Summary Table of Study Protocol

Title	The Cardiovascular Multi-dimensional Observational Investigation of the Use of PCSK9 Inhibitors (cvMOBIUS)
Protocol version identifier	20180059; **Amendment 1**
Date of last version of the protocol	**24 July 2019**
EU Post Authorization Study (PAS) Register No	Not Applicable
Active Substance	Evolocumab
Medicinal Product	Repatha®
Device	Not Applicable
Product Reference	EU/1/15/1016
Procedure Number	EMA/H/C/3766
Joint PASS	No
Research Question and Objectives	Research Question: What is the real-world effectiveness of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i) to reduce cardiovascular events among subjects with a recent atherosclerotic cardiovascular disease (ASCVD) event or revascularization procedure? Primary Objective: 1. Evaluate the real-world effectiveness of PCSK9is to reduce cardiovascular events in routine practice in a prospective cohort of adults presenting with a recent ASCVD event and/or revascularization procedure. Secondary Objectives: 2. Assess the baseline characteristics and comparability of subjects who have had a recent ASCVD event or revascularization who initiate a PCSK9i to those who have had a recent ASCVD event or revascularization who do not initiate a PCSK9i. 3. Assess longitudinal patterns of lipid control, clinical outcomes, and lipid-lowering therapies (LLT) including statins, ezetimibe, and PCSK9is in adults with an ASCVD event and/or revascularization. 4. Explore health-system heterogeneity of ASCVD risk factors and LLT and other secondary prevention therapies 5. Evaluate subject, provider, and systems-level factors associated with LLT strategies as well as the impact of these therapies on lipid trajectories

	6. Model the potential impact of utilization of PCSK9i therapy use across health systems. 7. Understand the strengths and limitations of data harvested directly from electronic health record (EHR) systems as compared with prospectively collected information.
Country(ies) of Study	United States, Canada
Authors	PPD , MD PPD , MD PhD PPD , MD MPH Duke Clinical Research Institute PPD , PhD MPH PPD , MD PhD US Medical Amgen Inc.

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	One Amgen Center Drive Thousand Oaks, CA 91320-1799 USA +1 (805) 447 3505

