 mmol/l) while receiving a stable dose of atorvastatin 10, 20, or 40 mg daily for ≥6 weeks. Drug-naive patients or patients either receiving a lipid-lowering therapy other than atorvastatin or not on a stable dose of atorvastatin 10, 20, or 40 mg daily for ≥6 weeks were eligible, provided that they met the inclusion criteria after discontinuing all other lipid-lowering therapy and completing a 6-week run-in of atorvastatin 10, 20, or 40 mg daily.

Females of childbearing potential not using an effective form of contraceptive, or pregnant or breastfeeding, were excluded, as were individuals with known sensitivities to monoclonal antibody therapies; type 1 diabetes or type 2 diabetes requiring insulin, or with HbA_{1c} ≥8.5%; any clinically significant endocrine disease; blood pressure >150/95 mm Hg; a history of major coronary event within 6 months of screening; a history of class II to IV heart failure; a positive serum or urine pregnancy test; a positive test for hepatitis B or hepatitis C; triglycerides >350 mg/dl; abnormal sensitive thyroid-stimulating hormone level; serum creatinine >1.5 × upper limit of normal (ULN) in men or >1.4 × ULN in women; creatine kinase >3 × ULN; or alanine aminotransferase or aspartate aminotransferase >2 × ULN.

Non–study-related lipid-altering therapy use was prohibited during the study. Thyroid preparations or thyroxin treatment (except in patients on replacement therapy) and insulin treatment were also prohibited. Nutraceutical products that may affect lipids were allowed if used at a stable dose for ≥6 weeks prior to and during screening, and if maintained at a stable dose throughout the study; initiation during the study of treatment with nutraceuticals that affect lipids, including >1,000 mg daily of omega-3 fatty acids, red yeast rice, and plant sterols, was prohibited.

Study design and procedures. The study comprised 3 periods: screening, 12-week double-blind treatment, and 8-week follow-up (Fig. 1). Screening period duration varied according to atorvastatin treatment status. For patients already receiving stable-dose atorvastatin 10, 20, or 40 mg for ≥6 weeks, the eligibility screening period was 1 week; for patients requiring the 6-week atorvastatin run-in, screening was at week −7 with eligibility assessment at week −1.

Visits during the treatment period were every 2 weeks. Patients continued on the same atorvastatin dose and were randomized 1:1:1:1:1:1 to placebo every 2 weeks (Q2W); SAR236553 50, 100, or 150 mg Q2W; or SAR236553 200 or 300 mg every 4 weeks (Q4W) alternating with placebo to mimic Q2W dosing. Randomization was stratified according to atorvastatin dose, to evaluate any effect of background

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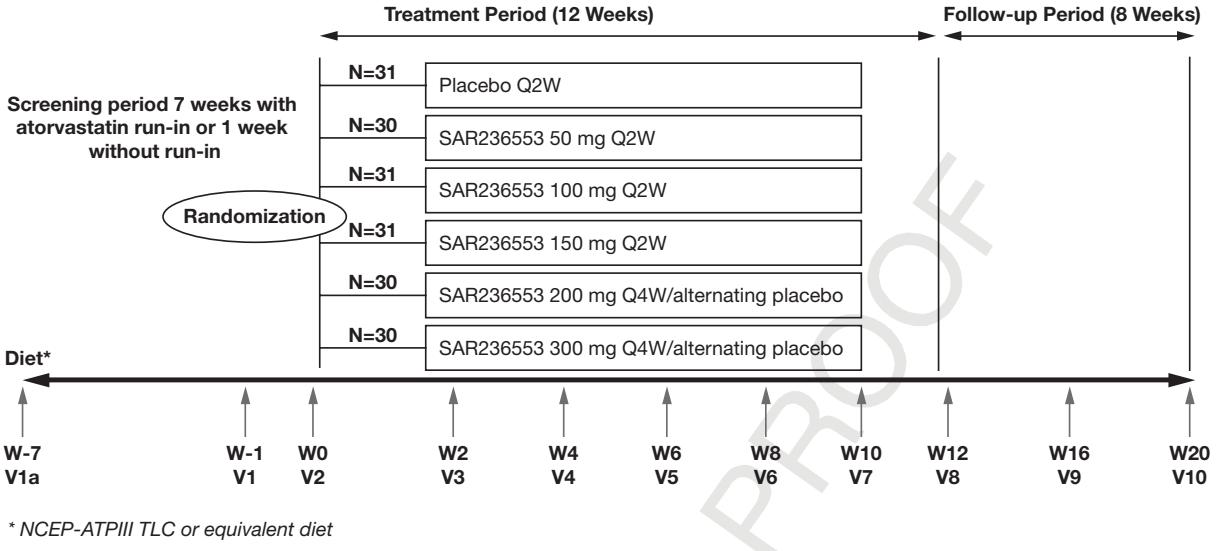

Figure 1 Study Design

Overview of study periods and treatment arms. W = week; Q2W = every 2 weeks; Q4W = every 4 weeks.

atorvastatin dose on the LDL-C–lowering efficacy of SAR236553. Visits during follow-up were every 4 weeks.

All laboratory samples were processed by Medpace Reference Laboratories (Cincinnati, Ohio), which maintained Part III certification by the CDC Lipid Standardization Program (22) and accreditation by the College of American Pathologists (23). All lipids, Apos, and safety laboratory tests were performed after 12-h overnight fasts (water only). Triglycerides and cholesterol were measured with enzymatic colorimetric tests (Olympus AU2700 or AU5400 Analyzer, Olympus, Center Valley, Pennsylvania) with calibration directly traceable to Centers for Disease Control reference procedures. Apo-B–containing lipoproteins were precipitated with dextran sulphate, and HDL-C was measured on the supernatant (24). Apo-A1, Apo-B, and Lp(a) were measured with rate immunonephelometry (Dade Behring BNII nephelometer, Siemens Healthcare Diagnostics, Deerfield, Illinois).

