ORIGINAL ARTICLE

# Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia

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## ABSTRACT

### BACKGROUND

Serum proprotein convertase subtilisin/kexin 9 (PCSK9) binds to low-density lipoprotein (LDL) receptors, increasing the degradation of LDL receptors and reducing the rate at which LDL cholesterol is removed from the circulation. REGN727/SAR236553 (designated here as SAR236553), a fully human PCSK9 monoclonal antibody, increases the recycling of LDL receptors and reduces LDL cholesterol levels.

### METHODS

We performed a phase 2, multicenter, double-blind, placebo-controlled trial involving 92 patients who had LDL cholesterol levels of 100 mg per deciliter (2.6 mmol per liter) or higher after treatment with 10 mg of atorvastatin for at least 7 weeks. Patients were randomly assigned to receive 8 weeks of treatment with 80 mg of atorvastatin daily plus SAR236553 once every 2 weeks, 10 mg of atorvastatin daily plus SAR236553 once every 2 weeks, or 80 mg of atorvastatin daily plus placebo once every 2 weeks and were followed for an additional 8 weeks after treatment.

### RESULTS

The least-squares mean (±SE) percent reduction from baseline in LDL cholesterol was 73.2±3.5 with 80 mg of atorvastatin plus SAR236553, as compared with 17.3±3.5 with 80 mg of atorvastatin plus placebo ($P<0.001$) and 66.2±3.5 with 10 mg of atorvastatin plus SAR236553. All the patients who received SAR236553, as compared with 52% of those who received 80 mg of atorvastatin plus placebo, attained an LDL cholesterol level of less than 100 mg per deciliter, and at least 90% of the patients who received SAR236553, as compared with 17% who received 80 mg of atorvastatin plus placebo, attained LDL cholesterol levels of less than 70 mg per deciliter (1.8 mmol per liter).

### CONCLUSIONS

In a randomized trial involving patients with primary hypercholesterolemia, adding SAR236553 to either 10 mg of atorvastatin or 80 mg of atorvastatin resulted in a significantly greater reduction in LDL cholesterol than that attained with 80 mg of atorvastatin alone. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT01288469.)


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Reducing levels of low-density lipoprotein (LDL) cholesterol is a cornerstone of the prevention of cardiovascular disease.[1,2] European and U.S. guidelines recommend lowering LDL cholesterol to less than 100 mg per deciliter (2.6 mmol per liter) in persons with established cardiovascular disease and to less than 70 mg per deciliter (1.8 mmol per liter), or by 50% or more, in those at highest risk.[3,4]

Statins are highly efficacious in lowering LDL cholesterol. However, many patients, especially those with very high initial LDL cholesterol levels and those who have unacceptable side effects with high-dose statins, do not reach recommended target levels of LDL cholesterol.[5,6] The addition of bile-acid sequestrants, niacin, or ezetimibe to statins produces an additional 10 to 20% reduction in LDL cholesterol,[7] but there remains a considerable unmet medical need for additional, more effective therapeutic options that have acceptable side-effect profiles.

Serum proprotein convertase subtilisin/kexin 9 (PCSK9) binds to LDL receptors and promotes their degradation, reducing the rate of removal of LDL cholesterol from the circulation.[8,9] Blocking the interaction between PCSK9 and LDL receptors with the use of REGN727/SAR236553 (designated here as SAR236553), a fully human monoclonal antibody that binds PCSK9, lowers LDL cholesterol levels in patients with hypercholesterolemia — both those who are being treated with statins and those who are not.[10-12] The purpose of the current study was to compare the effects of SAR236553 coadministered with high-dose or low-dose atorvastatin, as compared with high-dose atorvastatin alone, in patients with LDL cholesterol levels of 100 mg per deciliter or higher.

