Summary Table of Study Protocol

Title	EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care DA VINCI
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Research Question and Objectives	Research Question: How are EU patients requiring lipid-modifying therapy routinely managed? Primary Objective: To estimate the proportion of subjects in EU primary and secondary care, with or without established ASCVD and receiving LMT, with LDL-C above 2016 Joint ESC Guideline-recommended levels. Secondary Objectives To assess clinical characteristics and management of subjects in EU primary and secondary care, with or without established vascular/atherosclerotic disease and receiving LMT.
Country(-ies) of Study	EU multicountry
Author	PPD [redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	N/A
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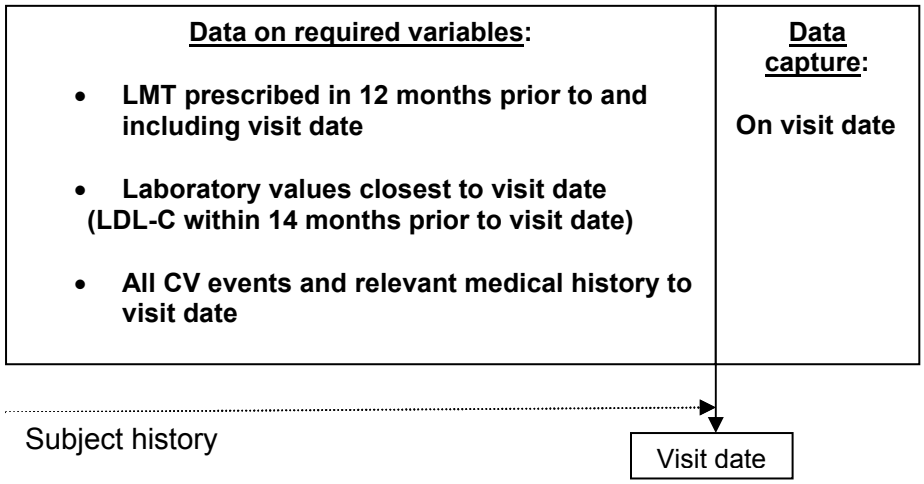
Investigator's Agreement

I have read the attached protocol entitled EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care DA VINCI, dated 07 March 2017, and agree to abide by all provisions set forth therein.

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



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2. List of Abbreviations

Abbreviation	Meaning
Apo A1; Apo B100	Apolipoprotein A1; Apolipoprotein B100
ASCVD	Atherosclerotic cardiovascular disease
CABG	Coronary artery bypass graft
CCT	Cholesterol Treatment Trialists
CHD	Coronary heart disease
CKD	Chronic kidney disease
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
eCRF	Electronic case report form
Enrolment	Subject is considered enrolled when informed consent/notification has occurred (if applicable according to local requirements), eligibility has been determined and data entry initiated into the eCRF.
ESC	European Society of Cardiology
EU	Europe(an)
FH	Familial hypercholesterolaemia
GP	General Practitioner
HbA1c	Haemoglobin A1c
HDL-C	High density lipoprotein-cholesterol
ICH GCP	International Committee for Harmonisation Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial College Trials Unit
IRB/IEC	Institutional Review Board/ Institutional Ethics Committee
IS	Ischaemic stroke
LDL-C	Low density lipoprotein-cholesterol
LMT	Lipid-modifying therapy
Lp(a)	Lipoprotein (a)
MI	Myocardial infarction
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
Non-HDL-C	Non-high density lipoprotein-cholesterol
NSTEMI	Non-ST-elevation myocardial infarction
PAM-13	Patient Activation Measure-13
PCI	Percutaneous coronary intervention

Abbreviation	Meaning
PRO	Patient Reported Outcome
PVD	Peripheral vascular disease
RCT	Randomised controlled trial
SOP	Standard Operating Procedure
Source data	Information from an original record or certified as a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). (ICH Guideline E6).
STEMI	ST-segment elevation myocardial infarction
Study start	Date on which data for first enrolled subject is first entered into EDC
TIA	Transient ischaemic attack
WHO	World Health Organisation

3. Responsible Parties

Amgen Ltd is the study sponsor, responsible for authoring the protocol and for conducting all data analysis.

Professor PPD, Professor of Public Health, Imperial College, is protocol co-author and Principal Investigator for this study.

Imperial College Trials Unit (ICTU) is responsible for all operational aspects of the study.

4. Abstract

- Study Title: EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care DA VINCI
- Study Background and Rationale:

Background

Cardiovascular disease (CVD) represents the leading cause of death and disability in the world, comprising over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) reported that CVD accounted for over 17 million deaths, nearly 80% of which were due to heart attacks and strokes alone.

Elevated cholesterol is among the leading risk factors for cardiovascular (CV) deaths, with an estimated prevalence of 39% globally among all adults (greater in high-income countries). It is estimated that up to 50% of the European population aged 35-64 years has a total cholesterol > 6.5 mmol/L (Tolonen et al, 2005), (equivalent to > 254 mg/dL). This high prevalence of dyslipidemia translates into significant CV morbidity and mortality, through development of atherosclerotic cardiovascular disease (ASCVD).