Safety assessments. Safety was assessed throughout the study by clinical examination, vital signs, AEs, serious AEs, laboratory tests, and 12-lead electrocardiogram. AE data were collected from screening onwards.

Statistical methods. The primary study endpoint was the percentage change in calculated LDL-C from baseline (mean of week −1 and week 0) to week 12. To detect a 30% difference in % LDL-C change with SAR236553 versus placebo, assuming a 20% to 30% standard deviation and a 5% rate of unevaluable primary endpoint, and using a 2-sided *t* test at 0.05 significance level, 30 patients per treatment arm were required AQ: 2 to achieve a power of >99% to 96%.

For the primary efficacy endpoint analysis, a hierarchical testing procedure was applied to ensure strong control of the overall type-I error rate at the 0.05 level when testing the 5 SAR236553 dose regimens versus placebo. The order used was SAR236553 150 mg Q2W versus placebo first; SAR236553 300 mg Q4W versus placebo second; SAR236553 100 mg Q2W third; SAR236553 200 mg Q4W fourth; and finally, SAR236553 50 mg Q2W. The hierarchical testing sequence continued only when the higher-order test was statistically significant at the 5% level. No further adjustment was performed for secondary analyses or endpoints, for which p values were provided for descriptive purposes only.

EFFICACY ENDPOINTS. The primary efficacy endpoint was analyzed in the modified intent-to-treat (mITT) population, defined as all randomized patients with an evaluable primary endpoint, using an analysis of covariance model with treatment group and randomization strata of atorvastatin dose as fixed effects, and baseline LDL-C as covariate. The treatment group factor had 6 levels: placebo; SAR236553 50 mg Q2W; SAR236553 200 mg Q4W; SAR236553 100 mg Q2W; SAR236553 300 mg Q4W; and SAR236553 150 mg Q2W. Patients in the mITT population were analyzed according to randomized treatment group. The last observation carried forward method was applied to impute missing week 12 LDL-C on-treatment values. Throughout the analysis of covariance model, each SAR236553 treatment group was compared with placebo using appropriate contrasts. Ninety-five percent confidence intervals of the difference versus placebo were not adjusted for multiple comparisons. Secondary efficacy endpoints were analyzed in the mITT population using the same analysis of covariance model, with treatment group and randomization strata of atorvastatin dose as fixed effect, and corresponding baseline value as covariate.

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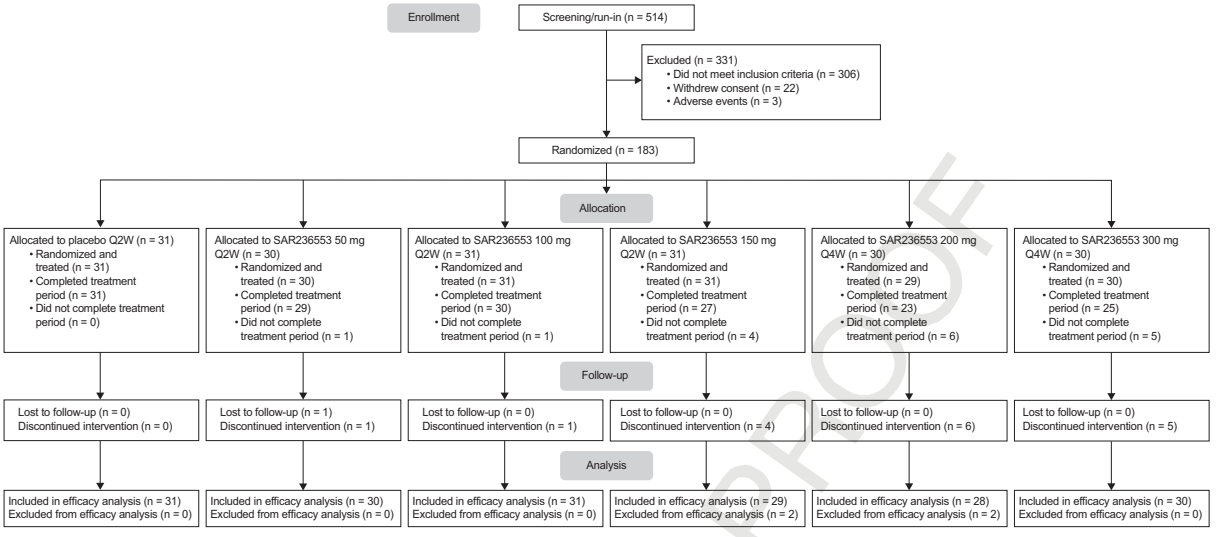

Figure 2 **Patient Disposition**

Numbers of patients included and excluded at each stage of the study.

SAFETY ENDPOINTS. All safety analyses were performed on the safety population (all randomized patients who received at least 1 full or partial dose of investigational product, analyzed according to the treatment actually received). Four patients received a dose at 1 (or several) visit(s) differing from the dose allocated (5 cases in 4 patients). For these patients, the treatment arm allocation for as-treated analysis was defined in a blinded manner using a pre-specified algorithm before the database was locked. Demographic and baseline data were summarized on the all-randomized population, and analyzed in the randomized treatment group.