Investigator's Agreement

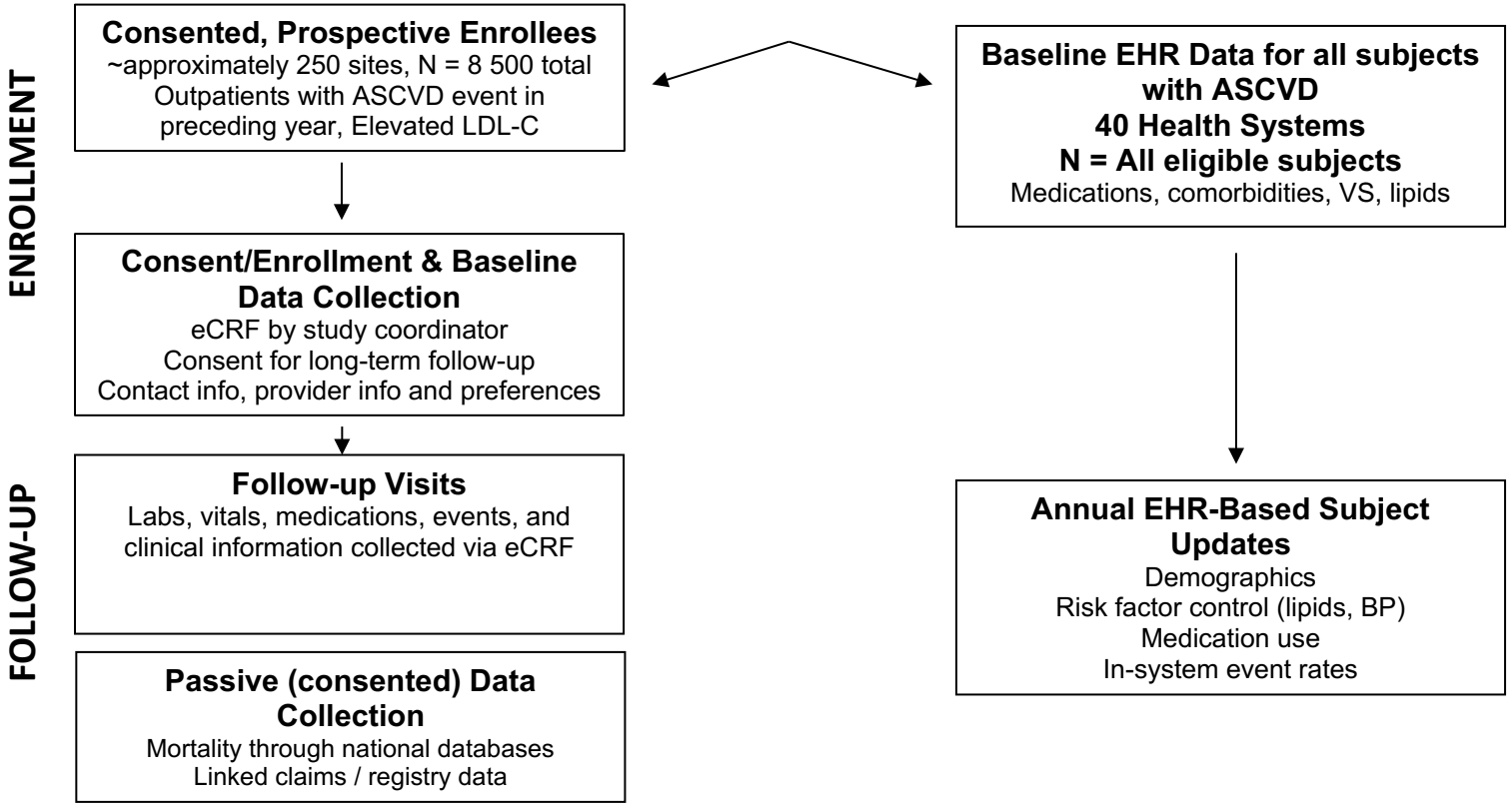
I have read the attached protocol entitled The Cardiovascular Multi-dimensional Observational Investigation of the Use of PCSK9 inhibitors (cvMOBIUS), dated **06 December 2019**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

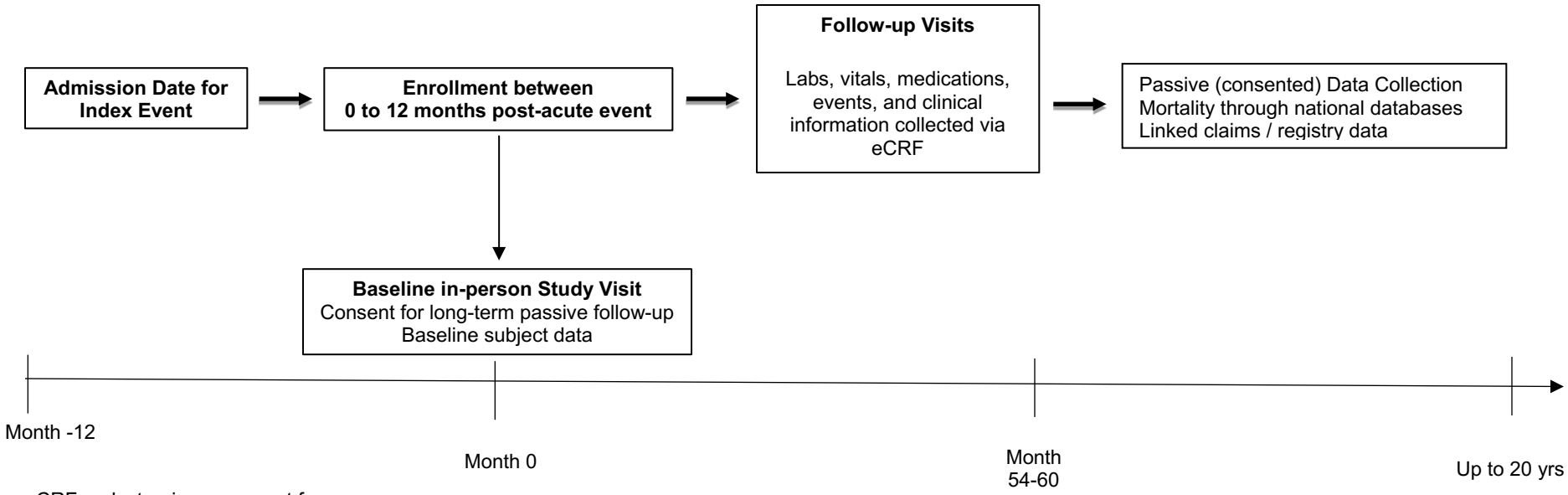
Name of Investigator <<*Coordinating Investigator*>> Date (DD-Month-YYYY)