Over 50 million patients in the United States, Europe, and Japan are currently treated with lipid modifying therapies (LMT). The rationale for treatment of dyslipidemia derives from extensive clinical trial data which demonstrate that reduction in total cholesterol, non-high density lipoprotein-C (HDL-C), and most importantly low density lipoprotein-C (LDL-C) through pharmacological therapies lowers the risk of CV events. The Cholesterol Treatment Trialists' (CTT) Collaborators meta-analyses (CTT et al, 2005, 2010, 2012) of data from 26 randomized controlled trials involving nearly 170,000 patients showed that for every 1 mmol/L (equivalent to 39 mg/dL) reduction of LDL-C there was an approximate 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke), and that this was similar in patients with and without a history of vascular disease. Furthermore, in patients with established vascular disease, high intensity statin

therapy offered a further 0.5 mmol/L reduction in LDL- C cholesterol than treatment with low or moderate intensity, indicating even greater predicted benefits than those observed when low or moderate intensity statin therapy was compared to placebo. More recently, clinical trials such as ASCOT, CARDS, JUPITER and HOPE 3 (Sever 2005, Colhouhn 2004, Ridker 2016, Yusuf 2016) have extended the evidence base for the benefit of statin use to populations which are at high risk of vascular disease by virtue of the presence of hypertension, diabetes, elevated C-reactive protein (CRP) or global (ie, multifactorial) risk. As such there is now compelling evidence in favour of regarding 0.7% as the lower risk threshold at which treatment is indicated in the primary prevention setting. Despite these compelling data there remains an apparent lack of appreciation of the benefits of lipid lowering therapies in such patients.

In recognition of the need for appropriate treatment of patients at elevated risk of experiencing a CV event, expert bodies at national and local levels (eg EAS/ESC, national bodies such as NICE in the UK) issue guidelines on classification and clinical management of these patients. However, beyond the EUROASPIRE surveys (Kotseva et al 2015, 2016) which included patients with recent myocardial infarction (MI), there is little published data describing EU-wide lipid profiles & treatment patterns in patients routinely prescribed LMT, in both primary and secondary care settings. This study is expected to contribute new information on the patterns of treatment in primary and secondary care within the same geographical region as well as cross-country comparisons of lipid modifying therapy utilisation, which to date have not been reliably quantified. It is expected that these results will estimate the gap between guidelines and clinical practice, in turn helping to inform public health initiatives across Europe; by identifying potential shortfalls in treatment the study will contribute data that could be used in the development of policies towards rectifying suboptimal treatment.

Study Rationale

This study is designed to facilitate assessment of current treatment choices and lipid profiles in patients with or without established ASCVD, who have been prescribed LMT within 12 months of enrolment into the study. The broad inclusion criteria permit enrolment of patients with established CV disease (defined in Appendix B, including peripheral vascular disease (PVD), ischaemic stroke (IS), and coronary disease) and high risk primary prevention cohorts such as those with diabetes, chronic kidney disease or elevated global risk; this enables description of clinical management across a broad spectrum of indications. The inclusion of patients treated in both primary and secondary

care settings allows the description of treatment patterns outside a narrowly selected environment. Consideration of how treatment relates to relevant guidelines provides insight into potential unmet medical need in patients with or without established ASCVD, and at known or unrecognised risk of experiencing a new or recurrent CV event. This study will provide unique insights into contemporary treatment approaches in a diverse pan-European population.

As an exploratory objective, the study will utilise the Patient Activation Measure (PAM-13) to assess patients' level of engagement with their health and condition. The PAM-13 is a widely accepted patient reported outcome measure (PRO) developed at the University of Oregon, USA. It is validated in 22 languages across 30 countries and its use has been widely published (Hibbard et al Health Services Research 2004; Hibbard and Gilburt, The Kings Fund 2014;). The level of patient activation (engagement), calculated by the PAM has been shown to correlate with differences in healthcare utilisation and outcomes. Patients with a low PAM score are considered to have low activation, and have poorer health outcomes and are at higher risk for costly utilisation of healthcare resources than patients with high scores. Having information on subgroups with low PAM scores may provide insight into the potential unmet need of patient education and engagement, to help support patients to improve the self-management of their prescribed treatment.

- Research Question and Objectives

Research Question: How are EU patients requiring lipid-modifying therapy routinely managed?

Primary Objective:

To estimate the proportion of subjects in EU primary and secondary care, with or without established ASCVD and receiving LMT, with LDL-C above 2016 Joint ESC Guideline-recommended levels.

Secondary Objectives:

To assess clinical characteristics and management of subjects in EU primary and secondary care, with or without established vascular/atherosclerotic disease and receiving LMT.

- Hypothesis

No formal hypothesis will be tested in this observational study

- Study Design/Type

Cross-sectional, observational, multicountry, multisite study.

- Study Population

The study population comprises subjects from primary and secondary care facilities in European countries, who have had LDL-C assessment and been prescribed LMT as part of routine clinical management, between February 2016 and December 2017.

