Evaluating bococizumab, a monoclonal antibody to PCSK9, on lipid levels and clinical events in broad patient groups with and without prior cardiovascular events: Rationale and design of the Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) Lipid Lowering and SPIRE Cardiovascular Outcomes Trials

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Background Although statins significantly reduce vascular event rates, residual cholesterol risk remains high in many patient groups, including those with known vascular disease as well as in the setting of high-risk primary prevention. Bococizumab is a humanized monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), prolongs the half-life of hepatic low-density lipoprotein (LDL) receptors, and reduces circulating atherogenic cholesterol levels.

Design The SPIRE program comprises 6 lipid-lowering studies and 2 cardiovascular outcomes trials, each comparing bococizumab (150 mg subcutaneously every 2 weeks) to matching placebo. The 6 SPIRE lipid-lowering studies include 3 parallel 12-month assessments of bococizumab on atherogenic lipids among statin-treated individuals at high residual risk (SPIRE-HR, SPIRE-LDL, SPIRE-LL), one 12-month study of bococizumab among individuals with familial hypercholesterolemia (SPIRE-FH), one 6-month study of bococizumab among those with statin intolerance (SPIRE-SI), and one 3-month study of bococizumab delivery using an auto-injector device (SPIRE-AI). The SPIRE-1 and SPIRE-2 event-driven cardiovascular outcome trials will assess the efficacy and safety of bococizumab in the prevention of incident vascular events in high-risk populations with and without clinically evident cardiovascular disease who have directly measured entry LDL cholesterol levels ≥70 mg/dL (SPIRE-1, n = 17,000) or ≥100 mg/dL (SPIRE-2, n = 11,000).

Summary The SPIRE trials, inclusive of more than 30,000 participants worldwide, will ascertain the magnitude of reduction in atherogenic lipids that accrue with bococizumab and determine whether the addition of this PCSK9 inhibitor to standard treatment significantly reduces cardiovascular morbidity and mortality in high-risk patients, including those without a history of clinical cardiovascular events. (Am Heart J 2016;178:135-44.)

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Randomized clinical trials conducted over the past 20 years have consistently demonstrated that the aggressive reduction of low-density lipoprotein cholesterol (LDLC) with statin therapy reduces cardiovascular risk in the settings of secondary prevention and high-risk primary prevention. When used as an adjunct to lifestyle interventions, statin therapy can be expected to reduce the rates of major coronary events by 24% for each 1-mmol/L reduction in LDLC (hazard ratio [HR] 0.76, 95% CI 0.73-0.79), stroke by 15% (HR 0.85, 95% CI 0.80-0.89), and coronary revascularization by 24% (HR 0.76, 95% CI 0.73-0.79).[1,2] Meta-analyses, however, also demonstrate that relative risk reductions with statin therapy are not related to baseline levels of LDLC. Rather, trial data as well as observational, ecologic, and genetic studies suggest that ever lower LDLC levels are likely to confer cardiovascular benefits regardless of starting cholesterol levels for an individual patient.[3-6] If anything, the greatest relative risk reductions observed with statin therapy accrue among those with lower rather than higher levels of absolute vascular risk, data consistent with the biologic view that aggressive reductions in circulating atherogenic lipids early in the disease process are likely to produce the greatest clinical benefits.[7] Low-density lipoprotein cholesterol reduction with statin therapy has also proven highly effective for reducing vascular risk in those with diabetes[8] and in some cases can lead to regression of coronary atherosclerosis.[9]

For individual patients, however, variability in LDLC response to statin therapy is exceptionally wide.[10] For example, in the JUPITER primary prevention trial where all individuals received a high-intensity statin regimen, fewer than half of the subjects achieved LDLC reductions greater than 50%, yet the magnitude of percentage change in LDLC was directly related to subsequent event rates.[11] Although the addition of ezetimibe to moderate dose statin therapy further reduced LDLC and clinical events in the contemporary secondary prevention IMPROVE-IT trial, the rate of recurrent vascular events in that study still exceeded 30% over the mean follow-up of 5.4 years.[4] Last, not all patients tolerate statin therapy. It has thus long been recognized that effective and safe treatments for residual cholesterol risk are needed, not only for those with a history of cardiovascular events but also for primary prevention patients at high vascular risk.