Study Design Schema



ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; eCRF = electronic case report form; EHR = electronic health record; LDL-C = low-density lipoprotein cholesterol; VS = vital signs

Study Design Timeline



eCRF = electronic case report form

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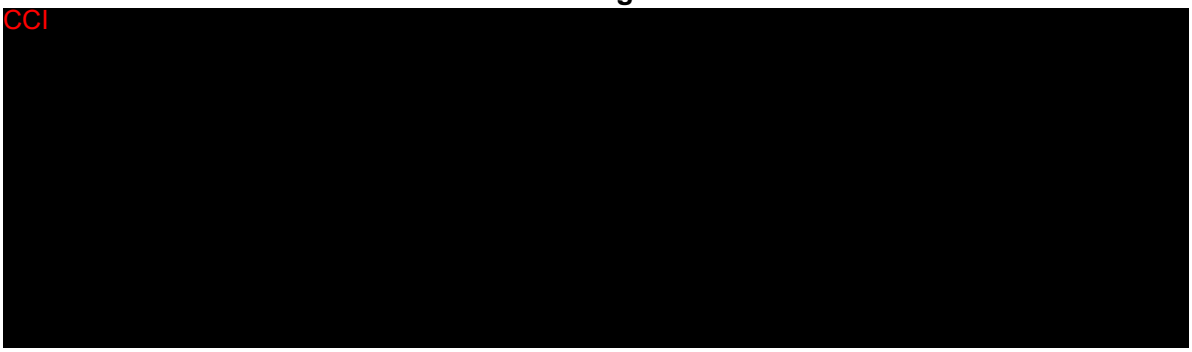

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2. List of Abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
ACE	angiotensin converting enzyme
AHA	American Heart Association
ApoB	apolipoprotein B-100
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor neprilysin
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CABG	coronary artery bypass graft
CHD	coronary heart disease
CHF	chronic heart failure
CKD	chronic kidney disease
CLI	critical limb ischemia
CT	computed tomography
CVA	cerebrovascular accident
cvMOBIUS	The Cardiovascular Multi-dimensional Observational Investigation of the use of PCSK9 inhibitors
DCRI	Duke Clinical Research Institute
ECG	electrocardiogram
eCRF(s)	electronic case report form(s)
EDC	electronic data capture
EHR	electronic health record
EMA	European Medicines Agency
ESRD	end stage renal disease
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
FSE	first subject enrolled
GCP	Good Clinical Practice
GLP1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholestrol
HeFH	heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	hazards ratio
ICD	International Statistical Classification of Diseases and Related Health Problems