## Methods

### Study Design and Oversight

We conducted a phase 2, randomized, double-blind, parallel-group, placebo-controlled study of atorvastatin with or without SAR236553 at 20 sites in the United States (see the Supplementary Appendix, available with the full text of this article at NEJM.org, for a list of sites and investigators). The trial was funded by Sanofi and Regeneron Pharmaceuticals. Sanofi was responsible for the design of the protocol, the collection and analysis of the data, and monitoring of the study sites. The trial protocol and patient consent form were approved by the institutional review board at each participating institution. The academic authors had full access to the data and drafted the manuscript. The first and last authors made the decision to submit the manuscript for publication, with approval of the sponsors. An employee of Publication Planning Services provided writing and editorial support, funded by Sanofi and Regeneron Pharmaceuticals. All the authors vouch for the accuracy and completeness of the data and the analyses as presented and for the fidelity of the study to the trial protocol, which is available at NEJM.org.

### Patients

Eligible patients included men and women 18 to 75 years of age with primary hypercholesterolemia who had an LDL cholesterol level of 100 mg per deciliter or higher at the end of the trial run-in period (see below). Exclusion criteria were type 1 diabetes, type 2 diabetes treated with insulin or poorly controlled (glycated hemoglobin level of 8.5% or higher), hepatic aminotransferase levels that were more than twice the upper limit of the normal range on repeat testing, triglyceride levels higher than 350 mg per deciliter (3.95 mmol per liter), or any cardiovascular or cerebrovascular event or procedure within 6 months before the screening visit. Women of childbearing potential were required to use suitable contraception throughout the study. Concomitant therapy with statins other than atorvastatin at the doses indicated in the protocol or with other lipid-modifying drugs was not allowed during the study. Patients receiving thyroid-replacement therapy could be included if the dose had been stable for at least 12 weeks before screening and if their serum thyrotropin level was within 10% of the normal range of the central laboratory. All patients provided written informed consent.

### Study Procedures

Patients who had been on a stable regimen of 10 mg of atorvastatin for at least 6 weeks before screening entered a 1-week run-in period, during which therapy with 10 mg of atorvastatin was continued. Patients who had not previously received atorvastatin or who had not been receiving 10 mg of atorvastatin for at least 6 weeks before screening entered a 7-week run-in period, during which they received open-label therapy with 10 mg of atorvastatin. All patients were instructed regarding adherence throughout the study to a thera-

peutic lifestyle change (TLC) diet, as outlined in the National Cholesterol Education Program Adult Treatment Panel III guidelines.[1]

Patients who had an LDL cholesterol level of 100 mg per deciliter or higher during the run-in period were randomly assigned, in a 1:1:1 ratio, to receive 80 mg of atorvastatin daily plus SAR236553 once every 2 weeks, 10 mg of atorvastatin daily plus SAR236553 once every 2 weeks, or 80 mg of atorvastatin daily plus placebo once every 2 weeks. Atorvastatin tablets of various doses (Pfizer) were overencapsulated to look the same in order to maintain blinding, and all patients took two capsules in the evening with dinner. In addition, either SAR236553 or placebo was administered subcutaneously in the abdominal area every 2 weeks from week 0 to week 6 (four treatments in total). SAR236553 was expressed and purified at Regeneron Pharmaceuticals and supplied at a concentration of 150 mg per milliliter in 10 mM histidine, pH 6.0, 0.2% polysorbate 20, and 10% sucrose. The placebo was prepared with the use of the same formulation. Patients were monitored at the investigational site for at least 30 minutes after each study-drug injection.

After completion of the active treatment phase (week 8), atorvastatin was no longer supplied as part of the trial. Patients received their pretrial therapy or no lipid-lowering treatment during the follow-up period through week 16.

### OUTCOMES

The primary efficacy outcome was the percent change in calculated LDL cholesterol level from the baseline level (which was the average of LDL cholesterol levels at week –1 and at randomization) to week 8. Secondary efficacy outcomes included the absolute changes from baseline to week 8 in calculated LDL cholesterol levels, total cholesterol levels, high-density lipoprotein (HDL) cholesterol levels, triglyceride levels, non-HDL cholesterol levels, and the ratio of apolipoprotein B to apolipoprotein A1; the percent changes from baseline to week 8 in levels of total cholesterol, HDL cholesterol, triglycerides, non-HDL cholesterol, apolipoprotein B, apolipoprotein A1, and lipoprotein(a); the proportions of patients achieving an LDL cholesterol level of less than 100 mg per deciliter and less than 70 mg per deciliter at week 8; and the effects of SAR236553 on fasting plasma glucose and glycated hemoglobin levels. Free and total PCSK9 concentrations were measured by means of enzyme-linked immunosorbent assays on microtiter plates coated with a PCSK9 monoclonal antibody as the capture reagent and a biotinylated mouse PCSK9 monoclonal antibody as the detection reagent. For the total PCSK9 assay, soluble PCSK9 complexes, including PCSK9:REGN727 complexes, were dissociated by means of an acid-wash step.