Bococizumab is a humanized monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), preventing PCSK9-mediated degradation of the LDL receptor.[12,13] In a dose-finding study among statin-tolerant patients, bococizumab substantially lowered LDLC when given at a regimen of 150 mg every 2 weeks,[14] data consistent with those of other monoclonal antibodies that interfere with the LDL receptor binding domain of PCSK9.[15,16]

To comprehensively address the efficacy and safety of bococizumab in broad patient populations at risk for cardiovascular events, the SPIRE development program was designed to include 6 lipid-lowering studies and 2 large-scale, event-driven, cardiovascular outcomes trials (SPIRE-1 and SPIRE-2), each comparing bococizumab (150 mg subcutaneously [SC] every 2 weeks) to matching placebo. As described here, the SPIRE program involves more than 30,000 individuals worldwide and will (*a*) formally ascertain the magnitude of reduction in atherogenic lipids that accrue with bococizumab and (*b*) determine whether the addition of this PCSK9 inhibitor to standard treatment significantly reduces cardiovascular morbidity and mortality in high-risk patients, including those without a history of clinical cardiovascular events.

Methods

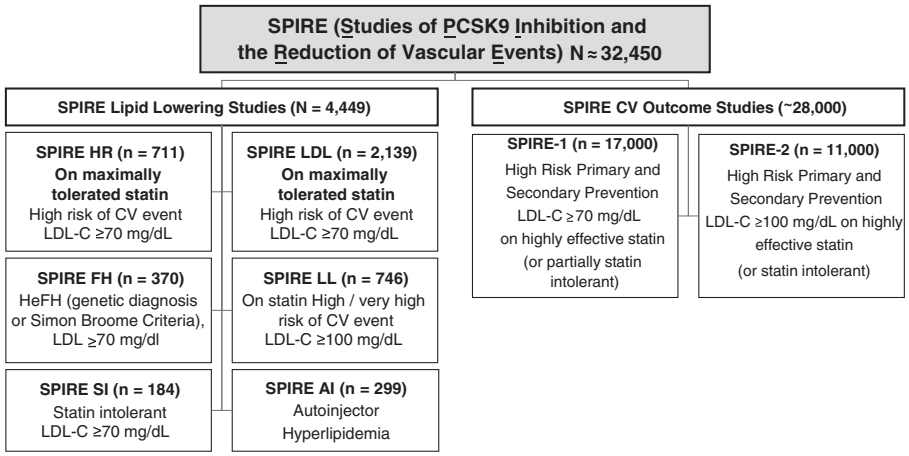
Overview

The SPIRE program and the research described in this article are sponsored by Pfizer, Inc (New York, NY). The SPIRE bococizumab development program consists of 2 parts, the SPIRE lipid-lowering studies and the SPIRE-1 and SPIRE-2 event-driven cardiovascular outcomes trials (Figure 1). The protocols for each SPIRE study were designed through a collaboration between academic members of the SPIRE Executive and Steering Committees and physician and statistician employees of the sponsor (Pfizer). Each protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable in the 37 countries involved in the SPIRE program. A single fully independent Data Monitoring Committee oversees safety monitoring of all SPIRE studies. Each SPIRE study has a prespecified statistical analysis plan reviewed by the trial Executive Committee. Academic researchers as well as an independent academic statistician at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Harvard Medical School, will have full access to the trial databases and will have independent responsibility for generating trial analyses for publication. The authors of all SPIRE manuscripts will be solely responsible for drafting and editing of manuscripts and their final contents. As prespecified in the SPIRE Publication Charter, should any disagreements arise between the sponsor and the academic leadership, final decisions for publication shall lie with the academic members of the SPIRE Executive Committee.

The SPIRE lipid-lowering program

The SPIRE lipid-lowering program (Figure 1, left) consists of 6 parallel multinational studies known as SPIRE-HR (NCT01968954, which includes 711 hyperlipidemic patients on maximally tolerated statin therapy at high risk for cardiovascular events), SPIRE-LDL (NCT01968967, which includes 2139 hyperlipidemic patients on maximally tolerated statin therapy with multiple cardiovascular risk factors and directly measured LDLC $\geq$70 mg/dL), SPIRE-FH (NCT01968980, which includes 370 individuals with heterozygous familial

Figure 1



Overview of the SPIRE bococizumab development program.

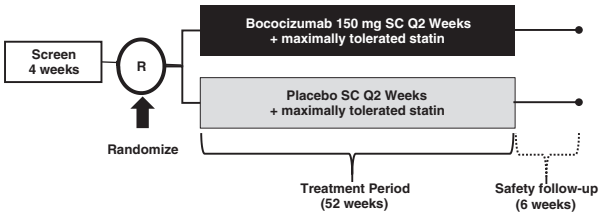
hypercholesterolemia), SPIRE-SI (NCT02135029, which includes 184 individuals with hyperlipidemia who were statin intolerant), SPIRE-LL (NCT02100514, which includes 746 individuals receiving statin therapy who had residual directly measured LDLC levels ≥100 mg/dL where additional lipid lowering was under consideration), and SPIRE-AI (NCT02458287, which includes 299 individuals with LDLC ≥70 mg/dL measured directly where bococizumab delivery is given with an auto-injector device).