Results

Study population. Of 514 patients screened at 34 centers between January and August 2011, 183 met the eligibility criteria and were randomized to treatment (Fig. 2). Ninety percent of patients completed the full 12-week treatment period. The most frequent cause of premature study withdrawal (6 patients) was treatment-emergent AEs (described later in the text). Other causes included noncompliance with study medication, difficulty with/unacceptability of subcutaneous injections, and loss to follow-up (Fig. 2).

Table 1 **Patient Demographic and Baseline Characteristics by Assigned Treatment Group (Randomized Population)**

	Placebo (n = 31)	50 mg Q2W (n = 30)	100 mg Q2W (n = 31)	150 mg Q2W (n = 31)	200 mg Q4W (n = 30)	300 mg Q4W (n = 30)	All (N = 183)
Age, yrs	53.3 (8.5)	58.5 (9.1)	58.1 (9.2)	59.9 (11.1)	54.9 (10.8)	55.5 (10.1)	56.7 (10.0)
Female	15 (48.4)	13 (43.3)	18 (58.1)	21 (67.7)	13 (43.3)	16 (53.3)	96 (52.5)
Race*							
White	27 (87.1)	26 (86.7)	24 (77.4)	25 (80.6)	28 (93.3)	28 (93.3)	158 (86.3)
Black	3 (9.7)	4 (13.3)	6 (19.4)	6 (19.4)	2 (6.7)	2 (6.7)	23 (12.6)
Other	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1)
Hispanic or Latino ethnicity	7 (22.6)	5 (16.7)	4 (12.9)	7 (22.6)	9 (30.0)	8 (26.7)	40 (21.9)
BMI, kg/m^2	27.9 (4.8)	30.0 (4.5)	29.3 (4.4)	28.2 (4.3)	29.1 (4.2)	30.5 (6.0)	29.2 (4.8)
Years since diagnosis of hyperlipoproteinemia	10.1 (8.8)	10.3 (8.7)	9.5 (7.5)	9.2 (10.1)	7.7 (6.5)	8.4 (6.7)	9.2 (8.1)
Previous treatment with a lipid-lowering agent	25 (80.6)	25 (83.3)	28 (90.3)	27 (87.1)	26 (86.7)	27 (90.0)	158 (86.3)
Hypertension	11 (35.5)	16 (53.3)	19 (61.3)	14 (45.2)	9 (30.0)	13 (43.3)	82 (44.8)
Type 2 diabetes	1 (3.2)	3 (10.0)	2 (6.5)	3 (9.7)	4 (13.3)	9 (30.0)	22 (12.0)
Coronary artery disease	2 (6.5)	2 (6.7)	1 (3.2)	2 (6.5)	2 (6.7)	1 (3.3)	10 (5.5)
Cerebrovascular disease	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	2 (6.7)	0 (0.0)	3 (1.6)
Peripheral vascular disease	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.7)	1 (3.3)	1 (3.3)	5 (2.7)
Current smoker†	8 (25.8)	5 (16.7)	3 (9.7)	9 (29.0)	4 (13.3)	8 (26.7)	37 (20.2)

Values are mean ± SD or n (%). *Patients may be included in more than 1 category. †Patients who have smoked ≥1 cigarette, as a mean, per day during the past 7 days.
BMI = body mass index; Q2W = every 2 weeks; Q4W = every 4 weeks.

Table 2 Changes in Lipid Parameters From Baseline to Week 12 by Treatment Group (mITT Population)