Blood samples were obtained in the morning under fasting conditions before injection of SAR236553. All laboratory analyses were performed at Medpace Reference Laboratories as described previously.[10] LDL cholesterol levels were calculated with the use of the Friedewald formula.[13] HDL cholesterol was measured after precipitation of apolipoprotein B–containing lipoproteins with dextran sulfate.[14] We calculated non-HDL cholesterol levels by subtracting HDL cholesterol levels from total cholesterol levels. Levels of apolipoprotein A1, apolipoprotein B, and lipoprotein(a) were measured by means of rate immunonephelometry (with the use of Dade Behring BN II nephelometer, Siemens Healthcare Diagnostics) as reported previously.[10]

Safety was assessed by means of clinical examination, reporting of adverse events, 12-lead electrocardiography, measurement of vital signs, and laboratory testing that included hematologic tests, liver-function tests, and measurement of creatine kinase levels. Anti-SAR236553 antibodies were assayed at baseline, week 4, and week 8, as well as at week 12 and week 16 (follow-up visits). Data on adverse events were collected from the time the patient signed the consent form until the end of the study.

### STATISTICAL ANALYSIS

Assuming that 5% of the patients would not be able to be evaluated for the primary outcome, we estimated that with 30 patients in each treatment group, the study would have 95% power to detect a 20% difference in the primary outcome between the patients assigned to 80 mg of atorvastatin plus placebo and those assigned to 80 mg of atorvastatin plus SAR236553, with a standard deviation of 20%, with the use of a two-sided t-test at the 0.05 significance level. The study was therefore designed to have 90 patients undergo randomization.

Primary and secondary efficacy outcomes were analyzed in the modified intention-to-treat population, which included all patients who underwent randomization and who had a primary end point that could be evaluated. An analysis of covariance

(ANCOVA) model was used, with the treatment group as the fixed effect and the corresponding baseline lipid value as the covariate. The last-observation-carried-forward method was used to impute missing values at week 8 during the treatment period. For the ANCOVA model, the group receiving 80 mg of atorvastatin plus SAR236553 was compared with the group receiving 80 mg of atorvastatin plus placebo, and the 95% confidence interval of the difference was calculated. For secondary analyses or end points, P values have been provided for descriptive purposes only and have not been adjusted for multiple testing. Although formal comparisons with the group receiving 10 mg of atorvastatin plus SAR236553 were not planned, they were performed post hoc for descriptive purposes. The safety population comprised all patients who underwent randomization and who received at least one dose or partial dose of SAR236553 or placebo. Safety outcomes were described with the use of descriptive statistics.

## RESULTS

### PATIENTS

The first patient entered the trial on January 11, 2011, and the last patient completed participation on September 21, 2011. Of 214 patients screened, 92 met the entry criteria and had no conditions that were specified as exclusion criteria; 30 patients were randomly assigned to 80 mg of atorvastatin daily plus SAR236553 once every 2 weeks, 31 were assigned to 10 mg of atorvastatin daily plus SAR236553 once every 2 weeks, and 31 were assigned to 80 mg of atorvastatin daily plus placebo once every 2 weeks (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients are shown in Table 1.