In SPIRE-HR, SPIRE-LDL, SPIRE-FH, and SPIRE-LL, eligible participants underwent identical baseline lipid evaluations, were randomly allocated (in a 1:1 ratio, except for SPIRE-LL which used a 2:1 ratio) to either bococizumab 150 mg SC every 2 weeks or to matching placebo, and were then followed up prospectively for 1 year. In SPIRE-SI, eligible participants were randomly allocated in a 2:1:2 fashion to bococizumab 150 mg SC every 2 weeks, atorvastatin 40 mg per os daily, or matching placebos, and were then followed up prospectively for 6 months. In all of these studies, participants were trained to self-administer study drug through subcutaneous injections, and study drug was administered by study site personnel only in rare circumstances where neither the patient nor a home caregiver or family member was capable of performing this task. By contrast, in SPIRE-AI, eligible participants were randomly allocated to bococizumab or matching placebo delivered with an auto-injector device and were followed up for 12 weeks; in this study, a 75-mg SC dose every 2 weeks was evaluated as well as the 150-mg dose used in the other SPIRE studies. Participants were randomized 2:2:1:1 to bococizumab 150 mg SC every 2 weeks, bococizumab 75 mg SC every 2 weeks, matching placebo 150 mg, or matching placebo 75 mg.

In the SPIRE-HR, SPIRE-LDL, and SPIRE-LL studies, an identical protocol was used that included a 4-week prerandomization screening period to verify eligibility and ensure that patients had been and are continuing to receive maximally tolerated statin dosing. In these trials, participants were stratified by geographic region and by prerandomization triglyceride levels (< or ≥200 mg/dL). Blood specimens were obtained at the face-to-face visits which were scheduled at baseline and at weeks 4, 8, 12, 24, 36, 48, and 52 and at study completion (Figure 2). A virtually identical protocol was followed in SPIRE-FH, with the exception that stratification by triglyceride levels was not performed. The SPIRE-SI protocol was again similar in structure, but enrolled only individuals with a history of statin intolerance due to muscle related symptoms, was stratified by country, and included a statin rechallenge arm (atorvastatin 40 mg daily). In the 12-month duration trials, protocol-driven dose reductions of bococizumab from 150 mg SC every 2 weeks to 75 mg SC every 2 weeks were triggered by the observation of directly measured LDLC levels ≤10 mg/dL (0.26 mmol/L) on 2 consecutive visits, with sham dose modifications made in the placebo group to maintain study blind. If directly measured LDLC levels remained in this range during continued follow-up, a second protocol-driven dose reduction of bococizumab (or matching placebo) to 75 mg every 4 weeks was made. In all studies, a 6-week follow-up visit off study drug was conducted after the end of the treatment period to systematically ascertain for any untoward effects.

The primary prespecified end point in all SPIRE lipid-lowering trials is the percent change from baseline in fasting LDLC measured with a direct assay at week 12, whereas long-term persistence of any effects on LDLC was also evaluated throughout the 1-year follow-up period for the longer-term studies. Secondary prespecified, type 1 error–controlled end points are the percent change in total cholesterol, apolipoprotein B, non–

Figure 2



Flow diagram representative of the 6 parallel studies that comprise the SPIRE lipid-lowering program.

high-density lipoprotein cholesterol (non-HDLC), lipoprotein(a), and HDLC at week 12. Type 1 error will be controlled using a combination of fixed sequence testing and the Hochberg procedure. Other prespecified end points include the percent change in apolipoprotein AI, apolipoprotein AII, very low density lipoprotein cholesterol, triglycerides, and, in the 12-month studies, high–sensitivity C-reactive protein (hsCRP). All plasma samples are to be obtained after a minimum 10-hour fast, and all plasma assays are performed in a central core laboratory. Levels of LDLC are assessed both directly and as a calculated value with the use of the Friedewald formula.