Abbreviation	Definition
ICH	International Council on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IPCW	inverse probability of censoring weights
IPD	**important protocol deviation**
IPTW	inverse probability of treatment weights
IRB	Institutional Review Board
IS	Ischemic stroke
IT	information technology
KM	Kaplan-Meier
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LLT	lipid-lowering therapy
LOINC	Logical Observation Identifiers Names and Codes
Lp(a)	lipoprotein(a)
LSE	last subject enrolled
MALE	major adverse limb events
MI	myocardial infarction
MRI	magnetic resonance imaging
MSM	marginal structural model
MedDRA	Medical Dictionary for Regulatory Activities
NOAC	novel oral anticoagulant
NSTEMI	non-ST-elevation myocardial infarction
PAD	peripheral arterial disease
PEED	**post enrolment eligibility deviation**
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor(s)
SADR	serious adverse drug reaction
SAP	statistical analysis plan
SAS	Statistical Analysis System
SGLT2	sodium-glucose cotransporter 2
SOCs	system organ classs
SOP(s)	standard operating procedure(s)
STEMI	ST-elevation myocardial infarction
TIA	transient ischemic attack
UA	unstable angina
US	United States

3. Responsible Parties

Sponsor Contact	PPD , PhD, MPH PPD 1 Amgen Center Dr. MS 27 2E Thousand Oaks, CA 90302

Amgen is the study sponsor, responsible for authoring the protocol and for conducting all operational aspects of the study. Amgen will identify appropriate sites in the United States and Canada. Amgen will initiate the protocol in these countries and sites after contract finalization.

4. Abstract

- **Study Title:** The Cardiovascular Multi-dimensional Observational Investigation of the Use of PCSK9 inhibitors (cvMOBIUS)

- **Study Background and Rationale**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9is) have been on the market (in the US and Canada) since 2015, yet little is known regarding their real-world use and effectiveness. This may be due to the relatively low uptake of the class in clinical practice (Baum et al, 2017), making it difficult to study their use in the real-world. However, recent changes in the US may improve utilization of PCSK9i therapies. First, new guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) now recommend PCSK9i for very high-risk atherosclerotic cardiovascular disease (ASCVD) patients with persistent low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL on maximally tolerated statin therapy and ezetimibe following a clinician-patient discussion about the net benefit, safety and cost of the medication (Class IIa) (Grundy et al, 2018). Second, recently the list price of PCSK9is has been reduced by 60%, resulting in decreased co-pays for Medicare beneficiaries. These recent changes in the US will most likely make it more feasible to study their uptake in clinical practice and their effectiveness in the real world.

To evaluate the effectiveness of PCSK9i in patients presenting with recent ASCVD events in the real world, as well as to understand which patient- and provider-level factors associated with achievement of appropriate low-density lipoprotein (LDL)-lowering in adults with ASCVD and initiation of PCSK9i, and which are at highest risk of recurrent ASCVD events, large-scale prospective observational data are needed. Better understanding of current utilization and the real-world effectiveness of PCSK9is

could foster the implementation of targeted interventions to improve lipid management and decrease the burden of ASCVD.

We propose to address these needs with a pragmatic electronic health record (EHR)-enabled registry in the US and Canada. The cvMOBIUS PCSK9 Inhibitor Registry consists of 2 major components:

1. A consented prospective cohort of individuals with recent ASCVD events (within 12 months) who are likely to meet eligibility requirements for PCSK9i; and,
2. A parallel EHR-based registry of hundreds of thousands of subjects hospitalized with an ASCVD event treated at participating study centers able to provide EHR-based data (approximately 40 sites).

The effectiveness of PCSK9i in adults with a recent ASCVD event will be assessed by comparing cardiovascular events in adults who are initiated on PCSK9i versus those who are not. In the EHR arm, lipid-lowering therapy (LLT) and secondary prevention goal attainment in a larger cohort of all adults with ASCVD from across the health system will be assessed.

- **Research Question and Objective(s)**

Objectives	**Endpoints**
Primary	
• Evaluate the real-world effectiveness of PCSK9is to reduce cardiovascular events in routine practice in a prospective cohort of adults presenting with a recent ASCVD event and/or revascularization procedure.	Primary endpoint: Composite of • All-cause mortality • Non-fatal myocardial infarction (MI) • Non-fatal ischemic stroke (IS) Secondary endpoint: • The individual components of the primary endpoint, coronary or peripheral revascularization procedures, major adverse limb events (MALE) including amputation, cardiovascular death, coronary heart disease (CHD) death, transient ischemic attack (TIA), unstable angina (UA). Registry Arm: Consented