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Atorvastatin, 80 mg, plus Placebo (N=31) | Atorvastatin, 10 mg, plus SAR236553 (N=31) | Atorvastatin, 80 mg, plus SAR236553 (N=30) | Total (N=92) |
|---|---|---|---|---|
| Demographic variables | | | | |
| Age | | | | |
| Mean — yr | 55.3±10.3 | 57.9±10.0 | 57.6±9.3 | 56.9±9.8 |
| ≥65 yr — no. (%) | 6 (19) | 9 (29) | 8 (27) | 23 (25) |
| Male sex — no. (%) | 13 (42) | 14 (45) | 10 (33) | 37 (40) |
| Race — no. (%)† | | | | |
| White | 24 (77) | 29 (94) | 27 (90) | 80 (87) |
| Black | 7 (23) | 2 (6) | 3 (10) | 12 (13) |
| Cardiovascular history and risk factors | | | | |
| Body-mass index‡ | 29.8±4.4 | 29.4±5.1 | 29.3±4.0 | 29.5±4.5 |
| Type 2 diabetes — no. (%) | 7 (23) | 4 (13) | 3 (10) | 14 (15) |
| Hypertension — no. (%) | 15 (48) | 17 (55) | 15 (50) | 47 (51) |
| Smoking history — no. (%) | | | | |
| Never smoked | 17 (55) | 17 (55) | 20 (67) | 54 (59) |
| Former smoker | 7 (23) | 10 (32) | 7 (23) | 24 (26) |
| Current smoker | 7 (23) | 4 (13) | 3 (10) | 14 (15) |
| Cerebrovascular disease — no. (%) | 2 (6) | 2 (6) | 1 (3) | 5 (5) |
| Coronary artery disease — no. (%) | 0 | 2 (6) | 1 (3) | 3 (3) |
| Peripheral vascular disease — no. (%) | 0 | 0 | 1 (3) | 1 (1) |
| Cardiovascular medications — no. (%) | | | | |
| Agents acting on the RAS | 5 (16) | 13 (42) | 9 (30) | 27 (29) |
| Beta-blockers | 2 (6) | 7 (23) | 5 (17) | 14 (15) |
| Diuretics | 4 (13) | 3 (10) | 7 (23) | 14 (15) |
| Calcium-channel blockers | 3 (10) | 2 (6) | 3 (10) | 8 (9) |

**Table 1. (Continued.)**

| Characteristic | Atorvastatin, 80 mg, plus Placebo (N=31) | Atorvastatin, 10 mg, plus SAR236553 (N=31) | Atorvastatin, 80 mg, plus SAR236553 (N=30) | Total (N=92) |
|---|---|---|---|---|
| Lipid and lipoprotein levels — mg/dl | | | | |
| LDL cholesterol | 121.2±18.1 | 119.7±15.5 | 126.9±21.8 | 122.6±18.7 |
| Total cholesterol | 200.8±26.3 | 199.2±20.4 | 210.3±29.8 | 203.4±25.9 |
| HDL cholesterol | 53.9±17.2 | 52.8±14.8 | 59.0±14.4 | 55.2±15.6 |
| Triglycerides | | | | |
| Median | 113.5 | 140.0 | 107.0 | 117.0 |
| Interquartile range | 87.0–145.0 | 93.0–169.0 | 79.0–159.0 | 84.8–158.0 |
| Non-HDL cholesterol | 146.9±23.5 | 146.4±19.0 | 151.3±26.3 | 148.2±22.9 |
| Apolipoprotein B | 100.4±16.3 | 103.9±16.0 | 107.0±19.5§ | 103.7±17.3 |
| Apolipoprotein A1 | 153.8±35.3 | 158.7±29.1 | 165.6±30.9§ | 159.2±31.9 |
| Lipoprotein(a) | | | | |
| Median | 18.0 | 23.0 | 27.0§ | 23.0 |
| Interquartile range | 6.0–53.0 | 10.0–51.0 | 5.0–76.0 | 6.0–56.0 |

* Plus–minus values are means ±SD. There were no significant differences among the groups in any of the characteristics listed except with respect to agents acting on the renin–angiotensin system (RAS), for which P=0.049 for the comparison between 10 mg of atorvastatin plus SAR236553 and 80 mg of atorvastatin plus placebo. Comparisons of means were performed with the use of Student's t-test for parametric variables and the Mann–Whitney test for nonparametric variables. Comparisons of percentages were performed with the use of Fisher's exact test. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data were missing for one patient.