Data from the 6 SPIRE lipid-lowering studies will be analyzed separately and combined into a single analysis set. Baseline demographic and lipid data will be summarized with the use of proportions for categorical variables, and medians (interquartile ranges) for continuous variables. Initial comparisons between treatment groups in the distributions of percent change at 12 weeks will use the Wilcoxon rank sum test, with accompanying Hodges-Lehman estimate of the location shift between groups with 95% CI. As specified in the individual protocols for each trial, the estimates of the treatment effect, its 95% CI, and *P*-value for comparison with placebo come from the primary analysis model, a repeated-measures, mixed linear model regression, estimated by restricted maximum likelihood. Each model will contain the following fixed effects: treatment (categorical variable), scheduled visit time point (categorical variable), baseline LDLC, interaction between treatment and scheduled visit time point, interaction between baseline LDLC and scheduled visit time, geographic region (country in SPIRE-SI; categorical variable), and prerandomization triglyceride level (≤ or >200 mg/dL, categorical variable in SPIRE-LL, SPIRE-LDL, and SPIRE-HR only). The default covariance structure is unstructured (except spatial power in SPIRE-SI), with alternative covariance structures specified in each protocol in case of convergence problems. The individual estimates of treatment effects at 12 weeks will be combined in a random-effects meta-analysis, using the approach of Dersimonian and Laird.[17] Safety analyses for specific adverse events will present incidence rates for the bococizumab and placebo groups along with 95% CIs on the incidence rates calculated using an exact Clopper-Pearson method for Poisson random variables. In addition, incidence rates will be combined across studies resulting in a rate ratio comparing bococizumab with placebo along with the exact CI for this rate ratio. Adverse events occurring in ≥2% of subjects in either treatment group will be highlighted.

In addition to changes in lipid levels, clinical data from the five SPIRE lipid-lowering trials with treatment duration of 6 months or more will be pooled to allow for a prespecified exploratory safety assessment of bococizumab as compared with placebo of the incidence of adjudicated cardiovascular events occurring after the time of randomization. Specific events contributing to the composite end point in this analysis are the first occurrence of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, other coronary revascularization procedures, or cardiovascular death. For the primary analysis, the composite end point will be analyzed using a log-rank statistic to compare the 2 treatment groups. The HR and the corresponding 95% CI will be estimated using a Cox proportional hazards model. As a supplemental assessment, the composite end point will be analyzed using a log-rank statistic stratified by study and the HR and 95% CI will be estimated using a Cox proportional hazards model stratified by study. All analyses will be conducted on an intention-to-treat basis, all *P* values 2 tailed, and all CIs computed at the 95% level.

The SPIRE-1 and SPIRE-2 cardiovascular outcome trials

The SPIRE cardiovascular outcomes program consists of SPIRE-1 (NCT01975376) and SPIRE-2 (NCT01975389), 2 parallel, multinational, randomized, placebo-controlled event-driven trials of bococizumab given at a dose of 150 mg SC every 2 weeks (Figure 1, right). To ensure evaluation of bococizumab among a representative population, each SPIRE cardiovascular outcome trial will enroll individuals across a broad range of cardiovascular risk, including patients with and without a history of clinical cardiovascular disease. All patients will be treated with an aggressive regimen of highly effective statin therapy (defined per protocol as the stable use for at least the past 4 weeks of atorvastatin ≥40 mg daily, rosuvastatin ≥20 mg daily, or simvastatin ≥40 mg daily) or demonstrate intolerance to high-intensity therapy (and be treated with a lower-intensity regimen) or, in the case of SPIRE-2, demonstrate complete statin intolerance (defined as documented failure to tolerate at least 2 different statin agents including one at the lowest available daily dose, or having a documented history of statin-induced rhabdomyolysis or statin-induced allergic reaction precluding rechallenge).

Table. Comparison of the SPIRE-1, SPIRE-2, FOURIER, and ODYSSEY Outcomes PCSK9 clinical trials

	SPIRE 1 (n = 17,000)	SPIRE 2 (n = 11,000)	FOURIER (n = 27,500)	ODYSSEY Outcomes (n = 18,000)
Monoclonal antibody	Bococizumab (humanized) 150 mg Q2W	Bococizumab (humanized) 150 mg Q2W	Evolocumab (human) 140 mg Q2W 420 mg Q4W	Alirocumab (human) 75-150 mg Q2W
Entry LDLC (mg/dL)	≥70	≥100	≥70	≥70
Statin requirement	Atorvastatin 40 or 80 mg Rosuvastatin 20 or 40 mg Simvastatin 40 mg (or 80 mg if >1 year) or documented intolerance to high intensity statin (SPIRE-1 and SPIRE 2) or documented complete statin intolerance (SPIRE-2)*		High-intensity statin preferred, minimum dose atorvastatin 20 mg or equivalent	Atorvastatin 40 or 80 mg Rosuvastatin 20 or 40 mg or the maximum tolerated dose of one of these agents
High-risk secondary prevention	Yes	Yes	Yes	Yes
High-risk primary prevention	Yes	Yes	No	No

* Allowed not to be taking statin if intolerant to any 2 statins (one at lowest dose) or a history of statin-induced rhabdomyolysis.

