Proposed Clinical Trial Protocol on Use of PCSK9 Inhibitors for Primary Prevention of Cardiovascular Disease

March 29, 2017

I. Background

A. Purpose of this document

The purpose of this document is to describe how a randomized clinical trial comparing the harms and benefits of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors with established therapies in the primary prevention of cardiovascular disease could be conducted.

The use of PCSK9 inhibitors for primary prevention was initially proposed to the Patient-Centered Outcomes Research Institute (PCORI) as a topic of interest by America’s Health Insurance Plans (AHIP). The PCORI Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options discussed the topic in October 2015\(^1\) and expressed enthusiasm for comparative effectiveness research, although the panel also raised concerns about the feasibility of a clinical trial. To outline possible parameters and considerations for a clinical trial on this topic, PCORI convened a meeting in June 2016 that included clinical trialists, lipid treatment specialists, health plan medical officers, and PCORI staff. The group sought to identify appropriate populations, comparators, and outcomes for such a trial. After the meeting, PCORI commissioned the Duke Evidence Synthesis Group to survey patients and healthcare providers to identify their concerns and questions that should be addressed as part of a patient-centered outcomes study on this topic. The trial outline and perspectives of patients and healthcare providers are summarized herein.

This document is not intended to serve as a final protocol for a clinical trial. There are several issues that would need to be resolved in the context of an actual study plan, including managing patients who are deemed to be statin-intolerant. Note that describing the plans herein does not imply an intention for PCORI to support such a trial at this time.

B. Description of clinical condition and problem being addressed

Low density lipoprotein cholesterol (LDL-C) is a major causal risk factor for cardiovascular disease, which is the leading cause of death in the United States. Approximately 735,000 Americans have a myocardial infarction each year\(^2\), and about 800,000 have a stroke.\(^3\) Most patients are treated with HMG-CoA reductase inhibitors, commonly known as statins. Approximately 56 million Americans are eligible for cholesterol-lowering medication, according to current guidelines.\(^4\)
High-intensity statin therapy reduces LDL-C and cardiovascular events more than moderate-intensity statin therapy. However, the response to statins is variable, and some patients are not able to tolerate the recommended statin intensity; between 7 percent and 29 percent of patients taking statins report having muscle symptoms, which is a principal reason for nonadherence. In addition, high-intensity statin therapy may have less benefit in low-risk primary prevention patients due to a modest increase in the incidence of diabetes in patients taking statins, and concern about diabetes may deter some patients from taking statins. Moreover, many patients remain at increased cardiovascular risk despite maximum tolerated statin therapy and could benefit from additional LDL-C reduction.

While PCSK9 inhibitors are currently indicated for some patients at high risk, including those with familial hypercholesterolemia or pre-existing cardiovascular disease, doctors are requesting permission for PCSK9 use for primary prevention of cardiovascular disease in lower-risk patients. They are particularly interested in using PCSK9 in those who experience muscle symptoms on statins. Insurance companies have expressed concerns about such use. Current guidelines recommend that patients whose 10-year risk of major cardiovascular events is 10 percent or greater take statins. Patients at this risk level are provided as an example of an eligible population for this trial. Notably, the annual cost for a single patient in the United States for PCSK9 inhibitors is approximately $14,000.

The perspectives of patients and providers were obtained and synthesized as part of PCORI’s efforts to specify clinical trial parameters. The Duke Evidence Synthesis Group performed surveys in 125 patients with high cholesterol and 14 healthcare providers. The surveys included patient scenarios that reflected key uncertainties faced when considering the use of PCSK9 inhibitors. Respondents were asked to identify topics of importance based on the scenarios, and then to prioritize items needed for their decision making. Based on the findings, it is recommended that any comparative effectiveness study of PCSK9 inhibitors gather information at baseline on patients’ concerns regarding treatment options and how these concerns are addressed or exacerbated by their experience over the duration of the trial, including assessment of treatment side effects, out-of-pocket patient costs, and specific barriers and facilitators of patient adherence to the different treatments.

C. Description of PCSK9 inhibitors

PCSK9 inhibitors are a new class of medications that have been found to be very effective in reducing LDL-C, either as monotherapy or when added to background statin therapy. Normally, PCSK9 binds to low-density lipoprotein cholesterol (LDL-C) receptors, reducing the activity of the LDL-C receptors. PCSK9 inhibitors prevent PCSK9 from binding to the LDL receptor, thereby increasing the activity of the receptors and enhancing removal of LDL-C from circulation.