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Objectives	Endpoints
Secondary	
• Assess the baseline characteristics and comparability of subjects who have had a recent ASCVD event or revascularization who initiate a PCSK9i to those who have had a recent ASCVD event or revascularization who do not initiate a PCSK9i.	Baseline characteristics include: • Demographics • Vital signs • Comorbidities • Prior ASCVD event(s) • Lab data • Cardiac catheterization and echocardiographic data • Concurrent medications • Current LLTs • Prior LLT experience • Prior statin or PCSK9i intolerance Registry arm: Consented
• Assess longitudinal patterns of lipid control, clinical outcomes, and LLT including statins, ezetimibe, and PCSK9is in adults with an ASCVD event and/or revascularization.	• Use of LLT including persistence with PCSK9i, statins, and ezetimibe • Lipid levels (LDL-C, non-high-density lipoprotein cholestrol [HDL-C], lipoprotein (a) [Lp(a)], etc.) • Composite of all-cause mortality, non-fatal MI, non-fatal ischemic stroke • Individual components of the composite • Coronary or peripheral revascularization • MALE • Cardiovascular death • CHD death • TIA • UA Registry arm: Consented and EHR
• Explore health-system heterogeneity of ASCVD risk factors and LLT and other secondary prevention therapies	• ASCVD Risk Factors: - Age, sex - Type of prior ASCVD event - Hypertension - Diabetes - Smoking - Obesity - Chronic kidney disease - Heart failure - Lipid levels - Other labs: Hemoglobin A1c (HbA1c), creatinine • LLT: PCSK9i, ezetimibe, statin (by intensity), icosapent ethyl • Other secondary prevention therapies: Aspirin, $P2Y_{12}$ receptor inhibitors, beta-blockers, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blockers (ARB)/angiotensin receptor neprilysin (ARNI), sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) agonists. Registry Arm: Consented and EHR

Objectives	Endpoints
Secondary (continued)	
• Evaluate subject, provider, and systems-level factors associated with LLT strategies as well as the impact of these therapies on lipid trajectories	• LLT: PCSK9i, ezetimibe, statin (by intensity), icosapent ethyl Registry Arm: Consented and EHR
• Model the potential impact of utilization of PCSK9i therapy use across health systems	• Using EHR data, estimate the potential number of candidates for PCSK9i and the potential number of in-system avoidable events by applying known relative risk reductions from trials to observed event rates at follow-up. Registry Arm: EHR
• Understand the strengths and limitations of data harvested directly from EHR systems as compared with prospectively collected information	• Among those enrolled in the registry, comparison of the agreement and consistency of the clinical data in the EHR vs prospective data collection. • A comparison of the characteristics of those enrolled in the registry vs those eligible for enrollment at EHR participating sites. Registry Arm: Consented and EHR

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- **Hypothesis(es)/Estimation**

In the real-world, PCSK9i use is associated with a reduction in cardiovascular events among subjects recently hospitalized with an ASCVD event or undergoing a revascularization procedure, compared to a similar cohort of subjects recently hospitalized with an ASCVD event or underwent a revascularization procedure who do not initiate a PCSK9i.

- **Study Design/Type**

A multicenter prospective observational registry in the US and Canada with approximately n = 8 500 **eligible,** consented adults with recent ASCVD events potentially eligible for PCSK9 therapy followed prospectively for 5 years and a parallel, 40-site EHR arm including all adults with ASCVD followed at those health systems.

- **Study Population or Data Resource**

In the “Consented Arm”, subjects with recent (within 12 months) MI, UA, IS, or critical limb ischemia (CLI), and subjects undergoing coronary or peripheral revascularization including percutaneous or surgical revascularization. In the “EHR arm”, all outpatient subjects with ASCVD seen within the health system, will be included.

- **Summary of Subject Eligibility Criteria**

Sites will be able to enroll subjects at outpatient visits that occur within 12 months of a qualifying hospitalization or revascularization procedure.