The SPIRE-1 trial will recruit 17,000 individuals with directly measured LDLC levels of ≥70 mg/dL (1.81 mmol/L), and the SPIRE-2 trial will recruit 11,000 individuals with directly measured LDLC levels ≥100 mg/dL (2.59 mmol/L). In recognition of the emerging importance of non-HDLC, patients are also eligible for SPIRE-1 if they have entry non-HDLC levels ≥100 mg/dL (2.59 mmol/L) and for SPIRE-2 if they have entry non-HDLC levels ≥130 mg/dL (3.36 mmol/L).

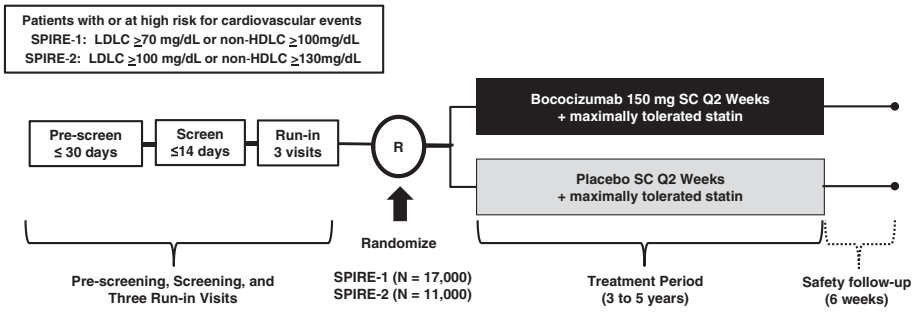
In addition to these entry LDLC and non-HDLC criteria, patients are eligible for SPIRE-1 and SPIRE-2 if they have a history of a cardiovascular event (secondary prevention cohort, defined as prior myocardial infarction, prior ischemic stroke, or prior coronary artery, or peripheral artery revascularization) or have a history of diabetes, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk conditions or risk factors, or a history of familial hypercholesterolemia (high-risk primary prevention cohort). To augment risk for the primary prevention cohort, individuals typically also have one or more additional risk factors such as smoking, levels of HDLC <40 mg/dL (1.03 mmol/L), levels of hsCRP >2.0 mg/L, levels of lipoprotein(a) >50 mg/dL, evidence of microalbuminuria, or evidence by cardiac imaging of asymptomatic coronary stenosis, and must be ≥50 years of age for men and ≥60 years of age for women (except if they have a history of familial hyperlipidemia, in which case the minimum age is 35 years for men and 45 years for women). With the exception of the entry lipid levels, the formal inclusion criteria for the SPIRE-1 and SPIRE-2 trials are virtually identical and are outlined in online Supplementary Table 1.

Patients are excluded from SPIRE-1 and SPIRE-2 if the qualifying vascular event was less than 30 days prior to screening (and <90 days for coronary revascularization) or if they have not yet completed planned coronary revascularization procedures. Other major exclusion criteria are the presence of New York Heart Association class IV congestive heart failure or known left ventricular ejection fraction <25%, end-stage renal disease on dialysis, creatinine clearance <30 mL min^{-1} 1.73 m^{-2}, poorly controlled hypertension, a history of hemorrhagic stroke, known hypersensitivity to monoclonal antibodies, a current cancer treatment, planned or previous gastric bypass surgery, creatine kinase levels ≥3 times the upper limits of normal (ULN), alanine transaminase or aspartate transaminase >2 times ULN, direct bilirubin >1.5 times ULN, or the presence of conditions that might reduce the likelihood of long-term study adherence and compliance. The formal exclusion criteria for the SPIRE-1 and SPIRE-2 trials are virtually identical and are outlined in online Supplementary Table 2.

In both SPIRE-1 and SPIRE-2, eligible patients enter a 6-week placebo run-in period designed to ensure compliance with SC drug administration. Participants are then randomized in a double-blind manner to either bococizumab (150 mg SC every 2 weeks) or matching placebo. As in the SPIRE lipid-lowering studies, protocol-driven dose reductions of bococizumab from 150 to 75 mg SC are triggered by the observation of LDLC levels <10 mg/dL (0.26 mmol/L) on 2 consecutive visits, with sham dose modifications made in the placebo group to maintain study blind. In addition, in both trials a further protocol-driven dose reduction for bococizumab (or matching placebo) from 75 mg SC every 2 weeks to every 4 weeks is triggered by the observation of LDLC levels <10 mg/dL (0.26 mmol/L) on 2 further consecutive study visits.