Of the 92 patients in the trial, 80 (87%) completed the 8-week double-blind treatment period. Four patients were not included in the modified intention-to-treat analysis because no LDL cholesterol measurements were available after the initial baseline values were obtained. In addition, no data on lipid levels were available from the visit during the 8-week visit window (day 50 to day 84) for 2 patients in the group that received 80 mg of atorvastatin plus SAR236553, 2 patients in the group that received 10 mg of atorvastatin plus SAR236553, and 5 patients in the group that received 80 mg of atorvastatin plus placebo; data from these patients were included in the analysis with the use of the last-observation-carried-forward method.

### PRIMARY OUTCOME

After 8 weeks of treatment, the least-squares mean (±SE) percent reduction in LDL cholesterol from baseline was 73.2±3.5 with 80 mg of atorvastatin plus SAR236553, as compared with 17.3±3.5 with 80 mg of atorvastatin plus placebo (least-squares mean difference of –55.9±4.9 percentage points; P<0.001). Because of a deviation from the assumption of a normal distribution and equality of variances required for ANCOVA testing, a sensitivity analysis with the use of a rank-based ANCOVA was performed and showed consistent results (effect-size estimate of –54.5 percentage points; P<0.001). The least-squares mean percent reduction from baseline in LDL cholesterol after 8 weeks with 10 mg of atorvastatin plus SAR236553 was 66.2±3.5. An analysis of the primary end point that included only patients with data at week 8 (without imputation of missing data by means of the last-observation-carried-forward method for patients who did not have data at week 8) yielded similar results. When arithmetic means rather than least-squares means were used in the calculations, the results were also similar (Table S1 in the Supplementary Appendix).

### SECONDARY OUTCOMES

All the patients in the two groups assigned to SAR236553, as compared with 52% in the group assigned to 80 mg of atorvastatin plus placebo, achieved the target LDL cholesterol level of less

than 100 mg per deciliter. A similar trend was observed for the target LDL cholesterol level of less than 70 mg per deciliter: 90% of the group that received 80 mg of atorvastatin plus SAR236553 and 97% of the group that received 10 mg of atorvastatin plus SAR236553, as compared with 17% of the group that received 80 mg of atorvastatin plus placebo, met that target.

The percent changes from baseline to week 8 in other lipid and apolipoprotein levels are shown in Table 2. Absolute changes are shown in Tables S2 and S3 in the Supplementary Appendix (calculated as both least-squares means and arithmetic means for normally distributed values and as medians with interquartile ranges for values that were not normally distributed). The changes in levels of apolipoprotein B, non-HDL cholesterol, and total cholesterol were similar to the changes in LDL cholesterol. A modest increase in HDL cholesterol was seen in patients treated with 80 mg of atorvastatin plus SAR236553, as compared with those treated with 80 mg of atorvastatin plus placebo. No significant changes were seen in apolipoprotein A1 levels in any of the three trial groups. Median lipoprotein(a) levels were substantially reduced, by 31.0%, in patients receiving 80 mg of atorvastatin plus SAR236553, as compared with a reduction of 2.7% in the group receiving 80 mg of atorvastatin plus placebo.

The results of laboratory measurements of lipid levels obtained at the week 12 and week 16 visits (follow-up period) (Fig. 1) are consistent with those that would be expected after the withdrawal of study-supplied lipid-lowering medications after week 8. No notable changes were seen in glycated hemoglobin or glucose levels in any of the treatment groups (Table S4 in the Supplementary Appendix).

The changes in total and free serum PCSK9 concentrations are shown in Figure S2 in the Supplementary Appendix. A large increase in total PCSK9 concentration was seen with the administration of SAR236553, owing to slower clearance of the bound complex from the circulation (Fig. S2A). In contrast, there was a marked reduction in free PCSK9 concentration with SAR236553 (Fig. S2B).