- Summary of Subject Eligibility Criteria

Inclusion:

- LDL-C measurement within 14 months of enrolment, obtained independently of participation in a clinical trial
- Use of any LMT (may include statin/ezetimibe/fibrate/PCSK9 inhibitor/bile acid absorption inhibitor/nicotinic acid/other) at time of enrolment, or any LMT prescribed within 12 months prior to date of enrolment, or any LMT prescribed at date of enrolment
- Age $\geq$ 18 years at enrolment
- Provided informed consent/notified according to local requirements
- Expected to survive for at least 1 year after enrolment

Exclusion*:*

- Diagnosis of FH and with history of CV event
- Currently receiving therapy for carcinoma (excepting squamous epithelial cell)
- Known HIV positive status
- Pregnant or breastfeeding at time of enrolment
- Participating in an interventional clinical trial within 6 months prior to enrolment

- Follow-up

Not applicable

- Variables

Individual site characteristics:

- Primary care/ secondary care/ speciality
- Number of patients with each relevant study indication seen per year
- Number of patients with each relevant study indication who are prescribed LMT during the conduct of the study
- Lipid guidelines followed at site (and if Yes then which ones)
- Previous/current experience of lipid-lowering randomized controlled trial (RCT) conduct

Subject level:

- Referral to study physician (eg referred from specialist or GP, and date referred)
- Demographics (gender, age at enrolment, ethnicity if permitted to record)
- Relevant medical history (CV events including dates, known risk factors [smoking, family history], diabetic/hypertension/renal/rheumatoid arthritis status, vascular bed involvement)
- Participation in a clinical study within previous 12 months
- Height/weight/BP/waist circumference
- Lipid profile (including fasting status) (total cholesterol, LDL, HDL, non-HDL, triglycerides, Lp(a), apo B100, apo A1), HbA1c, plasma glucose (including fasting status)
- LMT (type, dose, dose frequency, duration of prescription) at enrolment; in 12 months prior to enrolment, up to and including enrolment date
- History of intolerance to higher statin doses than currently prescribed, or to other statins
- Reason for prescription if non-ASCVD (eg diabetic, CKD, subject request)
- Other concomitant therapies of interest (antihypertensives, antidiabetics, antiplatelets, acetylsalicylic acid)

- Study Sample Size

The primary outcome measure for the study allows estimation of the percentage of study subjects with LDL-C level above 2016 Joint ESC Guideline-recommended levels (Piepoli 2016). The planned sample size for the study is approximately 6000 subjects across up to 18 countries; the number of subjects enrolled per country will vary according to size of country population and is not anticipated to be fewer than 200 subjects per country.

The sample size is expected to enable precise estimates of the primary outcome measure to be obtained for each participating country. Table 1 shows the expected precision of the primary outcome measure for subgroups of the full study population, assuming that 50% of subjects achieve the guidelines-recommended LDL-C levels (50% chosen as this results in the widest confidence interval). Sample sizes of 70-150 represent the potential size of cohorts of primary prevention or secondary prevention subjects within a country, while sample sizes of 200-300 represent the potential size of country cohorts.

Table 1. Estimated Precision of Primary Outcome Measure For a Range of Sample Sizes

Sample size	½ width of 95% CI
70	11.7
100	9.8
130	8.6
150	8.0
200	6.9
250	6.2
300	5.7

- Data Analysis

Primary analysis is descriptive: To estimate the proportion of subjects having LDL-C above the 2016 Joint ESC Guideline-recommended targets. Specifically, to estimate the proportion separately for subjects with and without established ASCVD.

Other analyses:

- Proportion of subjects with relevant clinical characteristics (ASCVD components, FH, diabetes, CKD)
- Proportion of subjects receiving maximally tolerated dose of statins
- Proportion of subjects receiving maximally tolerated dose of statin and with LDL-C above guideline stipulated levels
- Proportion of subjects receiving high, moderate or low intensity statin and with LDL-C above guideline-stipulated levels
- Lipid levels (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, Lp(a), apo B100, apo A1)
- Use of lipid lowering therapies (type, dose, frequency)
- Population distribution of CV risk scores (eg, REACH, SCORE and QRISK2)
- Predictive factors for subjects not achieving target LDL levels

Exploratory:

PAM score (PRO data will be assessed at enrolment, where PROs are able to be implemented as part of an observational study).

All summaries of the data will be descriptive in nature. No imputation of missing data is planned. A sensitivity analysis to explore the effect of influential subgroups (eg country, clinical characteristics) on the primary outcome measure may be conducted, if appropriate.

Subject demographics, baseline characteristics and PRO scores will be summarised. For categorical variables the frequency and percentage, with 95% confidence interval, will be given.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

Outcome measures may be presented by country and/or by study site type and/or by subject clinical characteristics, if sample size permits meaningful analysis.

Outcome measures may also be presented by different levels (eg, quartiles) of risk measures (eg REACH, SCORE, QRISK2).

Exploratory analysis will be conducted to identify which characteristics may be associated with subjects being in target, and which may be associated with subjects failing to achieve the LDL-C target.

An Interim Analysis may be conducted by Q1 2018 if required for Congress abstract submission.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection	April 2017
End of data collection	December 2017
Final report of study results	December 2018

7. Rationale and Background

Cardiovascular disease (CVD) represents the leading cause of death and disability in the world, comprising over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) reported that CVD accounted for over 17 million deaths, nearly 80% of which were due to heart attacks and strokes alone.