Once randomized, all SPIRE-1 and SPIRE-2 participants will be followed up prospectively for incident cardiovascular events and adverse effects until study completion. Figure 3 outlines the key phases of the parallel SPIRE-1

Figure 3



Flow diagram for the large-scale end point-driven SPIRE-1 and SPIRE-2 cardiovascular outcomes trials.

and SPIRE-2 trials. In each case, randomized participants return for study visits at weeks 4, 8, 14, and 26, and then at 12- to 18-week intervals until completion. Baseline and on-study drug blood samples are collected in a standardized manner and undergo lipid and safety evaluations in a central core laboratory. Among consenting participants, baseline and on-treatment blood samples are also stored for future biomarker and genetic studies. Study sites are asked to avoid nontrial ascertainment of lipid levels during the study and changes in postrandomization statin dosing are discouraged.

Safety will further be assessed through adverse events and serious adverse events collection, vital signs, physical examination results, 12-lead electrocardiogram recordings, and safety laboratory tests including hematology, blood chemistry studies (including liver function tests and creatine kinase tests), urinalysis studies, and antidrug antibody assessments. Neurocognitive function assessments, as outlined in online Supplementary Table 4, are planned in a substudy of approximately 500 subjects in each of the SPIRE-1 and SPIRE-2 trials.

The prespecified primary end point of both SPIRE outcome trials is a composite of adjudicated and confirmed nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death. The 4 key secondary end points are (*a*) the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death; (*b*) the composite of nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality; (*c*) the composite of nonfatal myocardial infarction, nonfatal stroke, all-cause mortality, and hospitalization for unstable angina needing urgent revascularization; and (*d*) hospitalization for unstable angina needing urgent revascularization. Type 1 error will be controlled using fixed sequence testing. All incident clinical events that are components of the primary or key secondary end points are adjudicated by a clinical end point committee unaware of study drug allocation using standardized criteria defined by the US Food and Drug Administration for cardiovascular outcome trials.[18] A full listing of all prespecified primary and secondary end points for the SPIRE cardiovascular outcome trials is provided in online Supplementary Table 3. All SPIRE participants are followed up for adverse events, with particular emphasis on muscle-related symptoms, incident diabetes, cognitive function, and laboratory changes in liver function, estimated glomerular filtration rate, creatine kinase, glucose, hemoglobin A1c, hsCRP, and anti-bococizumab antibodies.

Efficacy analyses in SPIRE-1 and SPIRE-2 will be conducted on an intention-to-treat basis, and safety evaluations will include any participant who received at least one dose of randomized study drug. The trial sample size for SPIRE-1 (n = 17,000, event driven for an anticipated 844 participants with an adjudicated and confirmed primary end point) should provide approximately 90% power to detect a 20% relative risk reduction in the trial primary end point, assuming a background annual event rate of at least 2.3% per year, a 1% per year premature discontinuation rate, and a trial duration of approximately 4.8 years. The trial sample size for SPIRE-2 (n = 11,000, event driven for an anticipated 508 participants with an adjudicated and confirmed primary end point) should provide approximately 90% power to detect a 25% relative risk reduction in the trial primary end point, assuming a background annual event rate of at least 2.7% per year, a 1% per year premature discontinuation rate, and a trial duration of 3.9 years. These trial durations include a requirement to continue each study until at least one year after the last randomization in that study.

In SPIRE-1 and SPIRE-2, the primary end point will be analyzed using a log-rank test stratified by geographic region. In SPIRE-1, additional stratification for baseline LDLC levels (<100 or ≥100 mg/dL) will be performed, whereas in SPIRE-2, additional stratification according to complete statin intolerance will be performed. Hazard ratios and 95% CIs will be computed in each trial following these stratification criteria using Cox proportional hazards

models. Kaplan-Meier estimates of time to event will be ascertained.

In addition to the main efficacy analyses, both SPIRE-1 and SPIRE-2 will address the percent change and nominal change from baseline to week 14 for a panel of lipid biomarkers including LDLC, non-HDLC, total cholesterol, triglycerides, very low density lipoprotein cholesterol, remnant lipoprotein cholesterol, apolipoprotein B, apolipoprotein A-I, and lipoprotein(a), as well as hsCRP. Methods for analysis of lipid and other biomarker changes in the SPIRE-1 and SPIRE-2 trials are also prespecified in the trial protocols and parallel those being used in the SPIRE lipid-lowering program as described above. Data on health care resource utilization will be ascertained throughout the trial period.

