Project: PCSK9 Inhibitors for Treatment of High Cholesterol

Research Protocol for Review of Comparative Clinical Effectiveness and Comparative Value:

PCSK9 Inhibitors for Treatment of High Cholesterol

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BACKGROUND, OBJECTIVES, AND RESEARCH QUESTIONS

Background

Approximately one-third of American adults have cardiovascular disease (CVD), making it the most common cause of death in the United States.[1] Biological and epidemiological evidence has linked high levels of circulating low-density lipoprotein cholesterol (LDL-C) with an increased risk of myocardial infarction (MI), stroke, and death from CVD.

Multiple randomized clinical trials have demonstrated that lowering LDL-C with statin therapy reduces the risk of MI, stroke, and death from CVD.[2-4] Many investigators believe that the greater the reduction in LDL -C the greater the reduction in cardiovascular events, but the topic remains controversial.[5-9] Several drugs that lower LDL-C – including hormone therapy, niacin, and torcetrapib – have not decreased cardiovascular disease events when evaluated in randomized trials despite lowering LDL-C.[10-14] On the other hand, the recently published IMPROVE-IT trial demonstrated that the LDL-lowering ability of ezetimibe added to statin therapy significantly reduced cardiovascular event rates by 6% (95% CI 1 to 11%) after a median follow-up of approximately 5 years.[15]

Patient populations with elevated cholesterol in which there is an unmet clinical need include patients with a genetic condition causing highly elevated LDL-C, patients on statins and/or other cholesterol lowering drugs who are felt to have had an inadequate reduction in LCL-C, and patients who are not able to tolerate statins.[16]

Higher levels of PCSK9 reduce the number of LDL-C receptors. If there are fewer LDL-C receptors, then LDL-C levels rise in the blood. Conversely, lower levels of PCSK9 in the blood leads higher LDL-C receptor density and lower levels of LDL-C in the blood. This biology suggests that drugs targeting PCSK9 have the potential to reduce LDL-C and cardiovascular disease.

In July and August 2015, after favorable votes from its Advisory Committee ranging from 11-4 to 15-0 for different indications, the FDA approved two new human monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) in the blood and markedly reduce LDL -C levels. Alirocumab (Praluent®, Sanofi/Regeneron) is a human monoclonal antibody that inhibits PCSK9. It is administered as a subcutaneous injection once every two weeks at doses of either 75 mg or 150 mg. Evolocumab (Repatha™, Amgen) is also a human monoclonal antibody and is administered as a subcutaneous injection 140 mg once every two weeks or 420 mg once every four weeks.

This project will evaluate the health and economic outcomes of alirocumab and evolocumab for individuals with elevated LDL cholesterol. We assess the evidence on the comparative effectiveness and value of the drugs across relevant populations including:

- Patients with familial hypercholesterolemia
- Patients with established cardiovascular disease
- Patients at elevated risk for cardiovascular disease

We will perform a systematic literature review (SLR) of available evidence to provide specific assessment of the clinical and cost outcomes associated with alirocumab and evolocumab for individuals with elevated LDL cholesterol. The project scope is defined using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from Phase II or III randomized controlled trials as well as high-quality systematic reviews where available.

Quality Assessment Criteria

The quality of individual studies will be assessed by considering the domains listed below, which are adapted from the methods guide of the Agency for Healthcare Research & Quality (AHRQ) [17:]

- Similarity of baseline characteristics and prognostic factors between comparison groups
- Well-described methods for randomization and concealment of treatment assignment
- Use of valid, well-described primary outcomes
- Blinding of subjects, providers, and outcome assessors
- Intent-to-treat analysis (all randomized subjects included)
- Limited and non-differential loss to follow-up
- Disclosure of any conflicts of interest

PICOTS Inclusion Criteria

All SLR search algorithms will be generated utilizing PICOTS related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting [or Study design].

Populations

The populations of interest include:

- Individuals with heterozygous familial hypercholesterolemia (FH) OR homozygous familial hypercholesterolemia whose cholesterol levels are not at goal
- Individuals with known cardiovascular disease (CVD) who are intolerant of statins or whose cholesterol levels are not at goal
- Individuals who are at high risk for CVD who are intolerant of statins or whose cholesterol levels are not at goal

Interventions

The interventions are the following PCSK9 inhibitors considered as a class:

- Alirocumab (Praluent®, Sanofi and Regeneron Pharmaceuticals, Inc.)
- Evolocumab (Repatha™, Amgen)

We will consider the PCSK9 inhibitors as a class rather than separately for several reasons. First, there are no randomized trials comparing the two, which would allow for direct comparison of the LDL-lowering effects. Second, network meta-analytic techniques are not yet widely available to perform indirect comparisons for continuous outcomes such as the percentage reduction in LDL cholesterol. Third, the magnitude of the reduction in LDL with PCSK9 inhibitors as a class is much greater than any potential differences between the different drugs or their dosing. Finally, the number of clinical events for the individual PCSK9 inhibitors is too small to offer meaningful comparisons.