		SAR236553				
	Placebo (n = 31)	50 mg Q2W (n = 30)	100 mg Q2W (n = 31)	150 mg Q2W (n = 29)	200 mg Q4W (n = 28)	300 mg Q4W (n = 30)
LDL-C, mg/dl						
Baseline	130.2 (27.3)	123.2 (27.9)	127.0 (30.4)	123.9 (26.7)	128.2 (19.2)	131.6 (24.8)
Week 12	120.5 (27.0)	73.2 (16.4)	46.0 (24.4)	34.2 (15.6)	71.1 (21.6)	66.0 (27.7)
% Change from baseline to week 12, LS mean* (SE)	−5.1 (3.1)	−39.6 (3.2)	−64.2 (3.1)	−72.4 (3.2)	−43.2 (3.3)	−47.7 (3.2)
p Value* for % change with SAR236553 vs. placebo		<0.0001***	<0.0001***	<0.0001***	<0.0001***	<0.0001***
TC, mg/dl						
Baseline	209.0 (27.9)	203.3 (28.1)	203.0 (31.4)	205.2 (29.7)	204.2 (25.4)	207.1 (30.2)
Week 12	203.1 (35.5)	155.1 (21.7)	122.7 (26.7)	111.1 (20.7)	146.0 (25.9)	143.0 (31.6)
% Change from baseline to week 12, LS mean* (SE)	−1.6 (2.3)	−23.0 (2.3)	−39.7 (2.3)	−45.2 (2.3)	−28.0 (2.4)	−29.8 (2.3)
p Value* for % change with SAR236553 vs. placebo		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HDL-C, mg/dl						
Baseline	49.0 (10.3)	53.8 (13.6)	52.6 (13.0)	53.3 (16.1)	46.7 (10.8)	48.0 (13.8)
Week 12	48.9 (13.2)	56.8 (14.4)	54.5 (15.4)	55.1 (14.8)	49.4 (10.5)	51.7 (15.6)
% Change from baseline to week 12, LS mean* (SE)	−1.0 (2.3)	6.7 (2.4)	4.1 (2.3)	5.5 (2.4)	6.3 (2.5)	8.5 (2.4)
p Value* for % change with SAR236553 vs. placebo		0.0218	0.1247	0.0570	0.0320	0.0047
TG, mg/dl						
Baseline	124.0 (92.0−187.5)	128.8 (98.0 to 157.0)	106.0 (80.0 to 149.0)	140.5 (92.5 to 177.5)	127.0 (95.8 to 169.3)	138.5 (103.5 to 176.0)
Week 12	127.0 (98.0 to 197.0)	117.0 (91.0 to 161.0)	101.0 (70.0 to 131.0)	99.0 (79.0 to 139.0)	124.5 (94.5 to 152.5)	127.5 (112.0 to 150.0)
% Change from baseline to week 12	9.7 (−15.0 to 30.7)	−6.6 (−17.7 to 7.1)	−5.5 (−22.1 to 10.7)	−18.9 (−31.7 to −6.1)	−10.8 (−25.4 to 13.3)	−8.4 (−21.5 to 10.1)
p Value** for % change with SAR236553 versus placebo		0.0987	0.0870	0.0006	0.0904	0.0533
Non–HDL-C, mg/dl						
Baseline	160.0 (28.9)	149.5 (29.4)	150.4 (30.1)	151.8 (34.6)	157.5 (22.8)	159.2 (28.5)
Week 12	154.2 (37.0)	98.3 (21.1)	68.2 (27.7)	56.0 (18.0)	96.6 (24.2)	91.3 (28.4)
% Change from baseline to week 12, LS mean* (SE)	−2.2 (2.9)	−33.6 (2.9)	−55.6 (2.9)	−62.5 (3.0)	−37.4 (3.0)	−40.7 (2.9)
p Value* for % change with SAR236553 versus placebo		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Apo-B, mg/dl						
Baseline	108.3 (19.3)	102.0 (24.5)	103.1 (17.0)	101.6 (26.6)	107.3 (17.5)	104.6 (20.9)
Week 12	109.2 (27.0)	73.0 (16.4)	54.0 (18.4)	44.1 (14.1)	74.9 (17.1)	68.6 (20.3)
% Change from baseline to week 12, LS mean* (SE)	2.2 (2.9)	−27.3 (2.9)	−48.1 (2.9)	−56.1 (2.9)	−28.7 (3.1)	−33.1 (2.9)
p Value* for % change with SAR236553 versus placebo		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Apo-A1, g/l						
Baseline	1.4 (1.3 to 1.6)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.7)	1.5 (1.3 to 1.7)	1.5 (1.3 to 1.7)	1.4 (1.3 to 1.6)
Week 12	1.4 (1.3 to 1.7)	1.6 (1.5 to 1.8)	1.5 (1.4 to 1.7)	1.6 (1.4 to 1.7)	1.5 (1.3 to 1.7)	1.5 (1.3 to 1.7)
% Change from baseline to week 12	0.0 (−7.2 to 5.3)	1.4 (−2.8 to 6.0)	0.3 (−4.9 to 4.7)	1.4 (−2.1 to 5.4)	1.5 (−2.9 to 15.1)	4.2 (−3.1 to 17.1)
p Value** for % change with SAR236553 versus placebo		0.0455	0.8713	0.1524	0.3019	0.0658
Lp(a), g/l						
Baseline	0.2 (0.1 to 0.9)	0.2 (0.1 to 0.6)	0.3 (0.1 to 0.8)	0.3 (0.1 to 0.6)	0.3 (0.1 to 0.7)	0.2 (0.0 to 0.5)
Week 12	0.2 (0.07 to 0.85)	0.1 (0.04 to 0.43)	0.2 (0.08 to 0.71)	0.1 (0.05 to 0.41)	0.2 (0.06 to 0.73)	0.1 (0.02 to 0.44)
% Change from baseline to week 12	0.0 (−11.8 to 11.5)	−13.3 (−33.3 to 0.0)	−26.1 (−36.7 to −8.0)	−28.6 (−46.9 to −22.2)	−16.7 (−33.3 to −6.3)	−7.9 (−18.8 to 0.0)
p Value** for % change with SAR236553 versus placebo		0.0022	<0.0001	<0.0001	0.0006	0.0203

Values are mean ± SD or median (interquartile range). p Values for all parameters other than % change in LDL-C from baseline to week 12 are not adjusted for multiplicity and are included here for descriptive purposes only. *LS means and p values come from covariance analysis with treatment group and randomization strata of atorvastatin dose as fixed effects and baseline as covariate. †p Value comes from a rank analysis of covariance including terms for treatment, randomization strata of atorvastatin dose, and baseline value. The treatment term had 2 levels: the considered SAR236553 dose and placebo. ‡Statistically significant p value according to hierarchical procedure.

Apo-A1 = apolipoprotein-A1; Apo-B = apolipoprotein-B; HDL-C = high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LS = least squares; TC = total cholesterol; TG = triglycerides.

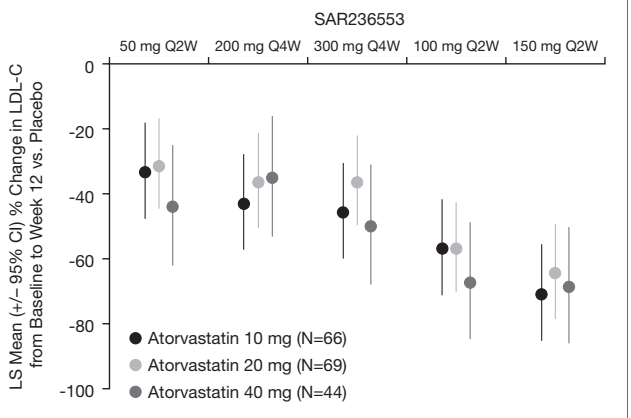

Figure 3 **Change in Calculated LDL-C From Baseline to Week 12 by Stratified Atorvastatin Dose**

Least squares (LS) mean (±95% confidence interval [CI]) percentage change in calculated low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 in the modified intent-to-treat population, by treatment group and atorvastatin dose. Abbreviations as in Figure 1.

