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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 SAR236553/REGN727 (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-density 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;59:2344–53) © 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 strongly supports a positive correlation between greater

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levels of LDL-C lowering and cardioprotective benefits (5–9). Accordingly, current U.S., 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).

SAR236553/REGN727 (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 age 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.

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

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