Elevated cholesterol is among the leading risk factors for cardiovascular (CV) deaths, with an estimated prevalence of 39% globally among all adults (greater in high-income countries). It is estimated that up to 50% of the European population aged 35-64 years has a total cholesterol > 6.5 mmol/L (Tolonen et al, 2005), (equivalent to > 254 mg/dL).

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Over 50 million patients in the United States, Europe, and Japan are currently treated with lipid modifying therapies (LMT). The rationale for treatment of dyslipidemia derives from extensive clinical trial data which demonstrate that reduction in total cholesterol, non-high density lipoprotein-C (HDL-C), and most importantly low density lipoprotein-C (LDL-C) through pharmacological therapies lowers the risk of CV events. The Cholesterol Treatment Trialists' (CTT) Collaborators meta-analyses (CTT et al, 2005, 2010, 2012) of data from 26 randomized controlled trials involving nearly 170,000 patients showed that for every 1 mmol/L (equivalent to 39 mg/dL) reduction of LDL-C there was an approximate 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke), and that this was similar in patients with and without a history of vascular disease. Furthermore, in patients with established vascular disease, high intensity statin therapy offered a further 0.5 mmol/L reduction in LDL- C cholesterol than treatment with low or moderate intensity, indicating even greater predicted benefits than those observed when low or moderate intensity statin therapy was compared to placebo. More recently, clinical trials such as ASCOT, CARDS, JUPITER and HOPE 3 (Sever 2005, Colhouhn 2004, Ridker 2016, Yusuf 2016) have extended the evidence base for the benefit of statin use to populations which are at high risk of vascular disease by virtue of the presence of hypertension, diabetes, elevated C-reactive protein (CRP) or global (ie, multifactorial) risk. As such there is now compelling evidence in favour of regarding 0.7% as the lower risk threshold at which treatment is indicated in the primary prevention setting. Despite these compelling data there remains an apparent lack of appreciation of the benefits of lipid lowering therapies in such patients.

In recognition of the need for appropriate treatment of patients at elevated risk of experiencing a CV event, expert bodies at national and local levels (eg EAS/ESC, national bodies such as NICE in the UK) issue guidelines on classification and clinical management of these patients. However, beyond the EUROASPIRE surveys (Kotseva et al 2015, 2016*)* which included patients with recent myocardial infarction (MI), there is little published data describing EU-wide lipid profiles & treatment patterns in patients routinely prescribed LMT, in both primary and secondary care settings. This study is expected to contribute new information on the patterns of treatment in primary and secondary care within the same geographical region as well as cross-country

comparisons of lipid modifying therapy utilisation, which to date have not been reliably quantified. It is expected that these results will estimate the gap between guidelines and clinical practice, in turn helping to inform public health initiatives across Europe; by identifying potential shortfalls in treatment the study will contribute data that could be used in the development of policies towards rectifying suboptimal treatment.

7.1 Diseases and Therapeutic Area

Relevant disease states include cardiovascular disease, diabetes, CKD and others considered to contribute to risk of experiencing a cardiovascular event.

7.2 Rationale

This study is designed to facilitate assessment of current treatment choices and lipid profiles in patients with or without established ASCVD, who have been prescribed LMT within 12 months of enrolment into the study. The broad inclusion criteria permit enrolment of patients with established CV disease (defined in Appendix B, including peripheral vascular disease (PVD), ischaemic stroke (IS), and coronary disease) and high risk primary prevention cohorts such as those with diabetes, chronic kidney disease or elevated global risk; this enables description of clinical management across a broad spectrum of indications. The inclusion of patients treated in both primary and secondary care settings allows the description of treatment patterns outside a narrowly selected environment. Consideration of how treatment relates to relevant guidelines provides insight into potential unmet medical need in patients with or without established ASCVD, and at known or unrecognised risk of experiencing a new or recurrent CV event. This study will provide unique insights into contemporary treatment approaches in a diverse pan-European population.

As an exploratory objective, the study will utilise the Patient Activation Measure (PAM-13) to assess patients' level of engagement with their health and condition. The PAM-13 is a widely accepted patient reported outcome measure (PRO) developed at the University of Oregon, USA. It is validated in 22 languages across 30 countries and its use has been widely published (Hibbard et al Health Services Research 2004; Hibbard and Gilburt, The Kings Fund 2014). The level of patient activation (engagement), calculated by the PAM has been shown to correlate with differences in healthcare utilisation and outcomes. Patients with a low PAM score are considered to have low activation, and have poorer health outcomes and are at higher risk for costly utilisation of healthcare resources than patients with high scores. Having information on subgroups with low PAM scores may provide insight into the potential unmet need of

patient education and engagement, to help support patients with the self-management of their prescribed treatment regimes.

7.3 Statistical Inference (Hypothesis)

No formal hypothesis will be tested in this observational study. The aim of the study is to describe the management of patients receiving lipid-modifying therapy. The sample size is expected to enable sufficiently precise estimates of the primary outcome measures to be obtained for each participating country.

8. Research Question and Objectives

Research Question: How are EU patients requiring lipid-modifying therapy routinely managed?

8.1 Primary Objective

To estimate the proportion of subjects in EU primary and secondary care, with or without established ASCVD and receiving LMT, with LDL-C above 2016 Joint ESC Guideline-recommended levels.