In addition to the above, guidelines are in place that would allow the independent Data Monitoring Committee, if it electively chose to do so, to consider early termination of the smaller SPIRE-2 trial for clinical efficacy after 75% of the anticipated primary end point and first key secondary end point events had accrued. Consideration of early termination for efficacy would only occur if the observed relative risk reduction for the primary end point and for the first key secondary end point is substantially greater than anticipated in the power calculations (at least 28.62% for the primary end point and 36.09% for the key secondary end point), is statistically extreme (P values of <.001 for both end points), and is consistent across geographic regions and major clinical subgroups. To control the overall α, the final α will be reduced by .00002. Early termination of SPIRE-2 is elective at the discretion of the Data Monitoring Committee and would only be considered if, in addition to the above, there is no excess of noncardiovascular mortality and no apparent safety issues for which additional data are deemed critical. To ensure adequate long-term exposure and safety evaluations in the bococizumab development program, no early stopping guidelines for clinical efficacy exist for the larger SPIRE-1 trial which is inclusive of 17,000 patients.

The SPIRE lipid-lowering and SPIRE cardiovascular outcomes trials are funded by Pfizer, New York, NY.

Discussion

Residual cholesterol risk among statin-treated patients and among statin-intolerant patients is a clinical concern in secondary prevention and in high-risk primary prevention. As described here, the SPIRE development program is designed to address the magnitude of additional LDLC reduction that can be achieved with bococizumab (150 mg SC every 2 weeks) in both of these broad patient groups, and to evaluate the long-term clinical efficacy and safety of this emerging treatment of hyperlipidemia.

SPIRE is one of 3 ongoing phase 3 programs evaluating monoclonal antibodies to PCSK9 in the prevention of cardiovascular events (Table). For example, the FOURIER trial of evolocumab (NCT01764633) is enrolling 27,500 secondary prevention patients (including those with symptomatic peripheral vascular disease) with LDLC $\geq$70 mg/dL,[19] whereas the ODYSSEY Outcomes trial of alirocumab (NCT01663402) is enrolling 18,000 patients after acute coronary syndromes with LDLC $\geq$70 mg/dL.[20] Thus, although there is overlap between programs, only the SPIRE bococizumab program is additionally evaluating the efficacy and safety of PCSK9 inhibition in an asymptomatic high-risk primary prevention cohort of individuals with diabetes, chronic kidney disease, or familial hypercholesterolemia but no known evidence of clinically evident atherosclerosis, as well as in those with complete statin intolerance. The SPIRE-2 trial, by limiting enrollment to those with LDLC $\geq$100 mg/dL, will also provide the largest efficacy and safety database for any PCSK9 inhibitor in this population that has been unable to reduce LDLC below this clinical threshold despite aggressive use of statin therapy and/or ezetimibe. Other potential differences between programs include the facts that evolocumab and alirocumab are fully human antibodies to PCSK9 that use incomplete binding to the LDL-receptor binding site, whereas bococizumab is a humanized PCSK9 antibody that provides near-complete binding overlap of the LDL-receptor binding site of PCSK9.[13,21,22] With regard to effector function, bococizumab also differs from evolocumab or alirocumab in that it uses IgG2ΔA binding to theoretically reduce activation of complement pathways. It is uncertain whether any of these potential between drug differences substantively matter in terms of clinical efficacy, safety, and tolerability.

Completed phase 2 trials for bococizumab, alirocumab, and evolocumab have found these monoclonal antibodies to PCSK9 highly effective in reducing LDLC when given as monotherapy, as adjuncts to statin therapy with or without ezetimibe, and among those with statin intolerance.[14,23-26] Monoclonal antibodies to PCSK9 are also effective at reducing LDLC among individuals with heterozygous familial hypercholesterolemia (for whom there is reduced LDL-receptor activity)[27,28] and for patients with homozygous familial hypercholesterolemia who are LDL-receptor defective, a clinical setting where statin efficacy is limited.[29,30] Preliminary data from the evolocumab and alirocumab phase 2 trials further suggest that PCSK9 inhibitors are promising agents for cardiovascular event reduction,[15,16] but questions must still be addressed on long-term efficacy and safety.

To date, no major safety issues have been uncovered with monoclonal antibodies to PCSK9, although initial data for alirocumab and/or evolocumab raise the possibility of small increases in neurocognitive and opthalmalogic events and potential small increases in arthralgia, headache, and fatigue.[15,16] Each of these is being closely followed in the