T1 Table 1 summarizes baseline patient characteristics. The efficacy analysis included 179 patients (98%). One randomized patient was not treated; the safety population therefore comprised 182 patients.

T2 **Primary efficacy outcomes.** Table 2 summarizes changes in lipid values from baseline to week 12. Mean baseline LDL-C across all treatment groups was similar at 123 to 132 mg/dl. SAR236553 demonstrated a clear dose-response pattern in LDL-C lowering for both Q2W and Q4W administration. Least squares mean ± standard error reductions in LDL-C from baseline were 39.6 ± 3.2% with 50 mg Q2W, 64.2 ± 3.1% with 100 mg Q2W, 72.4 ± 3.2% with 150 mg Q2W dose, 43.2 ± 3.3% with 200 mg Q4W, and 47.7 ± 3.2% with 300 mg Q4W, versus 5.1 ± 3.1% with placebo. LDL-C reductions with SAR236553 were similar among atorvastatin doses (Fig. 3). F3

Figure 4 illustrates percentage LDL-C change at 2-week intervals. LDL-C reduction among placebo recipients reached a maximum of 13.4% at week 6 and was 5.1% by week 12. LDL-C decreased significantly from baseline by 30.5%, 53.6%, and 62.9% at 2 weeks post-dosing with SAR236553 50 mg, 100 mg, and 150 mg Q2W, respectively, with further reductions reaching 39.6%, 64.2%, and 72.4%, respectively, at week 12 (last observation carried forward). For the 200- and 300-mg Q4W regimens, LDL-C reductions achieved 2 weeks after the first dose were 66.8% and 69.5%, respectively, which waned over the succeeding 2 weeks (after administration of a placebo dose) to 38.6% and 53.4%, respectively, at week 4. A similar pattern was observed with each subsequent 4-week dose, such that LDL-C reductions in these treatment arms appeared consistent at each 4-week period. F4

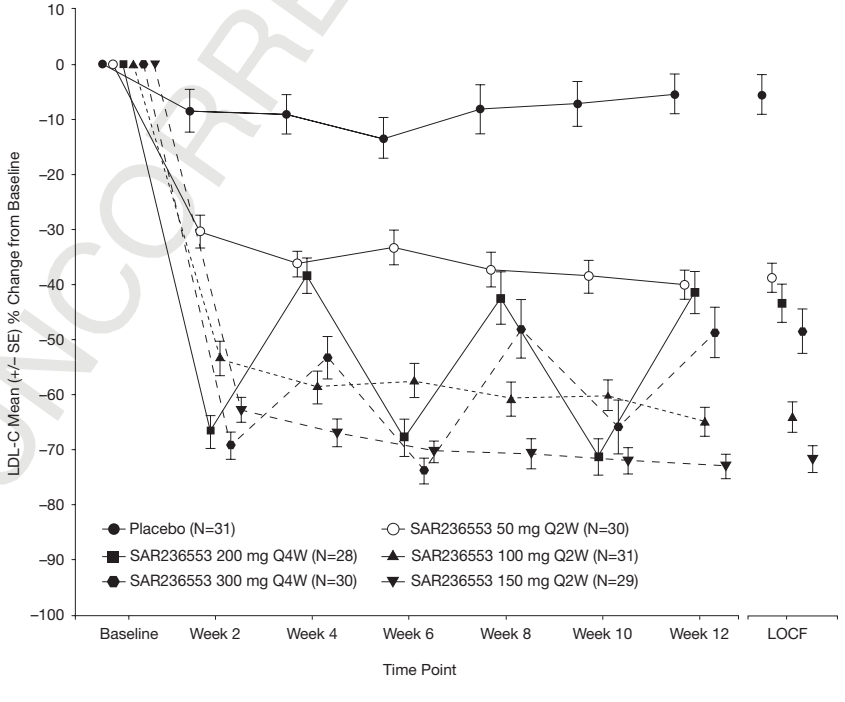

Figure 4 **Change in Calculated LDL-C at 2-Week Intervals From Baseline to Week 12**

LS mean (±SE) percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat population, by treatment group. Abbreviations as in Figures 1 and 3.

Secondary efficacy outcomes. Treatment effects on non-LDL lipid and Apo parameters are shown in Table 2. Total cholesterol, non–HDL-C, and Apo-B decreased substantially. Apo-B and non–HDL-C were reduced by 27% to 56% and 34% to 63%, respectively, and Lp(a) by 13% to 29% across SAR236553 Q2W regimens. Changes in Apo-B and related lipids were proportional with the changes in LDL-C. Changes in triglycerides were variable and mostly small; the exception to this was the 150-mg Q2W regimen, which reduced triglycerides by 19%. Increases in both HDL-C and Apo-A1 were variable, but greater with all SAR236553 regimens than with placebo.

Eighty-nine percent to 100% versus 16% of SAR236553 versus placebo recipients achieved a target LDL-C of <100 mg/dl (Fig. 5). The LDL-C <70 mg/dl target was achieved by 47%, 84%, and 100% of 50-, 100-, and 150-mg Q2W recipients, respectively, and by 46% and 57% of 200- and 300-mg Q4W recipients, versus 3% of placebo recipients. At week 12, the Apo-B target of <80 mg/dl was achieved by 67% to 100% and 59% to 77%, and the non–HDL-C treatment target of <100 mg/dl by 60% to 100% and 54% to 60% of patients assigned to 50 to 150 mg Q2W and 200 to 300 mg Q4W, respectively. Corresponding percentages for placebo were 10% and 3%, respectively.