Comparators

The comparators of interest include usual care (i.e., statin therapy, lifestyle and dietary changes), placebo, and/or ezetimibe (Zetia®, Merck & Co.).

Outcomes

Outcomes of interest include the impact of cholesterol-lowering interventions on:

- Mortality
- CVD mortality
- CVD events (myocardial infarction, stroke, unstable angina, revascularization)
- LDL-C reduction as an intermediate marker
- Short- and long-term complications and adverse events including neurocognitive events, myalgias, and local injection site reactions
- Economic outcomes, including payer costs, patient productivity, and cost-effectiveness

Timing

Evidence on intervention effectiveness will be drawn from phase 2 or 3 comparative studies with at least two months of follow-up for LDL-C reduction. Evidence on cardiovascular outcomes and harms will be derived from comparative studies of any duration.

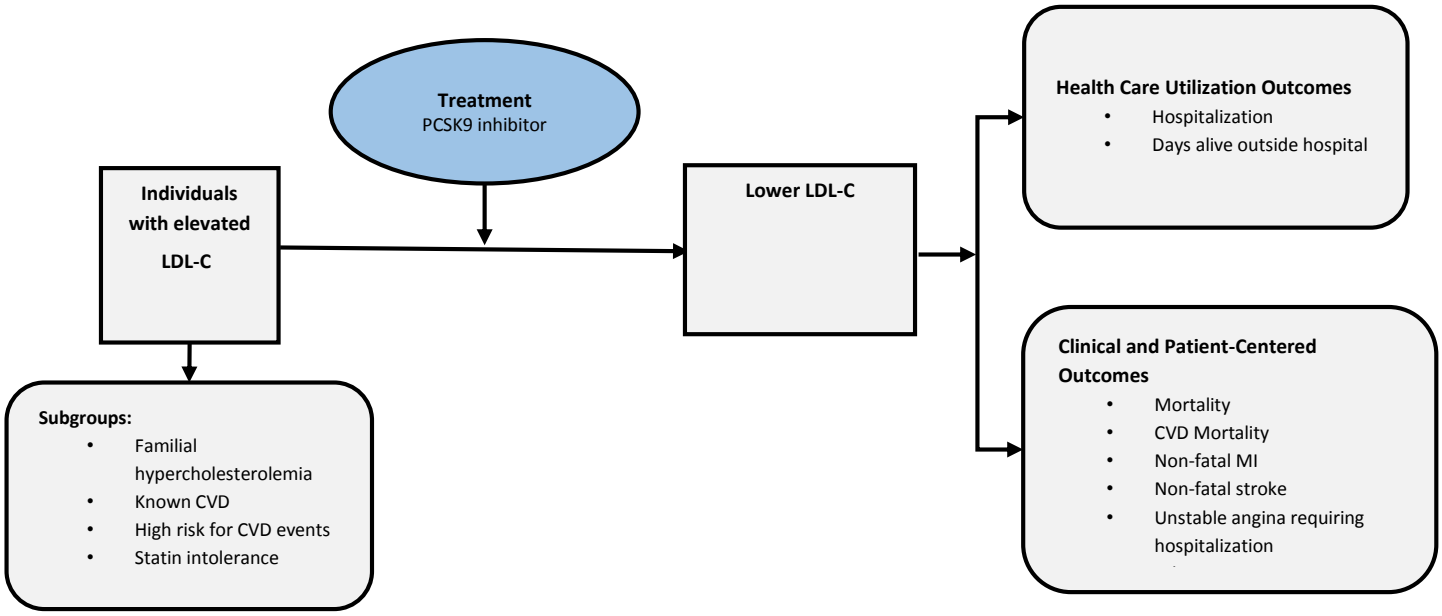
Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Analytic Framework

The analytic framework for assessments of the interventions of interest is depicted in Figure 1 below.