SPIRE program. As in the FOURIER and ODYSSEY programs for evolocumab and alirocumab, respectively, the SPIRE program for bococizumab will also contribute critical data related to long-term safety of achieving very low levels of LDLC. In statin trials[31,32] and in trials of ezetimibe added to statin therapy, on-treatment levels of LDLC below 40 mg/dL have generally been well tolerated.[4] However, because statins have been associated with a small increase in risk of developing new-onset diabetes,[33,34] all ongoing PCSK9 programs including SPIRE are closely monitoring this clinical end point. Theoretically very low LDLC in the peripheral compartment could have effects on hormone production and vitamins synthesized from cholesterol. However, such effects have not been clinically important with other PCSK9 inhibitors[35] and individuals with loss-of-function mutations of PCSK9 have been free of apparent adverse effects on this basis.[36,37] Nonetheless, PCSK9 may mediate several functions independent of its role in lipid homeostasis, such as trafficking of epithelial sodium channel, hepatic regeneration, pancreatic integrity and glucose homeostasis, antiviral activity, regulation of different cell signaling pathways, cortical neural differentiation, and neuronal apoptosis.[38] To date, there is no evidence that inhibition of PCSK9 in the management of dyslipidemic patients is associated with such effects, but the completion of large-scale trials as well as longer-term observational studies will be needed to fully address clinical safety.

In summary, the SPIRE development program for bococizumab will involve more than 30,000 individuals worldwide and will ascertain the magnitude of reduction in atherogenic lipids that accrue with bococizumab and determine whether the addition of this PCSK9 inhibitor to standard treatment significantly reduces cardiovascular morbidity and mortality in high-risk patients, including those without a history of clinical cardiovascular events. The SPIRE lipid-lowering trials and the SPIRE-2 trial are fully enrolled, whereas enrollment into SPIRE-1 is projected to complete by late 2016.

Disclosures

Through Brigham and Women's Hospital, Dr Ridker received research support from Pfizer related to the conduct, design, and analysis of the SPIRE clinical trial program and for oversight of the SPIRE Steering Committee. Dr Ridker has served as a consultant to Pfizer related to the study design and expert panel services associated with the SPIRE clinical trial program. Dr Ridker has received additional research grant support from Novartis, Amgen, and Kowa, and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. Brigham and Women's Hospital also received remuneration from Pfizer for Dr Glynn's services as a member of the Steering Committee and for analysis of data for the SPIRE clinical trial program. Dr Santos has received honoraria related to consulting and or speaker activities from Amgen, Aegerion, Akcea, AstraZeneca, Biolab, Boehringer Ingelheim, Cerenis, Eli Lilly, Genzyme, Kowa, Merck, Pfizer (including those for services as a member of the Steering Committee for the SPIRE clinical trial program), Sanofi/Regeneron, Torrent, and Unilever. Dr Koenig has received personal fees from AstraZeneca, Novartis, MSD, Actavis, Amgen, and Sanofi; has received consulting fees from Novartis, Pfizer (including those for services as a member of the Steering Committee for the SPIRE clinical trial program), The Medicines Company, Amgen, and AstraZeneca; and has research contracts with Abbott, Roche Diagnostics, Beckmann, and Singulex. Drs Brunell, Revkin, Schwartz, and Yunis are employees of Pfizer Inc and own Pfizer Inc stock. Dr Jukema has received research grants from and/or was speaker on CME-accredited meetings sponsored by Amgen, Astellas, Anthera, AstraZeneca, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck-Schering-Plough, Pfizer (including those for services as a member of the Steering Committee for the SPIRE clinical trial program), Orbus Neich, Novartis, Roche, Servier, Sanofi Aventis, The Medicine Company, Netherlands Heart Foundation, Netherlands Cardiovascular Research Committee (CVON), Interuniversity Cardiology Institute of the Netherlands, and the European Community Framework KP7 Programme. Dr Kastelein has received consultant and speaker fees from Regeneron, Sanofi, Pfizer (including those for services as a member of the Steering Committee for the SPIRE clinical trial program), and Amgen. Dr Nissen reports that the Cleveland Clinic Center for Clinical Research receives funding to perform clinical trials from AstraZeneca, Amgen, Cerenis, Eli Lilly, Esperion, Pfizer, The Medicines Company, Novartis, Novo Nordisk, Takeda, Orexigen, Vivus, and Eli Lilly. Dr Nissen is involved in these clinical trials but receives no personal remuneration for his participation. Dr Nissen consults for many pharmaceutical companies (including for Pfizer as a member of the Steering Committee for the SPIRE clinical trial program) but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. Dr Amarenco has received honoraria from Pfizer as a member of the Executive Committee of the SPIRE program; research grant support from Pfizer, Merck, and AstraZeneca related to the conduct of the Treat Stroke to Target trial; research grant support from Sanofi and Bristol-Myers Squibb related to the conduct of the TIAregistry.org project; research grant support from Boston Scientific related to the conduct of the WATCH-AF registry; honoraria from Bayer as a member of the Steering Committee of the XANTUS study; honoraria from GSK as a member of the Endpoint Committee for the

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Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.05.010.

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