Inclusion criteria for the consented arm are:

- Adults age ≥ 40 years
- One or both of the following:
  - Hospitalization for a clinical ASCVD event: acute (MI), UA, IS, or CLI within 12 months of enrollment
  - Coronary or peripheral revascularization including percutaneous or surgical revascularization in the past 12 months
- One of the following:
  - Low-density lipoprotein (LDL) ≥ 70 mg/dL (1.81 mmol/L) with no plans for immediate initiation or titration of statin therapy

    Note: Subjects should not be enrolled into study during initiation/titration of statins until they have a stable LDL-C measurement > 4 weeks after their last statin change and no immediate plans for future titration
  - Newly started on PCSK9i after the index hospitalization/procedure and prior to enrollment (but no more than 6 months prior to enrollment) with pre-PCSK9i treatment LDL-C value available and measured within 6 months of starting PCSK9i and known background LLT any time prior to PCSK9i initiation.
- One or both of the following:
  - The presence of an additional ASCVD event: prior history of MI, cerebrovascular accident (CVA), or symptomatic peripheral arterial disease (PAD)
  - One or more high-risk conditions: age ≥ 65 years old, heterozygous familial hypercholesterolemia (HeFH), history of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) outside of the major event, diabetes mellitus, hypertension, chronic renal insufficiency, current smoking, heart failure, or elevated lipoprotein (a) [Lp(a)] (≥ 50 mg/dL or > 125 nmol/L)
- Planned follow-up within the health system.

Summary of exclusion criteria for the consented arm are:

- Unable or unwilling to provide informed consent, including but not limited to cognitive or language barriers (reading or comprehension)
- Lack of phone or email for contact
- Evidence of end stage renal disease (ESRD) or stage 5 chronic kidney disease (CKD)
- Anticipated life expectancy less than 6 months
- On a PCSK9i prior to their qualifying event

Note: Subjects with prior PCSK9i use occurring and ending before the 12-month period prior to enrollment and before the index ASCVD event will be considered for inclusion.

EHR Arm-specific Inclusion Criteria

Subjects are eligible to be included in the "EHR arm" of the registry if they are:

- Adults age ≥ 40 years of age
- Have at least 1 inpatient or outpatient diagnosis of clinical ASCVD within 12 months prior to baseline including CHD, ischemic cerebrovascular disease, atherosclerotic PAD, or prior coronary or peripheral revascularization.

All subjects with ASCVD will be included in the EHR extract to simplify the procedure for data extraction for sites. Upon receiving data extracts from EHR sites, Duke Clinical Research Institute (DCRI) will review to ensure all subjects included do meet the eligibility criteria. Additional inclusion/exclusion criteria will be determined for individual analyses and detailed within corresponding statistical analysis plans (SAPs).

Subjects in the "EHR arm" will have baseline and annual extracts on all subjects with ASCVD through the end of study (year 5).

No exclusion criteria will be applied for the EHR arm.

- **Follow-up**

The study will enroll subjects for 1.5 years and the follow-up period will extend 4.5 years after the last subject is enrolled for a maximum planned follow-up of 5 years (for those enrolled during the first 12 months) and a minimum planned follow-up of 4.5 years. Follow-up visits will be performed approximately 6 months after enrollment, then at 12 months, 24 months, 36 months, 48 months, and 60 months. For subjects enrolled during the last 6 months of the enrollment period, their follow-up visits will occur at 6 months, 12 months, 24 months, 36 months, and 48 months, and then at study closeout. Thus, all subjects will have a baseline visit plus 6 follow-up visits.

Subjects will be censored from the study for the following reasons:

- Death
- Subject decision to disenroll early
- Discontinuation of a PCSK9i (defined by 6 months off therapy)

If feasible and scientifically informative, there may also be a 10-, 15-, and 20-year follow-up for events and mortality among subjects who consent for continued passive follow-up.

- **Variables**
  - Exposure:

    PCSK9i use (any type, any dose) is the exposure of interest. Initiation and continuation of PCSK9i will be assessed via medical record review and recorded in the electronic case report form (eCRF) upon enrollment, at 6-months, and at yearly follow-up.