Figure 1: Analytic Framework for the Assessment



EVIDENCE REVIEW METHODS

Search Methods and Data Sources

Initial review of the literature revealed a recent high-quality systematic review which evaluated phase 2 and 3 randomized trials of PCSK9 antibodies.[18] We built on the methods described in this publication to perform the current systematic review, and the details follow.

We will search the PubMed (i.e., Medline) database as well as a variety of databases maintained by the Cochrane Collaboration: Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE). The search will be performed for the period from 1945 through August 2015. No language restriction will be used. The bibliographies of systematic reviews and key articles will be manually searched for additional references. The abstracts of citations will be reviewed for relevance and all potentially relevant articles will be reviewed in full.

The search algorithm to be used in the searches of both the PubMed and Cochrane databases is presented below:

((((((alirocumab) OR evolocumab) OR pcsk9 inhibitor) OR pcsk9 antibody) OR amg 145) OR regn727) OR sar236553

Selection of Eligible Studies

Study selection will be accomplished through two levels of screening, at the abstract and full-text level. A single investigator will screen all abstracts identified through electronic searches according to the inclusion and exclusion criteria described above. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Full papers will be reviewed by one investigator.

Data Extraction Strategy

We will abstract data from each trial on the number of patients randomized, the duration of follow-up, age, sex, diabetes, heart disease, lipid levels, lipid therapy, trial quality measures, and the experimental and control interventions. We will extract data for intervention groups that evaluate the FDA approved doses for alirocumab and evolocumab. Key outcomes include changes in LDL-cholesterol levels, cardiovascular events, liver and muscle enzyme changes, neurocognitive outcomes, total adverse events, serious adverse events, discontinuations due to adverse events, and common adverse events.

(See Appendix A for examples of how the data may be presented).

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published in the peer-reviewed literature. We will provide qualitative analysis of the objectives and methods of these studies, in order to ascertain whether there may be a biased representation of study results in the published literature.

If meta-analyses of any outcome are deemed to be feasible, we will complement these with specific quantitative analysis of the potential for publication bias. Specifically, we will perform rank correlation-tau and Egger's regression tests on any meta-analyzed data. If either result is statistically-significant ($p<.05$), pooled meta-analysis estimates will be adjusted using the trim-and-fill method.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables as outlined in Appendix A.

Statistical Methods

Data on relevant outcomes will also be synthesized quantitatively if feasible. A minimum of two studies are required for meta-analysis of any given outcome within any particular stratum of patients. We will additionally evaluate the feasibility of meta-analysis on the basis of any clear indicators of study heterogeneity conferred by variation in study populations, intervention intensity or dosage, or analytic methods which would preclude meaningful quantitative synthesis.

If quantitative analyses are deemed feasible based on the structure of available evidence, both fixed- and random-effects models will be specified; the final choice of model will be made based on assessment of between- and within-study heterogeneity. Heterogeneity will be assessed using commonly-employed statistics (e.g., tau-squared, I-squared), quantification of variance in effect size between studies, and observations regarding overlap in estimates by intervention type as well as the width of the confidence interval around pooled estimates.

Analyses of continuous measures will be based on standardized and/or weighted mean differences, while assessment of dichotomous or categorical variables will be made using rate ratios or odds ratios. Findings will be displayed in both tabular fashion as well as graphically (i.e., forest plots).