Safety. AEs were similar for all treatment groups, with no dose relationship observed (Table 3).

Five serious AEs occurred in 4 patients during the study: a 64-year-old placebo-treated male required back surgery; a 68-year-old female assigned to SAR236553 200 mg Q4W underwent elective right knee total arthroplasty; a 69-year-old female with a history of chronic obstructive pulmonary disease, assigned to SAR236553 100 mg Q2W, was hospitalized during the follow-up period for worsening disease; and a 57-year-old male who, after the initial dose of SAR236553 300 mg Q4W, developed diarrhea followed by a rash on his arms, legs, and abdomen, and was diagnosed by biopsy with leukocytoclastic vasculitis. Prednisone treatment led to full resolution. The investigator considered this a significant medical event. No antidrug antibodies were found following the event, but the week 20 follow-up assessment found minimally detectable (30) anti-drug antibodies. Blood samples obtained about 6 months after the event were assessed for antinuclear antibodies, tryptase, high-sensitivity C-reactive protein, and immunoglobulin A, E, M, and G. The antinuclear antibody assessments were negative, and all other results were within normal limits. The same patient required surgery for a humerus fracture that occurred during the follow-up period.

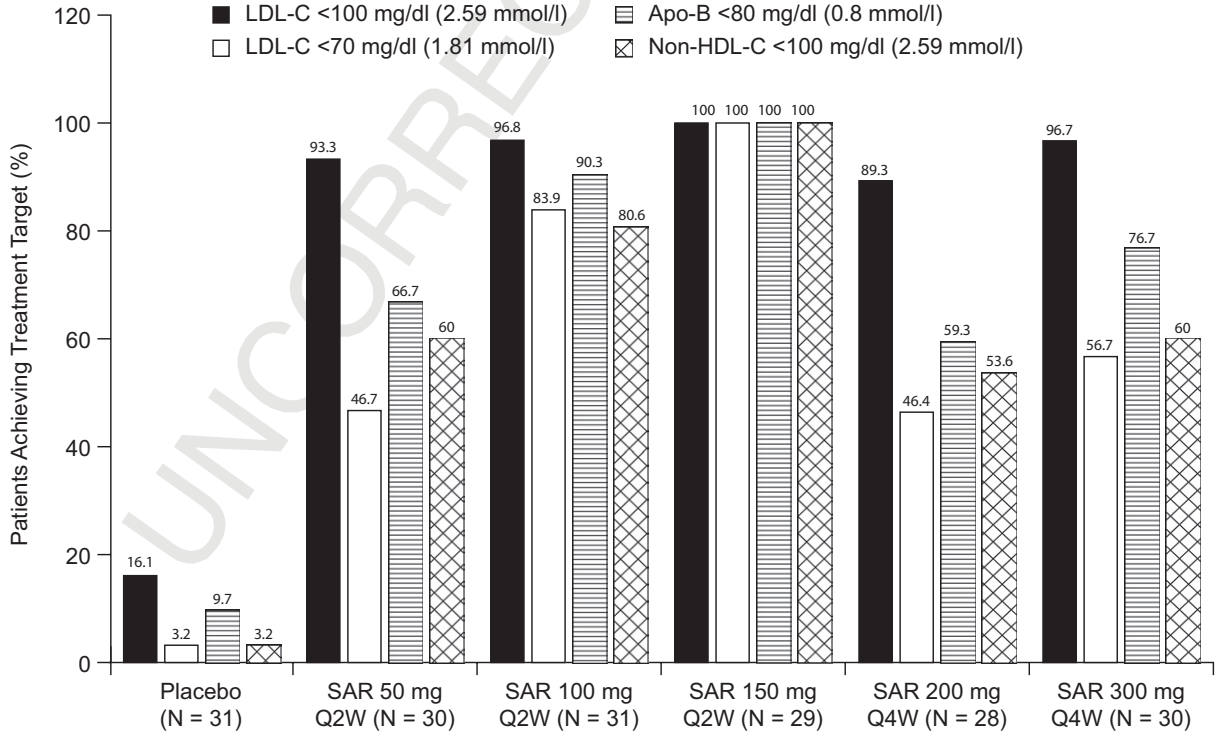

Figure 5 **Attainment of Treatment Targets for LDL-C, Non–HDL-C, and Apo-B**

The proportion of patients in each treatment arm achieving targets of: <100 mg/dl (2.59 mmol/l) and <70 mg/dl (1.81 mmol/l) for low-density lipoprotein cholesterol (LDL-C); <100 mg/dl (2.59 mmol/l) for non–high-density lipoprotein cholesterol (non-HDL-C); and <80 mg/dl (2.07 mmol/l) for apolipoprotein B (Apo-B). Abbreviations as in Figures 1 and 3.