8.2 Secondary Objective

To assess clinical characteristics and management of subjects in EU primary and secondary care, with or without established vascular/atherosclerotic disease and receiving LMT.

8.3 Exploratory

Describe patient reported outcome (PRO) score related to self-management of condition (PRO data will be assessed at enrolment, where PROs are able to be implemented as part of an observational study)

9. Research Methods

9.1 Study Design

The study is a multicountry, cross-sectional, observational study of routine clinical management of European patients in primary and secondary care, who may be at elevated risk of cardiovascular event. The cross-sectional design is appropriate to provide a contemporary landscape assessment of the clinical management of this patient population.

All data will be collected at the time of the clinic visit. The subject is considered to have been enrolled when written informed consent has been obtained (if required by local practice), eligibility has been confirmed and subject data entry into the eCRF has begun.

The study electronic database (InForm) is built and provided to sites by Imperial College Trials Unit (ICTU).

There are no formal visits or assessments required as part of the study, although subjects will be invited to complete the PAM 13 questionnaire (Appendix F) if permitted by local practice to do so as part of an observational study. The questionnaire will be self-administered by the subject on a device provided to the site, and subject responses will be downloaded remotely to be scored by the PRO provider (Insignia Health). If a subject is unable or unwilling to complete the PAM 13, the remainder of the subject's study data will still be analysed as normal.

This is a non-interventional, observational study and is not intended to alter the clinical management of patients.

It is intended that at least half of the subjects enrolled will be classified as primary prevention patients, ie, are without established ASCVD. The remainder will be classified as secondary prevention patients (as evidenced by a diagnosis of established ASCVD prior to enrolment).

Enrolment will not be formally stratified by clinical characteristics; site selection (secondary vs primary care physicians) and site enrolment caps will be employed to facilitate enrolment of the required proportion of primary and secondary prevention subjects.

In addition, being cognisant of the paucity of data available on patients with a history of PVD and IS as compared to MI, the optimal enrolment ratio of MI:PVD:IS subjects is 1:2:2. This ratio will be sought by selection of appropriate specialist sites (see Section 9.2.2 below).

9.2 Setting and Study Population

9.2.1 Study Period

At the study level, data spanning the period February 2016 to December 2017 is expected to be captured.

At the individual subject level, data will be captured for up to 14 months (for LDL-C measurement) prior to and including the visit date, and include historical data on previous relevant medical history.

9.2.2 Selection and Number of Sites

Site selection:

- Will be carried out according to normal feasibility and selection processes
- Will evaluate both primary and secondary care sites:
- At least 25% of sites will be primary care
- Secondary care sites will be selected proportionately according to speciality, to enable enrolment of a study population enriched for PVD and IS subjects
- Will require sites to demonstrate the ability to provide adequate study data ie, demographics and CV history, at least one LDL within the pre-specified window, and the previous/current LMT regimen

Selection is based on interest in participation as a study site, and willingness and ability to meet the criteria above, and to comply with the protocol and data entry conventions.

It is expected that approximately 160 sites will be selected, across approximately 18 EU countries.

9.2.3 Subject Eligibility

Inclusion Criteria

- LDL-C measurement within 14 months of enrolment, obtained independently of participation in a clinical trial
- Use of any LMT (may include statin/ezetimibe/fibrate/PCSK9 inhibitor/bile acid absorption inhibitor/nicotinic acid/other) at time of enrolment, or any LMT prescribed within 12 months prior to date of enrolment, or any LMT prescribed at date of enrolment
- Age $\geq$ 18 years at enrolment
- Provided informed consent/notified according to local requirements
- Subject expected to survive for at least 1 year after enrolment

Exclusion Criteria

- Diagnosis of FH and with history of CV event
- Currently receiving therapy for carcinoma (excepting squamous epithelial cell)
- Known HIV positive status
- Pregnant or breastfeeding at time of enrolment
- Participating in an interventional clinical trial within 6 months prior to enrolment

9.2.4 Matching

Not applicable

9.2.5 Baseline Period

Not applicable

9.2.6 Study Follow-up

Not applicable

9.3 Variables

Individual site characteristics:

- Primary care/ secondary care/ speciality
- Number of patients with each relevant study indication seen per year
- Number of patients with each relevant study indication who are prescribed LMT during the conduct of the study
- Lipid guidelines followed at site (and if Yes then which ones)
- Previous/current experience of lipid-lowering RCT conduct

Subject level:

- Referral to study physician (eg referred from specialist or GP, and date referred)
- Demographics (gender, age at enrolment, ethnicity if permitted to record)
- Relevant medical history (CV events including dates, known risk factors [smoking, family history], diabetic/hypertension/renal/rheumatoid arthritis status, vascular bed involvement)
- Participation in a clinical study within previous 12 months
- Height/weight/BP/waist circumference
- Lipid profile (including fasting status) (total cholesterol, LDL, HDL, non-HDL, triglycerides, Lp(a), apo B100, apo A1), HbA1c, plasma glucose (including fasting status)
- LMT (type, dose, dose frequency, duration of prescription) at enrolment; in 12 months prior to enrolment, up to and including enrolment date
- History of intolerance to higher doses than currently, or to other statins
- Reason for prescription if non-ASCVD (eg diabetic, CKD, subject request)
- Other concomitant therapies of interest (antihypertensives, antidiabetics, antiplatelets, acetylsalicylic acid)

9.3.1 Exposure Assessment

Not applicable.