### SAFETY

Overall, the percentages of patients who reported at least one adverse event occurring during study treatment were similar in the two groups assigned to 80 mg of atorvastatin (approximately 60%) and were lower in the group assigned to 10 mg of atorvastatin plus SAR236553 (45%). Five patients prematurely discontinued study treatment owing to an adverse event that occurred during treatment (four in the group that received 80 mg of atorvastatin plus placebo and one in the group that received 80 mg of atorvastatin plus SAR236553) (Table 3). The patient who discontinued treatment with 80 mg of atorvastatin plus SAR236553 reported a hypersensitivity reaction and rash, both occurring 12 days after the second injection of SAR236553. The rash was localized on both arms and responded to treatment with an antihistamine.

There was one serious adverse event of dehydration in a patient who received 80 mg of atorvastatin plus SAR236553; the event was not thought to be treatment-related. The patient recovered fully after treatment with intravenous fluids. There were no deaths. One patient in the group assigned to 80 mg of atorvastatin plus SAR236553, who had had a mildly elevated aspartate aminotransferase level before undergoing randomization, had a transient increase in the aspartate aminotransferase level to more than three times, but less than five times, the upper limit of the normal range (Table 3). Results regarding injection-site reactions are shown in Table S5 in the Supplementary Appendix; 1 patient in the groups assigned to SAR236553 therapy and 2 patients in the group assigned to 80 mg of atorvastatin plus placebo had an injection-site reaction. Antibodies against SAR236553 were detected at low titer in 7 of the 56 patients in the SAR236533 groups at week 8 (Table S6 in the Supplementary Appendix).

## DISCUSSION

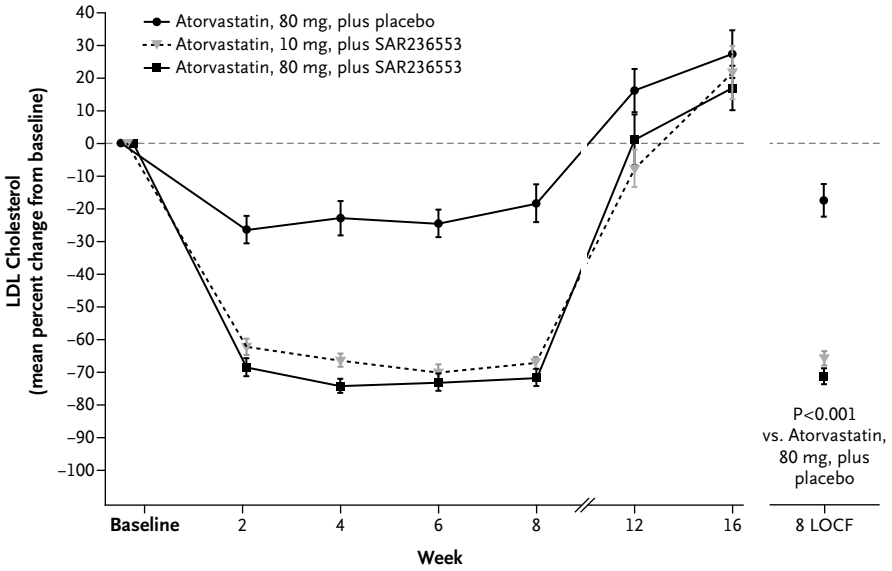
In this phase 2 trial, the combination of 80 mg of atorvastatin plus SAR236553 resulted in significantly greater reductions in LDL cholesterol levels than did 80 mg of atorvastatin plus placebo. In addition, twice as many patients who received 80 mg of atorvastatin plus SAR236553 reached the target LDL cholesterol levels of less than 100 mg per deciliter and more than five times as many reached the target levels of less than 70 mg per deciliter. No specific safety issues were identified, although larger studies will be necessary to assess the potential risk of adverse effects of SAR236553.