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Table 3 Summary of Treatment-Emergent Adverse Events (Safety Population)

	Placebo (n = 31)	SAR236553 50 mg Q2W (n = 30)	SAR236553 100 mg Q2W (n = 31)	SAR236553 150 mg Q2W (n = 31)	SAR236553 200 mg Q4W (n = 31)	SAR236553 300 mg Q$W (N = 28)
Overview of all TEAEs						
Patients with any TEAE	14 (45.2)	18 (60.0)	20 (64.5)	19 (61.3)	20 (64.5)	14 (50.0)
Patients with any treatment-emergent SAE	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	1 (3.2)	1 (3.6)
Patients with any TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with any TEAE or treatment-emergent SAE leading to permanent treatment discontinuation	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)	3 (9.7)	1 (3.6)
AEs of special interest						
ALT >3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST >3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0,0)	0 (0.0)	0 (0.0)
Muscle disorders (including pain, weakness)	1 (3.2)	1 (3.3)	2 (6.5)	1 (3.2)	1 (3.2)	2 (7.1)
CK >10 × ULN	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs occurring in >5% of patients in any treatment group						
Sinusitis	3 (9.7)	0 (0.0)	1 (3.2)	2 (6.5)	1 (3.2)	0 (0.0)
Influenza	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (3.2)	4 (13.3)	3 (9.7)	0 (0.0)	1 (3.2)	1 (3.6)
Upper respiratory tract infection	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	2 (6.5)	1 (3.6)
Urinary tract infection	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)
Anemia	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)
Headache	1 (3.2)	1 (3.3)	2 (6.5)	1 (3.2)	1 (3.2)	1 (3.6)
Bundle branch block left	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	1 (3.2)	2 (6.7)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)	1 (3.2)	2 (7.1)
Nausea	2 (6.5)	2 (6.7)	2 (6.5)	0 (0.0)	2 (6.5)	1 (3.6)
Arthralgia	1 (3.2)	0 (0.0)	1 (3.2)	1 (3.2)	1 (3.2)	2 (7.1)
Back pain	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	2 (6.5)	1 (3.6)
Pain in extremity	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (7.1)
Fatigue	0 (0.0)	1 (3.3)	1 (3.2)	2 (6.5)	0 (0.0)	0 (0.0)
Injection-site erythema	0 (0.0)	0 (0.0)	3 (9.7)	3 (9.7)	1 (3.2)	1 (3.6)
Injection-site pruritis	0 (0.0)	0 (0.0)	2 (6.5)	3 (9.7)	1 (3.2)	0 (0.0)
Injection-site swelling	0 (0.0)	1 (3.3)	1 (3.2)	2 (6.5)	1 (3.2)	0 (0.0)
Injection-site hematoma	0 (0.0)	2 (6.7)	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Injection-site rash	0 (0.0)	2 (6.7)	0 (0.0)	1 (3.2)	1 (3.2)	0 (0.0)
Influenza-like illness	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated blood CK	2 (6.5)	1 (3.3)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	0 (0,0)	0 (0.0)	1 (3.2)	1 (3.2)	2 (7.1)
Procedural pain	0 (0,0)	0 (0.0)	2 (6.5)	0 (0,0)	0 (0.0)	0 (0.0)

Values are n (%) and indicate the number and percentage of patients with at least 1 TEAE. Adverse events classified according to the Medical Dictionary of Regulatory Activities (MedDRA) Version 14.0. One of the 30 patients randomized to SAR236553 200 mg Q4W was not treated, and was therefore excluded from the safety population. Four patients received an incorrect dose: 1 in the 100-mg Q2W treatment arm, 1 in the 200-mg Q4W treatment arm, and 2 in the 300-mg Q4W treatment arm. For the safety population, the patients on 100 mg Q2W and 200 mg Q4W were maintained in their respective groups, whereas the 2 patients in the 300-mg Q4W arm were switched to the 200-mg Q4W treatment arm, giving a total of 31 patients in the 200-mg Q4W arm.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; SAE = serious adverse event; TEAE = treatment-emergent serious event; ULN = upper limit of normal.

Six patients prematurely discontinued SAR236553 owing to AEs: 1 each in the 100-mg Q2W (neutropenia) and 150-mg Q2W (fatigue) arms, 3 in the 200-mg Q4W arm (injection-site rash, chest pain, and combined headache and nausea), and 1 in the 300-mg Q4W arm (leukocytoclastic vasculitis described earlier in the text). No AE-related discontinuations occurred with placebo.

Mild injection-site reactions (this group term included erythema, pruritis, swelling, discoloration, hematoma, and rash) were the most common AEs (Table 3). These occurred in SAR236553 recipients only, and were more common with Q2W than Q4W dosing. Elevated creatine kinase >10 × ULN occurred in 1 patient (placebo-treated); none had hepatic transaminases >3 × ULN or significant changes in other laboratory values. Muscle complaints were infrequent and similar across treatment groups.

Discussion

This study demonstrated that SAR236553 is associated with dose-related and dose regimen–dependent LDL-C reductions in patients receiving stable atorvastatin therapy. LDL-C reductions with 100 and 150 mg Q2W were greater than with 200 and 300 mg Q4W at week 12, and reached a maximum of 72% (150 mg Q2W). SAR236553 150 mg Q2W reduced LDL-C to <70 mg/dl in 100% of

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patients. The continued trend towards lower LDL-C observed with multiple SAR236553 Q2W doses may indicate a potential for further LDL-C reductions with longer therapy duration. LDL-C reductions with SAR236553 were unaffected by atorvastatin dose (10, 20, or 40 mg daily), suggesting that, although both statin and PCSK9 monoclonal antibody therapies up-regulate LDLRs, their mechanisms of LDL-C reduction are independent. Further, these agents appear to provide additive LDL-C–lowering effects when administered in combination. LDL-C reductions achieved with SAR236553 result from increased numbers of LDLRs. The increase in LDLRs arises from PCSK9 inhibition, and enhances the clearance of any Apo-B–containing particles—including LDL, very-low-density lipoprotein, and possibly, Lp(a). To our knowledge, increasing LDLRs by combining SAR236553 with a statin is not associated with any adverse effects.