Two PCSK9 inhibitors are currently available and approved by FDA for use in the United States: evolocumab and alirocumab. These drugs are monoclonal antibodies (mAbs) administered by
subcutaneous injection bi-weekly or monthly and are currently approved for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C. At least 13 pharmaceutical companies have been reported to be developing new PCSK9 inhibitors,\textsuperscript{11} including oral preparations and an annual vaccine,\textsuperscript{12} although Pfizer recently reported that it dropped efforts to create bococizumab.\textsuperscript{13}

**D. Summaries of studies conducted to date**

There have been at least 25 clinical trials of LDL-C-lowering performed with PCSK9 mAbs, and several large trials with cardiovascular event outcomes are ongoing.\textsuperscript{10}

Two recent reports on the effects of evolocumab and alirocumab have raised expectations that these drugs will dramatically reduce cardiovascular events.\textsuperscript{14,15} In the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) study,\textsuperscript{14} 4,465 patients with high LDL-C or familial hyperlipidemia who had completed one of several short-term studies were randomly assigned in a 2:1 ratio to receive either evolocumab in one of two doses (140 mg every two weeks or 420 mg monthly) plus standard statin therapy or standard statin therapy alone. Median follow-up was 11.1 months. Evolocumab reduced LDL-C by 61 percent compared with standard therapy alone, from a median of 120 to 48 mg/dL, with the reduction remaining stable throughout follow-up. The composite cardiovascular outcome at one year was 2.18 percent in the standard therapy group and 0.95 percent in the evolocumab group (hazard ratio 0.47; 95 percent confidence interval 0.28 to 0.78; \(P=0.003\)).

In the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study,\textsuperscript{15} 2,341 patients with heterozygous familial hypercholesterolemia or established coronary heart disease or a coronary heart disease risk equivalent, receiving maximum tolerated doses of statins, and with an LDL-C \(\geq 70\) mg/dL were randomly assigned in a 2:1 ratio to receive an alirocumab 150 mg or placebo subcutaneous injection every two weeks for 78 weeks. The primary efficacy end point, the percentage change in calculated LDL-C level from baseline to week 24, was reduced by 62 percent to a mean LDL-C of 48 mg/dL. In a post hoc analysis, the rate of major cardiovascular events was lower with alirocumab than with placebo (1.7 percent versus 3.3 percent; hazard ratio 0.52; 95 percent confidence interval 0.31 to 0.90; \(P=0.02\)).

In addition, several trials are expected to report findings in 2017 or the first half of 2018 (see Table 1). None are in a primary prevention, low-to-moderate risk population.

**Table 1.** Recent and ongoing trials of PCSK9 inhibitors with cardiovascular endpoints
II. Study Design

A. Primary objective

To compare the effectiveness of a PCSK9 inhibitor plus maximum tolerated statin therapy vs. maximum tolerated statin therapy alone in the reduction of major cardiovascular events, including fatal and nonfatal coronary heart disease or fatal and nonfatal stroke and unstable angina requiring coronary revascularization.

B. Secondary objective

To compare the effectiveness of a PCSK9 inhibitor plus maximum tolerated statin therapy vs. maximum tolerated statin therapy alone in terms of LDL-C-lowering, muscle symptoms, quality of life, and incident diabetes.

To compare out-of-pocket patient costs and barriers and facilitators of patient adherence to the different treatments.

To compare the effectiveness in prespecified baseline subgroups defined by gender, age, ethnicity, diabetes status, and baseline CVD risk.

C. Single center or multicenter – multicenter

D. Phase – Phase III

E. Number and definition of arms – two arms
F. **Blinding** – While masking reduces differential outcome ascertainment and other potential differential biases based on group assignment, it would necessitate a placebo injection, which would likely reduce participation and adherence. Therefore, the value of blinding should be considered in the final formulation of the study.

G. **Eligible patient population** – Patients without familial hypercholesterolemia or existing cardiovascular disease who are eligible for cholesterol-lowering medication according to current guidelines. Particular consideration should be given to including patients with documented statin intolerance, lack of adequate responsiveness to statins defined as <30 percent lowering of LDL-C for moderate intensity statins and <50 percent of LDL-C for high-intensity statin, or estimated 10-year ASCVD risk >7.5 percent on maximally tolerated statin/ezetimibe.16

**Note:** The risk level of the population determines the patients to which the results would apply, as well as strongly influencing the size and cost of the trial. Including patients with risk levels <10 percent per year would represent a large departure from current clinical indications, greatly expand the eligible population, and require a much larger sample size than including those at higher risk. See the section on sample size considerations below.

H. **Duration** – Mean length of follow-up four years

III. **Ethical and Regulatory Considerations** – In an informal communication with the FDA, PCORI learned that this trial would require an Investigational New Drug Application.

IV. **Study drug and comparator**

A. **Drug administration**

**Intervention** – Evolocumab or alirocumab administered subcutaneously every two weeks + high-potency statins, such as atorvastatin or rosuvastatin, or the maximum tolerated dose of statin, with or without ezetimibe.

**Comparator** – High-potency statins, such as atorvastatin or rosuvastatin, or the maximum tolerated dose of statin, with or without ezetimibe.

**Note:** A final protocol would need to include appropriate evaluation and treatment of patients who have reported a history of symptoms during statin therapy.