**Table 2. Efficacy Outcomes in the Modified Intention-to-Treat Population.***

| Outcome | Atorvastatin, 80 mg, plus Placebo | Atorvastatin, 10 mg, plus SAR236553 | Atorvastatin, 80 mg, plus SAR236553 | P Value† | | |
|---|---|---|---|---|---|---|
| | | | | Atorvastatin, 80 mg, plus SAR236553 vs. Atorvastatin, 80 mg, plus Placebo | Atorvastatin, 10 mg, plus SAR236553 vs. Atorvastatin, 80 mg, plus Placebo | Atorvastatin, 80 mg, plus SAR236553 vs. Atorvastatin, 10 mg, plus SAR236553 |
| Mean least-squares percent change from baseline to week 8 | | | | | | |
| LDL cholesterol | −17.3±3.5 | −66.2±3.5 | −73.2±3.5 | <0.001 | <0.001 | 0.16 |
| HDL cholesterol | −3.6±2.3 | 2.6±2.3 | 5.8±2.3 | 0.005 | 0.06 | 0.33 |
| Apolipoprotein A1 | −5.2±2.3 | 0.4±2.3 | −2.2±2.3 | 0.37 | 0.09 | 0.41 |
| Median (interquartile range) percent change from baseline to week 8 | | | | | | |
| Triglycerides | −11.9 (−30.4 to 14.3) | −4.0 (−30.5 to 17.4) | −24.7 (−40.3 to −4.4) | 0.03 | 0.84 | 0.02 |
| Lipoprotein(a) | −2.7 (−19.5 to 16.7) | −34.7 (−50.0 to −24.7) | −31.0 (−50.0 to −15.4) | <0.001 | <0.001 | 0.70 |
| Total cholesterol | −16.6 (−25.1 to −3.2) | −40.5 (−44.8 to −36.0) | −47.2 (−51.5 to −37.8) | <0.001 | <0.001 | 0.04 |
| Non-HDL cholesterol | −22.3 (−31.4 to −3.7) | −58.3 (−63.9 to −50.2) | −63.9 (−73.9 to −56.1) | <0.001 | <0.001 | 0.01 |
| Apolipoprotein B | −12.0 (−23.6 to −3.5) | −54.4 (−60.2 to −48.3) | −58.0 (−67.1 to −46.1) | <0.001 | <0.001 | 0.31 |

* Plus–minus values are means ±SE. The modified intention-to-treat population included all patients who underwent randomization and who had a primary end point that could be evaluated. Since the assumptions of normal distribution and equality of variances were not verified for apolipoprotein B, non-HDL cholesterol, total cholesterol, lipoprotein(a) and triglycerides, values for these variables are expressed as median (interquartile range).

† The P value for the difference in the percent change in LDL cholesterol between 80 mg of atorvastatin plus SAR236553 and 80 mg of atorvastatin plus placebo was calculated with the use of an analysis of covariance including terms for treatment and baseline value. No other P values have been adjusted for multiple comparisons and are included for descriptive purposes only.




| No. of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin, 80 mg, plus placebo | 29 | 29 | 27 | 25 | 24 | 25 | 21 | 29 |
| Atorvastatin, 10 mg, plus SAR236553 | 29 | 29 | 26 | 26 | 27 | 27 | 24 | 29 |
| Atorvastatin, 80 mg, plus SAR236553 | 30 | 29 | 28 | 28 | 28 | 27 | 27 | 30 |

**Figure 1. Mean Percent Change from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels, According to Treatment Group.**

Shown are the results for the primary efficacy outcome: the mean percent change from baseline in LDL cholesterol levels to week 8, as calculated with the use of the last-observation-carried-forward (LOCF) method. Results are also shown for the entire double-blind treatment phase (week 0 to week 8) and the follow-up period (week 8 to week 16). All analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and who had a primary end point that could be evaluated. The P value was calculated with the use of an analysis of covariance including terms for treatment and baseline value. I bars indicate standard errors.

Although the results of this trial are preliminary, they suggest that administration of SAR236553 with statins may benefit patients in whom LDL cholesterol has not been reduced to recommended levels, either because of an inadequate lipid-lowering response with high-dose statins alone or because of unacceptable side effects with high-dose statins. The latter is a large and growing problem in routine clinical practice,[15] with few options other than statins currently available to clinicians to achieve substantial reductions in LDL cholesterol levels.

Although a comparison of various doses of statins combined with SAR236553 was not the intended focus of this trial, we did find that the effects on the reduction of LDL cholesterol levels of 80 mg of atorvastatin plus SAR236553 did not differ significantly from the effects of 10 mg of atorvastatin plus SAR236553. This finding suggests the possibility that there may be a limit to the up-regulation of LDL-receptor activity. Our study also supports previous observations that suggested that the effects of inhibitors of PCSK9 on LDL cholesterol levels are not synergistic when added to statins.