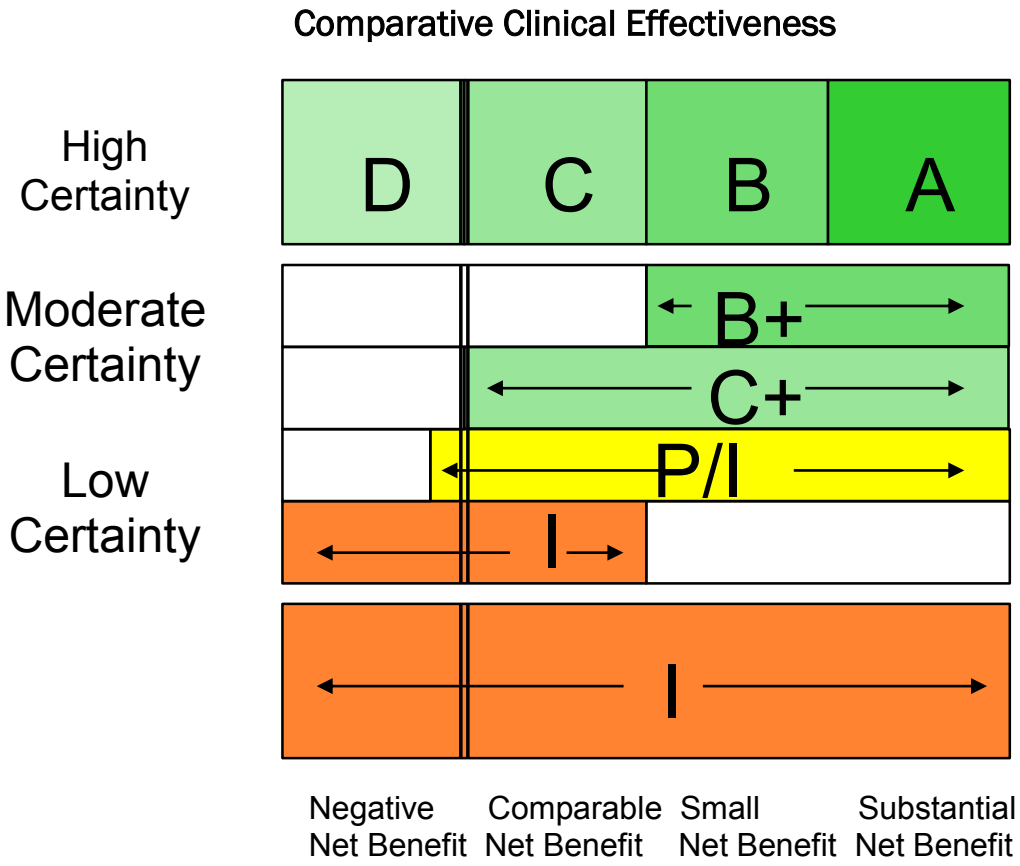
Evidence Rating

We will use the ICER Evidence Rating Matrix (see Figure xx on the next page) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

1) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND

2) The level of **certainty** in the best point estimate of net health benefit.

Figure 2. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D="Negative"- High certainty of an inferior net health benefit
B+="Incremental or Better" – Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" - Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

COST-EFFECTIVENESS ANALYSIS

To assess the incremental costs per outcomes achieved of PCSK9 inhibitors we will conduct a cost-effectiveness analysis using the CVD Policy Model, a previously validated model of cardiovascular disease in the contemporary adult population of the United States. The CVD Policy Model is a computer-simulation, discrete-state Markov model of coronary heart disease and stroke incidence, prevalence, mortality, and costs in the U.S. population over age 35 years.[19-21] The model was created at Harvard University in 1984 and has been used for more than 30 years to provide evidence on the value of cardiovascular disease prevention approaches in U.S. adults. The CVD Policy Model team has published

reports from a number of high-impact studies of public health and clinical interventions.[22-31] The last model software and input data update was completed in 2015.

For the purpose of this analysis, we will estimate the degree of LDL-reduction with PCSK9 inhibitors when used alone or in combination with statins. We will assume that the drugs are equally efficacious in all patient populations, i.e., the proportion of reduction in LDL-cholesterol from baseline will be made constant across all subgroups studied. We will also estimate the LDL-lowering effect of ezetimibe, another second-line LDL-lowering drug, alone or combination with statin.

We will assume that the effect of these drugs on cardiovascular outcomes (non-fatal MI, stroke and cardiovascular death) is proportional to the degree of reduction in LDL-cholesterol: for one unit decline in LDL-cholesterol, we will assume that statins, ezetimibe, and PCSK9 inhibitors reduce the risk of non-fatal MI, non-fatal stroke, and cardiovascular death by an identical amount. Since the effect of PCSK-9 inhibitors on stroke is not known, we will perform a sensitivity analysis that assumes no change in the risk of stroke among patients treated with PCSK9 inhibitors.

Sensitivity Analyses

We will conduct extensive deterministic and scenario-based sensitivity analyses to account for uncertainty in the input parameters. We will adhere to the recommendations of the Panel on Cost -Effectiveness in Health and Medicine where practicable.[32]

BUDGET IMPACT ANALYSIS

We will use the same model employed for the incremental cost-effectiveness analysis to estimate total potential budgetary impact. Potential budget impact will be defined as the total incremental cost of the therapy in each population: incremental health care costs (including drug costs) minus any offsets in these costs from averted cardiovascular events. All costs will be undiscounted and estimated over one- and five-year time horizons. In addition to patients with FH and those with a history of CVD who are (a) statin intolerant or (b) not at LDL-C target on statin therapy, we will also considere the budgetary impact if the treated population were limited to the higher-risk subset patients with a history of CVD who received PCSK9 inhibitors immediately following an incident (i.e., first-ever) MI in 2015. Our calculations will assume that utilization of new drugs is “unmanaged” – i.e., without payer or pharmacy benefit management controls in place – to provide an upper bound for likely patterns of drug uptake by five years after launch.