B. **Efficacy analyses.** The primary analysis would be based on the intention-to-treat principle using a Cox proportional hazards model. Stratification factors, such as site, that are used in the design would also be used to stratify the analyses; this would allow for the shape of the hazard function to differ among strata. The
primary outcome would be tested at the 0.05 significance level. Study time would be measured from randomization and would continue until the first event in the primary composite outcome (for participants with at least one event). For participants who do not have an event during the study, the study time would be determined by the last date of event ascertainment using a standardized assessment schedule.

C. **Safety analyses.** Use a combination of Cox models (for events that are time-to-event) and mixed models (for outcomes measured on a continuous scale).

D. **Other analyses.** Generally, the analysis approach to analyzing outcomes such as quality of life and other patient-reported outcomes would be similar to that of the safety analyses and would depend on the specific selected measures.

E. **Sample size considerations.** The sample size for a time-to-event study is almost entirely dependent upon the number of events observed. The number of events needed for a study using a test at the 0.05 significance level for a variety of hazard ratios is presented in Table 2. This assumes a constant hazard ratio over the course of the study.17

Table 2. Number of events needed when using a two-sided test at the 0.05 significance level by the detectable hazard ratio and the power.

<table>
<thead>
<tr>
<th>HR</th>
<th>80% Power</th>
<th>90% Power</th>
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<tr>
<td>0.60</td>
<td>126</td>
<td>168</td>
</tr>
<tr>
<td>0.65</td>
<td>174</td>
<td>234</td>
</tr>
<tr>
<td>0.70</td>
<td>252</td>
<td>337</td>
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<tr>
<td>0.75</td>
<td>385</td>
<td>515</td>
</tr>
<tr>
<td>0.80</td>
<td>636</td>
<td>851</td>
</tr>
<tr>
<td>0.85</td>
<td>1194</td>
<td>1598</td>
</tr>
<tr>
<td>0.90</td>
<td>2833</td>
<td>3793</td>
</tr>
<tr>
<td>0.95</td>
<td>11938</td>
<td>15981</td>
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</table>

For a five-year study that includes two years of recruitment, which results in an average follow-up of four years per participant; assumes a 2 percent per year loss to follow-up; and uses a two-sided statistical test at the 5 percent level, the number of participants needed for 90 percent power are presented in Table 3. Note that this five-year period does not include time for study initiation or data analysis. The required sample size varies greatly as a function of the detectable hazard ratio and the event rate in the control group.
Table 3. Sample sizes needed for 90 percent power assuming a two-sided test at the 0.05 significance level for a five-year study with two years of recruitment and a 2 percent annual loss to follow-up by detectable hazard ratio and control group event rate.

<table>
<thead>
<tr>
<th>HR</th>
<th>0.5%</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
<th>4%</th>
<th>5%</th>
<th>6%</th>
<th>7%</th>
<th>8%</th>
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<tr>
<td>0.60</td>
<td>11736</td>
<td>5898</td>
<td>2980</td>
<td>2008</td>
<td>1522</td>
<td>1230</td>
<td>1036</td>
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<td>792</td>
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<tr>
<td>0.65</td>
<td>15524</td>
<td>7804</td>
<td>3946</td>
<td>2660</td>
<td>2016</td>
<td>1632</td>
<td>1374</td>
<td>1192</td>
<td>1054</td>
</tr>
<tr>
<td>0.70</td>
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<td>5462</td>
<td>3684</td>
<td>2796</td>
<td>2262</td>
<td>1908</td>
<td>1656</td>
<td>1466</td>
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<tr>
<td>0.75</td>
<td>31482</td>
<td>15838</td>
<td>8018</td>
<td>5412</td>
<td>4110</td>
<td>3328</td>
<td>2808</td>
<td>2438</td>
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</tr>
<tr>
<td>0.80</td>
<td>50198</td>
<td>25262</td>
<td>12796</td>
<td>8642</td>
<td>6566</td>
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<tr>
<td>0.85</td>
<td>91214</td>
<td>45916</td>
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<td>9696</td>
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</table>

For example, a trial in a patient population with an event rate of 1 percent per year (equivalent to a 10-year risk of 10 percent, considered “intermediate” risk) would require 25,262 participants to detect an HR of 0.80 or less (an effect of 20 percent or more) with 90 percent power.

V. Summary

A clinical trial comparing the effectiveness of PCSK9 inhibitors added to maximum tolerated statin therapy vs. maximum tolerated statin therapy alone in patients who have not had cardiovascular disease or familial hypercholesterolemia would provide information about the use of this new class of cholesterol-lowering medication in primary prevention of cardiovascular disease. Depending on the cardiovascular risk of the selected population, the required sample size would vary greatly, but a scenario that includes a population with a 1 percent annual risk of events followed for four years would require approximately 25,000 patients. The outcomes should include not only clinical cardiovascular events but also capture patient concerns about medication side effects, costs, and discomfort associated with using injectable medications compared to taking pills.
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