We found a consistent and fairly robust reduction of nearly one third in the median lipoprotein(a) level when SAR236553 was added to either 80 mg of atorvastatin or 10 mg of atorvastatin. This effect was first observed in the phase 1 trials[10] and has been confirmed as well in two other phase 2 studies.[11,12] Although the mechanism underlying this effect is unknown, one possible explanation is that with very low levels of LDL-associated apolipoprotein B, the apolipoprotein B component of lipoprotein(a)

**Table 3. Adverse Events and Potentially Clinically Significant Abnormalities in the Safety Population.***

| Event or Abnormality | Atorvastatin, 80 mg, plus Placebo (N=31) | Atorvastatin, 10 mg, plus SAR236553 (N=31) | Atorvastatin, 80 mg, plus SAR236553 (N=30) |
|---|---|---|---|
| | *number of patients (percent)* | | |
| Adverse events occurring during study treatment | | | |
| Any | 19 (61) | 14 (45) | 18 (60) |
| Any serious | 0 | 0 | 1 (3) |
| Resulting in death | 0 | 0 | 0 |
| Resulting in permanent discontinuation of treatment | 4 (13) | 0 | 1 (3) |
| Potentially clinically significant abnormalities | | | |
| Alanine aminotransferase >3× ULN | 0 | 0 | 0 |
| Aspartate aminotransferase >3× ULN | 0 | 0 | 1 (3) |
| Total bilirubin >1.5× ULN | 0 | 0 | 1 (3) |
| Creatine kinase >3× ULN | 1 (3) | 0 | 0 |
| Adverse events occurring during study treatment in ≥10% of patients in any treatment group | | | |
| Nervous system disorders | 4 (13) | 0 | 5 (17) |
| Dizziness | 0 | 0 | 3 (10) |
| Headache | 2 (6) | 0 | 3 (10) |
| Gastrointestinal disorders | | | |
| Any | 7 (23) | 4 (13) | 3 (10) |
| Diarrhea | 3 (10) | 1 (3) | 3 (10) |
| Musculoskeletal and connective-tissue disorders | | | |
| Any | 6 (19) | 2 (6) | 5 (17) |
| Pain in extremity | 5 (16) | 0 | 1 (3) |

* The safety population included all patients who underwent randomization and who received at least one dose or partial dose of SAR236553 or placebo. Adverse events were classified according to the *Medical Dictionary of Regulatory Activities* (MedDRA), version 14.0. ULN denotes the upper limit of the normal range.

becomes more accessible and is taken up by the highly up-regulated LDL receptor. Alternatively, low apolipoprotein B levels might contribute directly to a decrease in lipoprotein(a) synthesis.

The reductions in median triglyceride levels were greater in the group assigned to 80 mg of atorvastatin plus SAR236553 than in the group assigned to 80 mg of atorvastatin plus placebo, suggesting that the effect of atorvastatin on triglyceride levels may be enhanced slightly by SAR236553. However, evaluation of these effects was confounded by the relatively low baseline triglyceride levels, and further studies involving patients with hypertriglyceridemia are required to fully investigate the effects of SAR236553 on triglyceride-rich lipoproteins.

A small increase in HDL cholesterol levels was observed in patients treated with 80 mg of atorvastatin plus SAR236553 as compared with those treated with 80 mg of atorvastatin plus placebo. This finding is consistent with the changes in HDL cholesterol levels seen in previous studies.[13-15] Again, larger studies of longer duration will be required to fully elucidate these observations.

In conclusion, treatment with 80 mg of atorvastatin plus SAR236553 was associated with significantly greater reductions in LDL cholesterol levels than was treatment with 80 mg of atorvastatin plus placebo. Substantially more patients who received SAR236553 than patients who received placebo attained target LDL choles-

terol levels of less than 100 mg per deciliter and less than 70 mg per deciliter. The results of this small study of short duration warrant further investigation in large, longer-term studies.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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