    All enrolled subjects will also be evaluated for statin use (including type and dose) and ezetimibe use via medical record review upon enrollment, at 6-months, and at yearly follow-up.

  - Outcome:

    Primary Endpoint: Time to event from baseline for the first of:

    - All-cause mortality
    - Any non-fatal MI
    - Any non-fatal IS

    Secondary Endpoint(s): the individual components of the primary endpoint, coronary or peripheral revascularization procedures, major adverse limb events (MALE) including amputation, cardiovascular death, CHD death, TIA, UA.

  - Covariates: A variety of relevant covariates will be collected upon enrollment, at 6-months and at yearly follow-up.
    - Demographics (age, race, ethnicity, sex, geographic region)
    - Socioeconomic status: education, marital status, income
    - Insurance information
    - Vital signs (blood pressure)
    - Physical measurements (height, weight, and body mass index [BMI])
    - Comorbidities (hypertension, diabetes, heart failure, atrial fibrillation/flutter, renal disease, thyroid disease, liver disease, PAD, chronic heart failure [CHF], etc)
    - Type of ASCVD and time since last event, including prior revascularization
    - Interval events including MI, stroke (ischemic and hemorrhagic), UA, TIA, acute limb ischemia (ALI), renal artery disease, coronary revascularization, peripheral revascularization, PAD, and death
    - Limited cardiac catheterization (number of diseased vessels) and echocardiographic data (ejection fraction)
    - All available lipid panels
    - Prior statin or PCSK9i intolerance
    - Current and priorLLTs (including statin dose)
    - Current and prior non-lipid lowering cardiovascular medications

- **Study Sample Size**

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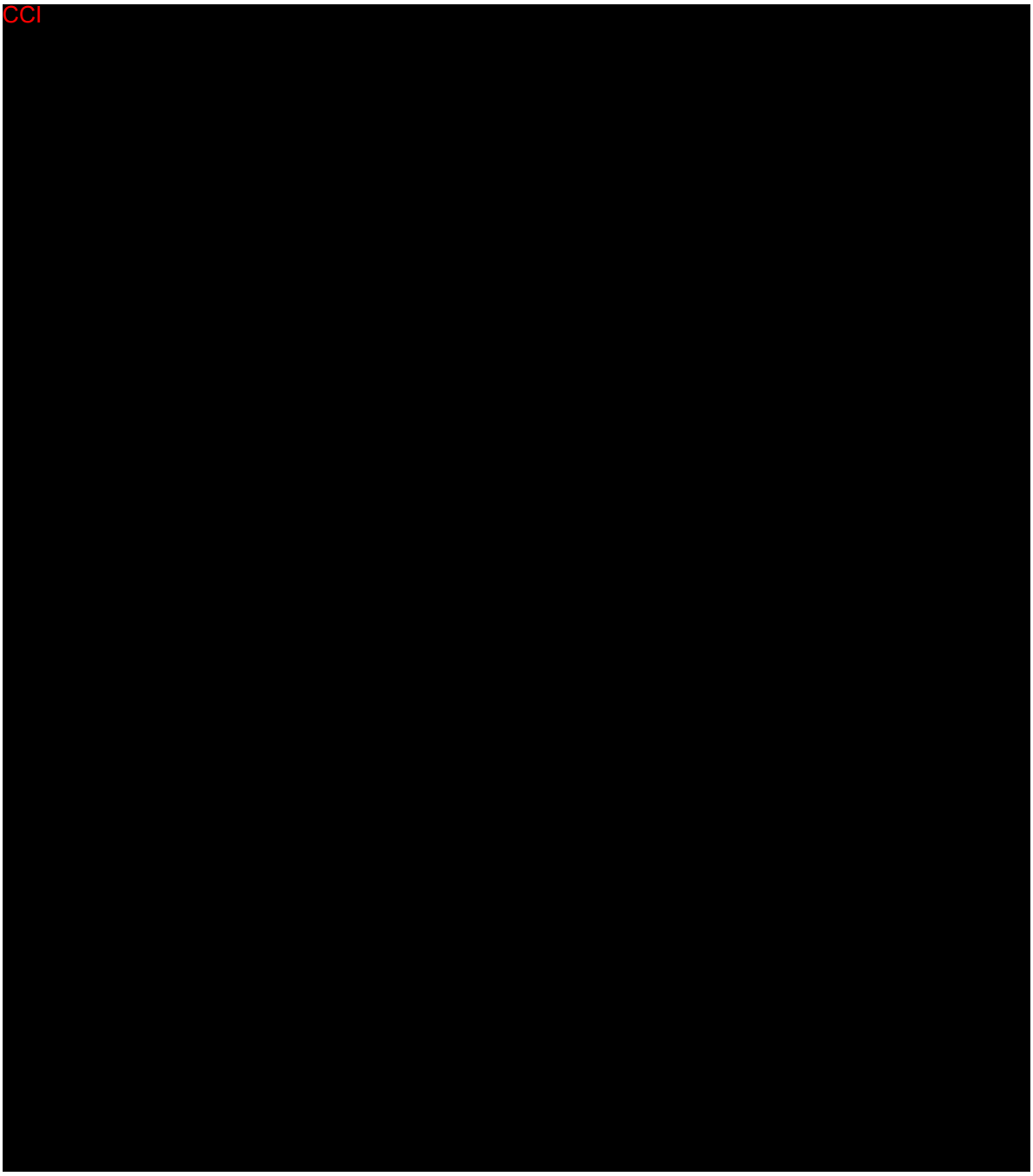