Our findings suggest that patients who are unable to achieve LDL-C treatment targets with statin monotherapy may do so with the addition of SAR236553. Because LDL-C increased after 2 weeks post-dosing, Q2W administration appears the most favorable dosing schedule.

SAR236553 100 and 150 mg Q2W reduced Apo-B by 48% and 56%, respectively, allowing 90% and 100% of patients to achieve the <80 mg/dl Apo-B goal. Statin trials indicate that no threshold exists, below which further LDL-C reduction provides no additional benefit (25). However, post hoc analyses of large outcomes trials suggest that LDL-C does not represent the vascular burden of all atherogenic lipoproteins, and that non–HDL-C and, even more so, Apo-B levels may correlate better with outcomes (3,26), especially in secondary cardiovascular disease prevention and in high cardiometabolic risk patients (27,28). Adding ezetimibe and/or bile acid sequestrants to statins further reduces LDL-C by 12% to 18%, but reduces Apo-B by only around 6%. This may account for the observed failure to reach Apo-B targets when LDL-C goals are met (29). The potential of SAR236553 to enable nearly all patients to attain both LDL-C and Apo-B targets may thus offer an opportunity for further cardiovascular risk reduction.

In this study, the effects of SAR236553 on triglycerides were minimal; however, baseline triglyceride levels were fairly low at 117 to 146 mg/dl. Statins, which also up-regulate LDLR activity, similarly have little effect on triglycerides in normotriglyceridemic patients (30). Very-low-density lipoprotein particles are the principal carriers of triglycerides. These particles contain Apo-B and are therefore subject to enhanced clearance as a result of LDLR up-regulation by SAR236553. Thus, greater triglyceride reductions would be expected in patients with higher baseline triglycerides, and assessment of the true triglyceride-lowering potential of SAR236553, with or without statins, will require studies in patients with elevated baseline levels.

As in the earlier phase 1 trial (31), there was a trend towards HDL-C and Apo-A1 increases with SAR236553 versus placebo. HDL-C may increase as a result of reduced cholesteryl ester transfer protein–mediated transfer of cholesterol from HDL to LDL or very-low-density lipoprotein, owing to the reduction of LDL to very low levels. This inability to transfer cholesterol from HDL leads to relative increases in HDL-C, as evidenced by the minimal change in Apo-A1, the major apolipoprotein in HDL.

The consistent, robust 13% to 29% Lp(a) reduction with SAR236553 Q2W confirms phase 1 data showing similar effects in SAR236553 patients receiving atorvastatin, but not in those on diet alone (31). As the LDLR up-regulation induced by statins, ezetimibe, and bile acid sequestrants has no impact on Lp(a), it is possible that, with the large LDL-C reductions, remaining competition from the Apo-B on LDLR is minimal, enabling LDLR uptake of the lower-affinity Apo-B on Lp(a). The actual mechanism of Lp(a) reduction will require further study.

SAR236553 was well tolerated during this short study. The frequency of injection-site reactions—which were generally mild, transient, and nonprogressive—requires much larger, longer trials to determine clinical and compliance impacts. There was no evidence of increasing clinical or laboratory side effects with increasing SAR236553 dosage. Specifically, this short study produced no evidence of increases in either hepatic or muscle-related enzymes. The occurrence of leukocytoclastic vasculitis in 1 patient 9 days after initiation of SAR236553 300 mg was not associated with other organ involvement, and the patient responded rapidly to SAR236553 withdrawal and steroid therapy initiation. No similar reactions were reported in prior SAR236553 studies. Although the exact causality of the leukocytoclastic vasculitis in this subject cannot be determined, it was deemed by the investigator to be SAR236553-related. Again, larger, longer trials are required to determine the frequency and severity of this potential side effect.

Leukocytoclastic vasculitis is a generally benign disease that occurs in 40 to 60 individuals/million persons/year, with drug therapy identified as the cause of about 20% of cases (32). Numerous classes of agent have been implicated in its development, including antibiotics and nonsteroidal anti-inflammatory drugs (33), and leukocytoclastic vasculitis is listed as an AE in the prescribing information for most commercially available monoclonal antibody therapies. A recent review of articles published between 1990 and 2008 reports 118 cases of cutaneous leukocytoclastic vasculitis in patients receiving TNF monoclonal antibody therapy (34).

Our study is the largest and longest reported to date with SAR236553, and included the most diverse patient population. It confirms the finding of earlier proof-of-concept trials that PCSK9 inhibition with monoclonal antibodies robustly reduces levels of all Apo-B–containing atherogenic lipoproteins, especially LDL-C. This effect was uniform, irrespective of baseline atorvastatin dose, and greater sustained efficacy was seen with Q2W dosing than with higher doses given Q4W. The 72% LDL-C reduction with SAR236553 150 mg Q2W surpasses that achieved with

almost any other lipid-lowering therapy. These encouraging results suggest the need for further evaluation of SAR236553 in larger, even more diverse patient populations, and with different background therapies, to fully assess its efficacy and safety.

Acknowledgments

The authors would like to thank: all the study investigators; the Data Monitoring Committee members (Anders Olsson, MD; David Waters, MD; Dominique Larrey, MD; Robert S. Rosenson, MD; and Geert Molenberghs, PStat); Herbert Thijs, PhD, of the Centre for Statistics (CenStat), Universiteit Hasselt, Belgium, for assisting with the statistical analyses; and Sandralee Lewis, PhD, of PPSI, for scientific writing and editorial support, funded by Sanofi and Regeneron.

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Key Words: apolipoprotein-B hypercholesterolemia ■ low-density lipoprotein cholesterol ■ PCSK9 ■ REGN727/SAR236553 ■ safety ■ statin.