9.3.2 Outcome Assessment

Primary Outcome Measure:

LDL-C measurement most recent to enrolment (within previous 14 months)

Secondary Outcome Measures:

- Lipid levels (total cholesterol, non-HDL-C, HDL, triglycerides, Lp(a), apo B100, apo A1) most recent to enrolment (within previous 14 months)
- Use of LMT (type, dose, frequency) including combination therapy, in 12 months prior to enrolment, up to and including enrolment date
- Clinical characteristics at time of enrolment as assessed in relation to:
  - FH status (diagnosed/ not diagnosed)
  - CV history (see Appendix B for a list of diagnoses/events)
  - Diabetic status (diabetic/not diabetic; Type 1 or Type II)
  - CKD status (stage, if applicable)
  - CV Risk scores

Exploratory Outcome Measure:

PAM 13 score

9.3.3 Covariate Assessment

Not applicable

9.3.4 Validity and Reliability

Study variables stated in this protocol are objective, and relevant to the question under study. Variables are parameters which are routinely measured as part of clinical management of patients considered or suspected to be at elevated risk of CV event.

9.4 Data Sources

Data will be provided by study site staff, utilising subject medical notes to abstract information in order to complete eCRFs in the electronic study database ('InForm'), which will be provided by ICTU. Sites participating in the study will be fully trained by ICTU in data entry and use of InForm and eCRFs.

9.5 Study Size

The primary outcome measure for the study allows estimation of the percentage of study subjects with LDL-C level above 2016 Joint ESC Guideline-recommended levels. The planned sample size for the study is approximately 6000 subjects across up to 18 countries; the number of subjects enrolled per country will vary according to size of country population and is not anticipated to be fewer than 200 subjects per country.

The sample size is expected to enable precise estimates of the primary outcome measure to be obtained for each participating country.

Table 2 shows the expected precision of the primary outcome measure for subgroups of the full study population, assuming that 50% of subjects achieve the guidelines-recommended LDL-C levels (50% chosen as this results in the widest confidence interval). Sample sizes of 70-150 represent the potential size of cohorts of primary prevention or secondary prevention subjects within a country, while sample sizes of 200-300 represent the potential size of country cohorts.

Table 2. Estimated Precision of Primary Outcome Measure For a Range of Sample Sizes

Sample size	½ width of 95% CI
70	11.7
100	9.8
130	8.6
150	8.0
200	6.9
250	6.2
300	5.7

9.6 Data Management

Data are abstracted by site staff from subject notes into InForm, the electronic database provided by ICTU. ICTU will provide protocol-specific training to all site staff delegated to abstract subject data. An eCRF Completion Guideline is provided.

The Amgen and ICTU representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected. This may also take place remotely by ICTU, as specified by the monitoring plan.

The Clinical Monitor or designee is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The Clinical Monitor, or designee is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic, with the exception of reporting of safety events which are to be recorded on a paper form and submitted via fax directly to Amgen (see Section 11.2):

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a central clinical data management review is performed at regular intervals on subject data received at ICTU. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in InForm for site resolution and closed by the ICTU monitor.
- Only the Principal Investigator may sign the Investigator Sign Off page for this study. This signature indicates that the Investigator inspected or reviewed the data on the eCRF, the data queries and site notifications, and agrees with the content.

9.6.1 Obtaining Data Files

N/A

9.6.2 Linking Data Files

N/A

9.6.3 Review and Verification of Data Quality

Automatic edit checks within InForm and further manual review by ICTU help to ensure quality and completeness of the data. Data queries are sent to site electronically by ICTU for clarification and resolution of discrepancies.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis

An Interim Analysis may be conducted by Q1 2018 if required for Congress abstract submission.

9.7.1.2 Primary Analysis

The primary analysis will be conducted after completion of enrolment.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

All summaries of the data will be descriptive in nature. No imputation of missing data is planned. A sensitivity analysis to explore the effect of influential subgroups (eg country, clinical characteristics) on the primary outcome measure may be conducted, if appropriate.

Subject demographics, baseline characteristics and PRO scores will be summarised. For categorical variables the frequency and percentage, with 95% confidence interval, will be given.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

Outcome measures may be presented by country and/or by study site type and/or by subject clinical characteristics, if sample size permits meaningful analysis.

Outcome measures may also be presented by different levels (eg, quartiles) of risk measures (eg REACH, SCORE, QRISK2).

Exploratory analysis will be conducted to identify which characteristics may be associated with subjects being in target, and which may be associated with subjects failing to achieve the LDL-C target.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing/incomplete data is a possibility on this study, but is not expected to be significant: Subjects are likely to be followed regularly by their physicians and the variables collected in the eCRF are those captured as part of routine care of this patient population. The feasibility process is intended to identify sites which can provide key inclusion/exclusion data for the study, including key analysis variables (LDL-C, LMT).

No imputation of missing data is planned.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrolment

All eligible patients at each study site will be invited by the Investigator to provide informed consent to be enrolled into the study, in chronological order of presenting for a routine visit.