- **Data Analysis**

The primary analysis on the real-world effectiveness of PCSK9i in clinical practice will use a marginal structural model (MSM) approach to evaluate the relative risk of the primary composite event (all-cause mortality, non-fatal MI, and non-fatal IS) in PCSK9i users versus non-users, while accounting for the time varying nature of PCSK9i initiation and discontinuation (Hernan et al, 2000; Westreich et al, 2010; Breskin et al, 2018). The MSM, with inverse probability of treatment weights (IPTW) can be used to account for

both factors related to PCSK9i initiation and PCSK9i discontinuation, while controlling for these factors as they change over time. This approach allows patient treatment status and confounders to vary over time. First, an IPTW model is built to evaluate the association between potential time-varying confounders and the outcome of interest. This model outputs weights which are then incorporated into a Cox proportional hazard model to estimate the risk of the outcome of interest among subjects starting and remaining on PCSK9i, versus never starting (Breskin et al, 2018), after the ACSVD index event. Additionally, inverse probability of censoring weights (IPCW), which control for imbalances in censoring (due to treatment discontinuation, lost to follow-up, etc.) between the treated and untreated arms, will be employed. We will also estimate the associated cumulative event curves (weighted Kaplan-Meier [KM]) (Westreich et al, 2010).

Following the database lock and prior to the primary effectiveness analysis, as described above, we will implement a descriptive analysis to evaluate whether baseline characteristics (prior to PCSK9i initiation) are balanced between users and non-users of PCSK9is enrolled in the registry.

Following the descriptive analysis of baseline covariates, the adequacy of the MSM, to control for measured confounding, will be evaluated in the following ways:

If either the appropriate balance of baseline covariates cannot be achieved between the treated and untreated cohorts enrolled in the registry (evaluation described in step 1 above) or if the MSM models do not perform adequately (evaluation described in steps 2 to 5), the formal comparative effectiveness analysis and corresponding statistical tests will not proceed. Instead, we will describe baseline characteristics, achieved LDL-C levels, and rates of the specified cardiovascular outcomes in the treated and untreated cohorts. We will also describe the findings from the evaluations described above in steps 1 to 5, highlighting the lack of baseline comparability and/or the inability of the MSMs to adequately perform in this real-world therapeutic setting.

Duke Clinical Research Institute statistical teams will lead all analyses and will work in collaboration with Amgen to develop a detailed SAP.

5. Amendments and Updates

None.