Findings from both the cost-effectiveness and budget impact analyses will also be used to develop device and drug price benchmarks for value-based discussions during the public meeting.

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APPENDIX A.DATA EXTRACTION SUMMARY TABLE SHELL

A6Table8:1LDL2outcomes

Reference	Study	Intervention	Baseline1LDL	Final1LDL	LDL3<370mg/dL,2%	Q2W %2reduction3in2LDL3vs3placebo	Q4W %2reduction3in2LDL3vs3placebo	Q2W %2reduction3in2LDL3vs3ezetimibe	Q4W %2reduction3in2LDL3vs3ezetimibe
Alirocumab									
Heterozygous4(HeFH)2or3mixed3familial3hyperlipidemia4(FH)									
Stein2012	2-	Alirocumab	147	50	81	57.2	23.5		
		Placebo	151	136	0				
2-2	ODYSSEY3FH1	Alirocumab	140	70	77	57.9			
		Placebo	139	145	7				
2-2	ODYSSEY3FH3II	Alirocumab	140	70	77	51.4			
		Placebo	139	145	7				
2-2	ODYSSEY3HIGH3FH	Alirocumab	196	113	32	39.1			
		Placebo	201	188	3				
Robinson2015	ODYSSEY1Long3Term	Alirocumab	123	48	79	61.9			
		Placebo	122	119	8				
McKenney2012	2-	Alirocumab	124	34	100	53.5	40.4		
		Placebo	130	127	3				
Roth2012	2-	Alirocumab	127	54	90	48.9			
		Placebo	121	104	17				
Hypercholesterolemia4(HC)									
2-2	ODYSSEY3ALTERNATIVE	Alirocumab	191	92	42			30.4	
		Ezetimibe	194	157	4				
Kereiakas2015	ODYSSEY3COMBO1	Alirocumab	100	52	5	45.9			
		Placebo	106	102	9				
Cannon2015	ODYSSEY3COMBOII	Alirocumab	109	52	77			29.8	
		Ezetimibe	105	82	46				
Roth2014	ODYSSEY3MONO	Alirocumab	141	87	NR			31.6	
		Ezetimibe	138	121	NR				
Bays2015	ODYSSEY3OPTIONS1	Alirocumab	110	52	78			27.2	
		Ezetimibe	100	78	52				
2-2	ODYSSEY3OPTIONSII	Alirocumab	113	43	68			30.5	
		Ezetimibe	110	69	49				
Evolocumab									
Homozygous3familial3hyperlipidemia4(HoFH)									
Raal2015	TESLA3Part3B	Evolocumab	356	282	NR		30.9		
		Placebo	336	356	NR				
Heterozygous4(HeFH)2or3mixed3familial3hyperlipidemia4(FH)									
Raal2012	RUTHERFORD	Evolocumab	151	70	65		56.4		
		Placebo	162	162	0				
Raal2015	RUTHERFORD2	Evolocumab	158	68	66	59.2	61.3		
		Placebo	151	153	2				
Koren2014	MENDEL2	Evolocumab	143	62	69	49.6	52.8	35.8	34
		Ezetimibe	144	117	1.4				
		Placebo	142	141	0.7				
Hypercholesterolemia4(HC)									
Sullivan2012	GAUSS	Evolocumab	204	99	NR		47.3		35.9
		Ezetimibe	183	154	0				
Stroes2014	GAUSS2	Evolocumab	192	90	44			38.1	37.6
		Ezetimibe	195	162	1				
Giuliano2012	LAPLACE3TIMI57	Evolocumab	120	63	83	66.1	50.3		
		Placebo	124	122	1				
Koren2012	MENDEL	Evolocumab	139	72	NR	47.2	52.5	36.7	34.1
		Ezetimibe	143	122	NR				
		Placebo	145	147	NR				
Hirayama2014	YUKAWA	Evolocumab	139	41	86	68.6	63.9		
		Placebo	143	139	0				
Robinson2014	LAPLACE2	Evolocumab	110	44	89	70.9	61.9	43.4	40
		Ezetimibe	109	89	37				