9.7.2.3.2 Description of Subject Characteristics

Subjects are adult patients who have been prescribed lipid-modifying therapy as part of routine treatment at primary and secondary care centres in Europe, and who provide informed consent to participate in the study.

Inclusion criteria have been written to be as inclusive as possible of this population.

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Outcome Measures

9.7.2.4.1 Analysis of Primary Outcome Measure

Summaries displaying the frequency and percentage with 95% confidence interval will be presented for LDL-C within or above the 2016 Joint ESC Guideline-recommended targets. Subjects will be presented overall and split into subgroups with and without established ASCVD.

Subjects included in the secondary prevention cohort will fulfil the following:

- Documented history of MI or revascularisation (peripheral, carotid or coronary), ischaemic stroke, or symptomatic PVD, as defined in Appendix B, except for patients diagnosed with familial hypercholesterolaemia (FH).
- Subjects without a history of MI or revascularisation are eligible if they have DOCUMENTED angiographic evidence of atherosclerosis defined as ≥ 30% stenosis in at least one coronary artery using either standard coronary angiography or CT coronary angiography.

9.7.2.4.2 Analysis of Secondary Outcome Measures

Summaries displaying frequency and percentage, with 95% confidence intervals, will be presented for clinical characteristics (ASCVD components, FH, diabetes, CKD) and for subjects receiving maximally tolerated dose of statins. Also, summaries will be presented for subjects receiving maximally tolerated dose of statin and subjects receiving high, moderate or low intensity statin where LDL-C is above guideline stipulated levels.

Summary statistics displaying the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum will be presented for lipid levels (total cholesterol, LDL-C, HDL-C, non-HDL-C,

triglycerides, Lp(a), apo B100, apo A1) and for CV risk scores (REACH, SCORE and QRISK2).

Summaries displaying frequency and percentage, with 95% confidence intervals, will be presented for use of lipid lowering therapies (subdivided by type, dose, frequency).

To further investigate predictive factors for subjects not achieving target LDL levels, the proportion (frequency, percentage and 95% confidence intervals) of subjects achieving target LDL levels will be presented by subgroups; demographics, clinical characteristics, site characteristics, country or region.

9.7.2.4.3 Exploratory Outcome Measure

Descriptive summaries of PAM 13 scores will be presented.

9.7.2.5 Sensitivity Analysis

A sensitivity analysis to explore the effect of influential subgroups (eg country, clinical characteristics) on the primary outcome measure may be conducted, if appropriate.

9.7.2.5.1 Subgroup Analysis

Subgroup analysis will be conducted to be supportive of the analysis of the primary, secondary and exploratory endpoints. The subgroup analysis will be the planned analysis stratified by country.

9.7.3 Analysis of Safety Outcomes

No formal analysis of Safety data is planned for this study.

9.8 Quality Control

Source data verification will be performed at the study site, in accordance with ICTU SOPs.

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from ICTU, Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRF, informed consent forms, as applicable, and subject identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the IRB/IEC or other relevant ethical review board and ICTU

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with ICTU.

Amgen retains all data, programmes and outputs generated for the study. At data cleaning completion, data are uploaded from InForm, transferred to Amgen and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Information Bias

For the primary objective, information bias is not anticipated to be applicable, as having an LDL-C measurement within the 14 months preceding enrolment is an Inclusion criterion; if several measurements are available then the two most recent to enrolment will be reported and used in the study analysis.

For the secondary objectives, LMT use is an Inclusion criterion so reliable prescription details will be known and reported by the Investigator. It is also expected that Investigators will be well aware of variables concerning the secondary objectives around clinical characteristics and other laboratory values, as typically these are well documented and the subjects will be known to the Investigators.

Information bias may arise in recording reasons for LMT regimen change and/or history of statin intolerance, as these are more liable to be subjective and based on individual judgement; accurate and truthful reporting is encouraged in the eCRF through provision of a range of pre-populated response options and a free text field for Investigator comments. Interpretation of these objectives should take these factors into account.

9.9.1.2 Selection Bias

Inclusion/exclusion criteria are sufficiently broad to allow enrolment of a variety of subjects, although the potential difficulty in achieving the ideal balance of primary and secondary prevention subjects, whilst enriching for PVD and IS subjects, from primary and secondary care sites, is acknowledged. Care in site selection, as described in Section 9, is critical to success in this regard.

At the site level, to avoid enrolment bias via selective invitation of a particular subject profile to participate in the study, all eligible patients will be invited to enrol in chronological order of attending the clinic, until the local enrolment cap has been reached. This also minimises selection of study subjects based on Investigator preference.

9.9.1.3 Confounding

N/A

9.9.2 External Validity of Study Design

The broad eligibility criteria are intended to prevent exclusion of particular disease groups and to encourage enrolment of as diverse a subject population as possible. The geographic spread (across approximately 18 EU countries) and inclusion of subjects from both primary and secondary care are designed to provide a representative sample of EU patients receiving lipid modifying therapy. The study population will comprise both primary and secondary prevention subjects, of differing CV risk, and the intent is that this study sample reflects the wider background population who are prescribed LMT. However, regional health authorities' access policies will determine which patients are eligible for LMT prescription, and this will have a bearing on the clinical characteristics of subjects in different locations. In addition, the study will not enrol patients receiving LMT but who do not have a recent (within 14 months) LDL-C measurement, so will miss patients who may be less well managed in routine care. As the primary objective of the study is to provide a picture of contemporary lipid management to ESC target, this limitation is unavoidable and will be taken into account in interpretation of the data.

9.9.3 Analysis Limitations

See Section 9.9.4 below.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Missing/incomplete data is a possibility on this study, but is not expected to be significant: Key variables of LDL-C and LMT are inclusion criteria so cannot be missing.

Subjects are expected to be followed closely by their specialist physicians and the variables collected in the eCRF are those captured as part of routine care of this patient population. Additionally, ICTU will review all study data thoroughly on an ongoing basis throughout the study conduct period, and will follow up directly with study sites to query for information which seems to be missing from InForm.

9.10 Other Aspects

N/A

10. Protection of Human Subjects

10.1 Informed Consent

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the ICTU Study Manager to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a subject, to the subject's participation in the study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from ICTU to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study, and before any protocol-specific activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a subject/patient, to the subject's/patient's participation in the study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, as applicable, other written subject/patient information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol, and informed consent form, as applicable must be received by ICTU before the study can be initiated.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other safety event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval /renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to ICTU.

10.3 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to ICTU.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- Documents that are not for submission to ICTU (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

Subject to compliance with local country regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the sponsor, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the subject's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obliged to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11. Collection of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

In this study, the collection, recording and reporting of safety information (adverse events, product complaints and other safety findings) is required only for subjects exposed to Repatha®. See below for further details.

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product(s), or medical device, whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product (ie, is an adverse drug reaction) prior to reporting the adverse event to Amgen.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalisation meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse drug reaction) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorised use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. This study will collect only those product complaints related to Repatha® use.

11.2 Safety Reporting Requirements

The Investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur in the 14 months prior to or at time of enrolment into the study are collected and recorded in the subject's appropriate study documentation. Safety events must be submitted as individual case safety reports via the Amgen Primary Data Collection Safety Reporting Form (paper-based form) within 1 business day of investigator's awareness. Safety events that are suspected to be related to any

medicinal product other than Repatha® should be reported to the local authority in line with the local country requirements.

See Appendix C for a sample of the Primary Data Collection Safety Reporting Form (paper-based form), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Worksheets.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study forms where safety data may also be recorded (eg, Primary Data Collection Safety Reporting Form or Pregnancy and Lactation Notification Worksheet).

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to ICTU.

Amgen reserves the right to terminate the study at any time. Amgen, ICTU and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to ICTU.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

The intent is to publish the results from this study. Publication may be in the form of Congress abstracts or posters, and/or manuscript(s).

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. References

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15. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. Components of Clinically Evident Cardiovascular Disease

- Myocardial infarction:

  STEMI

  NSTEMI

- Revascularisation:

  Carotid surgery (carotic endarterectomy or stenting)

  Coronary Artery Bypass Graft (CABG)

  Peripheral vascular disease surgery (stenting, bypass)

  Percutaneous Coronary Intervention (PCI)

- Ischaemic stroke (confirmed by imaging)

- Peripheral arterial disease:

  Symptomatic claudication

  Claudication (ankle brachial indices, angiography)

Appendix C. Sample Primary Data Collection Safety Reporting Form

Project ID: 20150333 *Repatha® (evolocumab)*	AMGEN	**Safety Reporting Form** Primary Data Collection	Date of Report:
		Fax reports to: Amgen Local Office: *<<applicable Local Amgen Office Fax Number here>>*	

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details

name	phone	fax
address		
city	state/province	
postal code	country	

3. Reporter ID

Name or ID	phone	fax
address		
city	state/province	
postal code	country	

4. HCP Contact Details (if other than reporter)

name		
country		
address		
city	state/province	postal code
phone	fax	

5. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

6. Medical History (include primary diagnosis)

7. Suspect Product Information (include dosing details)

Product: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq.

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial size

8. AE, other safety finding, or product complaint information — HCP ONLY

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: _____ (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx _____ (provide discharge summary); Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard	Action Taken: 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug rechallenge (state outcome)	Outcome: 1=resolved 2=resolved w/ sequelae 3=resolving	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/ Device: Is there a reasonable possibility that this event may have been caused by the Product/ Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of _____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
For vendor surveys of Health Care Professionals

FORM-067756 Ver. #: 3.0 Effective date: 07-Jul-2014 Page 1 of 1 ADR Form Created: 07-FEBRUARY-2017

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix E. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax (_____)**_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm_____ / dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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Appendix F. PAM 13 Questionnaire

Level 1	When all is said and done, I am the person who is responsible for taking care of my health
	Taking an active role in my own health care is the most important thing that affects my health
Level 2	I am confident I can help prevent or reduce problems associated with my health
	I know what each of my prescribed medications do
	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.
	I am confident that I can tell a doctor concerns I have even when he or she does not ask.
	I am confident that I can follow through on medical treatments I may need to do at home
	I understand my health problems and what causes them.
Level 3	I know what treatments are available for my health problems
	I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising
	I know how to prevent problems with my health
Level 4	I am confident I can figure out solutions when new problems arise with my health.
	I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress.