Summary Table of Study Protocol

Title	Characterizing Repatha use among adult pregnant women, adult women of childbearing age and within the adult general population
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Date of last version of the protocol	09 May 2019
EU Post Authorization Study (PAS) Register No	NA
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Medicinal Product	Repatha
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	To describe the use of Repatha among adult (≥16 years of age) pregnant women, adult women of childbearing age (16-54 years) and within the adult general population.
Country(ies) of Study	United States
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Marketing Authorization Holder

Marketing authorization holder(s)	Amgen, Inc.
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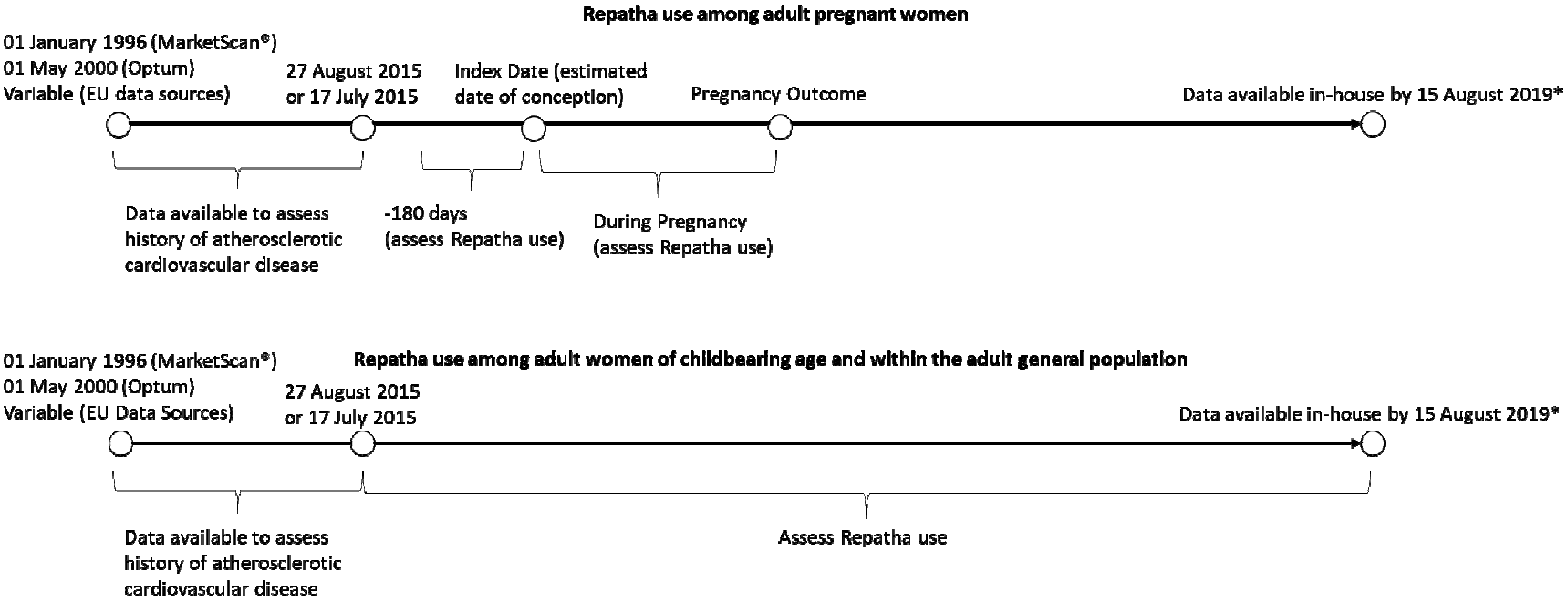
Study Design Schema



*We anticipate having data available as follows:
MarketScan® = 30 September 2018
Early View MarketScan® = 30 June 2019
Optum = 31 March 2019
EU Data Sources = Variable

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2. List of Abbreviations

Acronym	Definition
AMI	Acute Myocardial Infarction
ASCVD	AtheroSclerotic Cardiovascular Disease
CABG	Coronary Artery Bypass Grafting
CfOR	Center for Observational Research
EDC	Estimated Date of Conception
FDA	Food and Drug Administration
HoFH	Homozygous Familial Hypercholesterolemia
ICMJE	International Committee of Medical Journal Editors
IS	Ischemic Stroke
LDL-C	Low-Density Lipoprotein Cholesterol
MEPREP	Medication Exposure in Pregnancy Risk Evaluation Program
PCI	Percutaneous Coronary Intervention
PCSK9i	Proprotein Convertase Subtilisin Kexin type 9 inhibitor
TIA	Transient Ischemic Attack
UA	Unstable Angina

3. Responsible Parties

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4. Abstract

- Study Title:

  Characterizing Repatha use among adult pregnant women, adult women of childbearing age and within the adult general population

- Study Background and Rationale:

  Repatha (evolocumab) is a proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) antibody indicated to (1) reduce the risk of myocardial infarction, stroke and coronary revascularization in adults with established cardiovascular disease (2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including

heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C) and (3) as an adjunct to diet and other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Repatha was approved by the United States Food and Drug Administration (FDA) on August 27th, 2015 and, as part of that approval, was given a post-marketing requirement to create a prospective registry to study the use of Repatha during pregnancy. To date, this United States based registry has enrolled 0 pregnant women exposed to Repatha. Thus, the purpose of this study is to evaluate the use of Repatha among adult (≥16 years of age) pregnant women, adult women of childbearing age (16-54 years) and overall in the adult general population. This analysis will help to better understand the adoption of Repatha in the overall population and specifically in the prospective registry target population.

- Research Question and Objective(s):

Objectives	Endpoints
Primary	
• To describe the use of Repatha among adult (>16 years of age) pregnant women, adult women of childbearing age (16-54 years) and within the adult general population	• Counts and proportions of Repatha use in each of our three cohorts

  - Hypothesis(es)/Estimation

    This is a descriptive study. No formal hypotheses will be tested.

- Study Design/Type:

  Retrospective Cohort Study

- Study Population or Data Resource:

  We will utilize data from two United States based healthcare claims databases. These databases are the IBM Watson Health MarketScan® Commercial Claims and Encounters with Medicare Supplemental Research Database (i.e., MarketScan®) and the UnitedHealth Group Optum Analytics (i.e., Optum). Included in our MarketScan® database assessment will be the Early View MarketScan® data, which will allow us to capture the most recent medication claims (including Repatha) and a preview of hospital claims (e.g., obstetrics to identify births). Additionally, we will utilize multiple data sources from the European Union (EU) that cover countries including the United Kingdom (Clinical Practice Research Datalink), Germany (IMS

Germany Disease Analyzer Electronic Medical Records), Denmark (Danish Health Data Authority), Sweden (Swedish National Board of Health and Welfare) and Norway (Norwegian Institute of Public Health Prescription Database). Data will be available as early as January 01, 1996 (in MarketScan®) and May 01, 2000 (in Optum) to allow for an assessment of history of atherosclerotic cardiovascular disease (ASCVD). Follow-up data will be available based on access and integration into the in-house Amgen analytic platform by August 15, 2019. We anticipate that we will have data available in MarketScan® through September 30, 2018, Early View MarketScan® through June 30, 2019 and Optum through March 31, 2019 to assess Repatha exposure and to identify our cohorts of interest. Data availability from the EU countries will vary based on data source.

- Summary of Patient Eligibility Criteria:

  Inclusion Criteria:

  Pregnant Women Cohort

  - Female
  - 16 years of age or older (as of August 27, 2015 or July 17, 2015)
  - Have at least one birth (live or non-live) claim during the study period (August 27, 2015 or July 17, 2015 until the end of available data)
  - Have continuous medical and pharmacy health insurance coverage during the 480 days (includes up to 300 pregnancy days + 180 days prior to the estimated date of conception) prior to the birth claim, with an allowable 45-day gap in coverage. See Appendix A for cohort creation.

  Women of Childbearing Age Cohort

  - Female
  - 16 to 54 years of age (as of August 27, 2015 or July 17, 2015)

  General Population Cohort

  - 16 years of age or older (as of August 27, 2015 or July 17, 2015)

- Follow-up:

  Patients will be followed from the time they are eligible to enter the cohort (i.e., meet the inclusion criteria for one of the cohorts above, as early as August 27, 2015 (for US specific analyses) or July 17, 2015 (for EU specific analyses)) through the end of available data or loss to follow-up, whichever occurs first.

- Variables:
  - *Outcome Variable(s)*

    No outcomes will be assessed

- *Exposure Variable(s)*

  At least one pharmacy dispense record (using all available NDC codes) for Repatha

- *Other Covariate(s)*

  Age

  Gender (general population cohort only)

  Calendar Year

  History of ASCVD* including:

  Acute Myocardial Infarction (AMI)

  Unstable Angina (UA)

  Ischemic Stroke (IS)

  Percutaneous Coronary Intervention (PCI)

  Coronary Artery Bypass Grafting (CABG)

  Cerebrovascular disease

  Transient Ischemic Attack (TIA)

  Aneurysm

  Carotid Endarterectomy

  Carotid / Vertebral / Basilar Stenting

  Coronary Atherosclerosis / Angina / Old AMI

  Endovascular Stent Graft

  Arterial Bed Atherosclerosis (not previously defined)

  Pregnancy Trimester of Exposure (pregnancy cohort only)

  *History of ASCVD will be identified using ICD-9-CM, ICD-10-CM and CPT codes.

  Familial Hypercholesterolemia (EU specific analyses)

- Study Sample Size:

  This is a descriptive study with the primary objective being to determine the sample size (Repatha exposure) in of each of our three cohorts.

- Data Analysis:

  We will estimate the number of exposures (how many separate exposures; separate exposures defined as a >30-day gap in Repatha use), duration of each exposure(s) (how many months of Repatha exposed; cumulative and by each exposure) and frequency of dosing (how many pharmacy dispense records for Repatha; cumulative and by each exposure) of Repatha within each of our three cohorts of interest (pregnant women, women of childbearing age and general population). Among those exposed to Repatha, we will further characterize these patients by age, calendar

year of exposure(s), history of ASCVD (yes/no), gender (for the general population only) and by trimester of exposure(s) (for the pregnant women cohort only).

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Repatha (evolocumab) is a proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) antibody indicated to (1) reduce the risk of myocardial infarction, stroke and coronary revascularization in adults with established cardiovascular disease (2) as an adjust to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C) and (3) as an adjunct to diet and other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

6.2 Rationale

Repatha was approved by the United States Food and Drug Administration (FDA) on August 27th, 2015 and, as part of that approval, was given a post-marketing requirement to create a prospective registry to study the use of Repatha during pregnancy. To date, this United States based registry has enrolled 0 pregnant women exposed to Repatha. Thus, the purpose of this study is to evaluate the use of Repatha among adult ($\geq$16 years of age) pregnant women, adult women of childbearing age (16-54 years) and overall in the adult general population. This analysis will help to better understand the adoption of Repatha in the overall population and specifically in the prospective registry target population.

6.3 Statistical Inference (Estimation or Hypothesis[es])

This is a descriptive study. Although the adult general population cohort will be used as a baseline for overall Repatha use, no formal hypothesis testing will be performed to compare the use of Repatha across our three cohorts (pregnant women, women of childbearing age and general population).

7. Research Question and Objectives

7.1 Primary

To describe the use of Repatha among adult (≥16 years of age) pregnant women, adult women of childbearing age (16-54 years) and overall in the adult general population.

8. Research Methods

8.1 Study Design

We will utilize a retrospective cohort study design.

8.2 Setting and Study Population

We will identify three cohorts of patients. The first is a cohort of adult (≥16 years of age) pregnant women. The second is a cohort of adult women of childbearing age (ages 16-54 years). The third is a cohort of adults in the general population.

8.2.1 Study Period

The study period will be from August 27, 2015 (the date Repatha entered the United States market) until March 31, 2019 (Optum), September 30, 2018 (MarketScan®) or June 30, 2019 (Early View MarketScan®), given the data are available within the in-house Amgen analytic platform. However, data will be available as early as January 01, 1996 (MarketScan®) or May 01, 2000 (Optum) to ascertain history of ASCVD. Data availability from the EU countries will vary based on data source, however, the study period will begin on July 17, 2015, the date Repatha entered the market in the EU.

8.2.2 Subject/Patient/Healthcare Professional Eligibility

8.2.2.1 Inclusion Criteria

Pregnant Women Cohort

- Female
- 16 years of age or older (as of August 27, 2015 or July 17, 2015)
- Have at least one birth (live or non-live) claim during the study period (August 27, 2015 or July 17, 2015 until the end of available data)
- Have continuous medical and pharmacy health insurance coverage during the 480 days (includes up to 300 pregnancy days + 180 days prior to the estimated date of conception) prior to the birth claim, with an allowable 45-day gap in coverage. See Appendix A for cohort creation.

Women of Childbearing Age Cohort

- Female
- 16 to 54 years of age (as of August 27, 2015 or July 17, 2015)

General Population Cohort

- 16 years of age or older (as of August 27, 2015 or July 17, 2015)

8.2.2.2 Exclusion Criteria

None.

8.2.3 Matching

None.

8.2.4 Baseline Period

Data will be available as early as January 01, 1996 (MarketScan®) or May 01, 2000 (Optum) to ascertain history of ASCVD. However, identification of study subjects will begin on August 27, 2015, the date Repatha entered the United States market. Data availability from the EU countries will vary based on data source. Identification of study subjects in the EU will begin on July 17, 2015, the date Repatha entered the EU Market.

8.2.5 Study Follow-up

Patients will be followed from the time they are eligible to enter the cohort (i.e., meet the inclusion criteria for one of the cohorts above, as early as August 27, 2015 or July 17, 2015) through the end of available data or loss to follow-up, whichever occurs first.

8.3 Variables

8.3.1 Exposure Assessment

Repatha exposure will be defined as at least one pharmacy dispense record for Repatha identified using all available NDC codes.

8.3.2 Outcome Assessment

No outcomes will be assessed.

8.3.3 Covariate Assessment

- Age
- Gender (general population cohort only)
- Calendar Year
- History of atherosclerotic cardiovascular disease (ASCVD)* including:
    - Acute Myocardial Infarction (AMI)
    - Unstable Angina (UA)
    - Ischemic Stroke (IS)
    - Percutaneous Coronary Intervention (PCI)
    - Coronary Artery Bypass Grafting (CABG)
    - Cerebrovascular disease
    - Transient Ischemic Attack (TIA)
    - Aneurysm

- Carotid Endarterectomy
- Carotid / Vertebral / Basilar Stenting
- Coronary Atherosclerosis / Angina / Old AMI
- Endovascular Stent Graft
- Arterial Bed Atherosclerosis (not previously defined)

- Pregnancy Trimester of Exposure (pregnancy cohort only)

*History of ASCVD will be identified using ICD-9-CM, ICD-10-CM and CPT codes.

- Familial Hypercholesterolemia (EU specific analyses)

8.3.4 Validity and Reliability

Within our pregnancy cohort we will be using both ICD-9-CM and ICD-10-CM codes to determine when and for how long each female patient was pregnant. These codes are part of Amgen's internally developed algorithms that are used to match fetal outcomes with pregnant mothers to calculate the estimated date of conception (EDC). Although many of these algorithms have been previously validated (see Appendix A) there may be some issues with the validity and reliability of these codes to accurately measure gestational age. Additionally, we will be using Early View MarketScan® data. These data are distinct from the traditional MarketScan® data in that the in-patient and out-patient diagnoses are not fully adjudicated, which could impact the validity and reliability of the data. Approximately 97% of drug claims, 64% of in-patient services, 65% of facility claims and 74% of professional claims have been adjudicated[1]. For the EU data analyses, all available codes that indicate a pregnancy or a birth outcome among a woman with a claim for Repatha will be described (see Appendix B), when available and data source dependent.

8.4 Data Sources

We will utilize data from two United States based healthcare claims databases. The first is the IBM Watson Health MarketScan® Commercial Claims and Encounters with Medicare Supplemental Research Database (i.e., MarketScan®). This MarketScan® database captures person-specific clinical utilization, expenditures and enrollment across inpatient, outpatient, prescription drug and carve-out services from a selection of large employer, health plan, and government and public organizations. This database links paid claims and encounters data to detailed patient information across sites, types of providers and over time. The annual medical databases include private sector healthcare data from approximately 100 payers. Historically, more than 500 million claim records are available in MarketScan® and data from over 240 million unique patients

(more than half the United States population) are available since 1995. These data represent the medical experience of insured employees and their dependents for active employees, early retirees, COBRA continuees and Medicare-eligible retirees with employer-provided Medicare supplemental plans. In addition to the standard MarketScan® database we will also have access to the Early View MarketScan® data. This data allows us to capture the most recent medication claims (including Repatha) and a preview of hospital claims (e.g., obstetrics to identify births) within one month of the service date. Most of this data is complete (specifically pharmacy records are at least 97% adjudicated[1]), however, in-patient and out-patient diagnoses may not be fully-adjudicated. This data will, however, provide us with a supplement to the standard MarketScan® database to allow for more recent data capture. The second database is the UnitedHealth Group Optum Analytics (i.e., Optum). The Optum database contains claims and laboratory data from approximately 85 million unique patients beginning on May 01, 2000. This database contains claims and laboratory data received through Optum Insight from UnitedHealth Group. Data include de-identified eligibility, pharmacy, laboratory, medical, and standard pricing data for patients enrolled in a large U.S. health plan which provides fully-insured coverage for physician, hospital and prescription drug services. In addition, it includes data from Medicare patients with Part D only or medical + Part D coverage. Additionally, we will utilize multiple data sources from the European Union (EU) that cover countries including the United Kingdom (Clinical Practice Research Datalink), Germany (IMS Germany Disease Analyzer Electronic Medical Records), Denmark (Danish Health Data Authority), Sweden (Swedish National Board of Health and Welfare) and Norway (Norwegian Institute of Public Health Prescription Database). One of these data sources, Clinical Practice Research Datalink (CPRD), utilizes data from the United Kingdom (UK) National Health Service (NHS) observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). CPRD linkages allow primary care data to be linked with secondary care (specialist) and hospitalization data. CPRD has access to Office for National Statistics (ONS) complete central mortality data. The record contains both the date and the cause of death. The main primary care database held by CPRD is known as GOLD (formerly GPRD). GOLD contains the anonymous, longitudinal medical records of patients registered with contributing primary care practices across the UK. The GOLD database covers approximately 8.5% of the UK population, including practices in England, Scotland, Wales and Northern Ireland. As of September 2013, there were 13.1 million

acceptable (research quality) patients in GOLD, of which 5.4 million were active (still registered with a contributing general practitioner (GP) practice). Data has been collected from GP practices since 1987. CPRD GOLD contains patient registration information and all care events that general practice staff record in order to support the ongoing clinical care and management of their patients. This includes demographic information (age, sex, weight etc.), records of clinical events (medical diagnoses), referrals to specialists in secondary care settings, prescriptions issued in primary care, immunization/vaccination records, diagnostic testing, lifestyle information (e.g. smoking and alcohol status), and other types of care administered as part of routine general practice. Furthermore, once anonymized, free text notes which are routinely entered into the comment field of the electronic patient record can also be accessed.

8.5 Study Size

This is a descriptive study with the primary objective being to determine the sample size (Repatha exposure) in of each of our three cohorts.

8.6 Data Management

8.6.1 Obtaining Data Files

MarketScan®, Optum, IMS Germany Disease Analyzer Electronic Medical Records and CPRD databases are available to Amgen as part of the Center for Observational Research (CfOR) Real World Data platform. The remaining EU data sources are publicly maintained.

8.6.2 Linking Data Files

The MarketScan® database links paid claims and medical encounter data to detailed patient information across sites in the United States. Enrollees are provided with a unique identifier that allows the data linkage. These identifiers are maintained, even if the patient changes health plans while working with the same employer. The data that will be used for this study has already been linked. The Optum database includes de-identified data and no additional linkage will be completed for this study. However, we will be using previously linked mother and infant pairs. Algorithms for linking mothers and their infants in administrative data have been validated in the MarketScan® Databases and other claims databases[2–7]. Linking mother and baby claims is necessary to obtain information on medication exposure during pregnancy, since the infant has no individual pharmacy claims until after birth. Insurance identification numbers typically consist of an encrypted Social Security Number for the primary insured person, plus an additional number for each dependent covered under the primary insured's plan. We will

be using the same methods to link mothers and infants as was developed by FDA Sentinel pregnancy module[8]. The EU databases have variable linking techniques. For CPRD, primary care data is linked with secondary care (specialist) and hospitalization data. CPRD also has access to Office for National Statistics (ONS) complete central mortality data. This record contains both the date and the cause of death.

8.6.3 Review and Verification of Data Quality

The MarketScan® databases are constructed through collection and standardization of raw data from the appropriate payers. File linking is completed across time and data type to create a comprehensive and efficient set of database tables. Variables specific to employers are added, as are details on clinical information such as therapeutic class and group and generic product identifier. Other enhancements are made to improve the data quality and efficiency, for example: updating diagnosis and procedure codes to reflect changes in codes over time if necessary; creating a common synthetic patient identifier that enables patients to be tracked over time and across data types; integrating benefit plan characteristics, enrollment, outpatient pharmaceutical claims, and medical/surgical data, etc. A comprehensive series of edits on the reasonableness and validity of the data are conducted. For example, checking diagnosis against age and gender, checking charge against payment, checking zip codes, diagnosis and procedure codes against lists of valid values, etc. Data are collected when close to 100% of claims have been paid, which results in a lag time between date of service and date of payment of about 6 months. The Optum Insight's de-identified Clinformatics Datamart (Eden Prairie, MN, USA) is an administrative claims database for members of United Healthcare who were enrolled in commercial plans (including ASO, 36.31 M) that included both medical and prescription drug coverage. Source codes used in Optum include: conditions: ICD-9-CM; drugs: NDC, HCPCS, ICD-9-CM; procedures: CPT-4, HCPCS, ICD-9-CM; laboratory: LOINC. For the EU data sources, the data quality has been well documented in the literature. Specifically, for CPRD, the documentation suggests that most exposures or diagnoses are of high research quality (CPRD, 2014; Herrett et al., 2010; Khan et al., 2010). No data editing, beyond what is applied in the database production process, will be employed for this study.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

We will estimate the number of exposures (how many separate exposures; separate exposures defined as a >30-day gap in Repatha use), duration of each exposure(s) (how many months of Repatha exposed; cumulative and by each exposure) and frequency of dosing (how many pharmacy dispense records for Repatha; cumulative and by each exposure) of Repatha within each of our three cohorts of interest (pregnant women, women of childbearing age and general population). Among those exposed to Repatha, we will further characterize these patients by age, calendar year of exposure(s), history of ASCVD (yes/no), gender (for the general population only) and by trimester of exposure(s) (for the pregnant women cohort only).

8.7.2 Planned Method of Analysis

This is a descriptive study. There are no primary or secondary outcomes.

8.7.2.1 General Considerations

This study is descriptive. Only summary statistics will be produced in the form of n's/% or means/medians/standard deviations for duration of exposure.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Patients will be identified according to diagnosis, procedure, and medication codes. Therefore, our study will only capture patients to the extent that the two databases are appropriately populated with the appropriate codes.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Patients will be identified according to meeting the inclusion criteria for one of the three cohorts: (1) being an adult (≥16 years of age) pregnant woman (2) being an adult woman of childbearing age (16-54 years) or (3) being an adult in the general population. There are no exclusion criteria. We will assess all information that is available.

8.7.2.3.2 Description of Subject/Patient Characteristics

Patients will either be adult (≥16 years of age) pregnant women, adult women of childbearing age (16-54 years) or adults in the general population identified in one of our two databases. Further information on subject/patient characteristics will be explored as part of this study.

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Not applicable.

8.7.2.5 Sensitivity Analysis

Not applicable.

8.7.2.5.1 Subgroup Analysis

Not applicable.

8.7.2.5.2 Stratified Analysis

Not applicable.

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

8.7.2.5.4 Other Sensitivity Analysis

Not applicable.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Safety data will not be collected or analyzed in this study.

8.8 Quality Control

Please see section 9.6.3 “Review and Verification of Data Quality”

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

There is the possibility of exposure misclassification in this study (i.e. drug use is misclassified as occurring/not occurring during pregnancy). First, while a patient may have a prescription claim for a medication, we are unable to verify that the patient used the medication. Thus, we will also count the number of Repatha prescriptions, knowing that multiple prescriptions will increase the likelihood that the patient took the drug. Second, the pregnancy period is estimated based on ICD-9-CM and ICD-10-CM codes for gestational age assigned at birth. This gestational age algorithm was developed by the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) and other Sentinel and non-Sentinel pregnancy-related projects (see Appendix A). Each gestational age code is assigned an associated pregnancy duration and priority. If a code is observed within a requester defined window before and after delivery, the duration associated with the code is used to calculate pregnancy duration. If multiple codes are observed, priority is used to determine appropriate duration. If no codes are observed, the requester defines the number of days used to define pregnancy duration.

Because only a small percentage of deliveries are matched to gestational age-specific claims, the remainder are assigned as standard gestational age of 273 days. Additionally, some codes provide a 2-week range for gestational age (e.g. 27–28 completed weeks of gestation) in which case the higher number of weeks are assigned. Thus, a woman who is 27 weeks into her pregnancy at delivery would be assigned an additional week of pregnancy. Any drug use occurring during that week would be incorrectly counted as occurring during pregnancy, when it is occurring during the pre-pregnancy period. Similarly, mismeasurement of gestational age could also result in misclassification of drug use by trimester. Additionally, there may be misclassification of FH (with respect to the EU analyses examining FH) due to misdiagnosis, as FH is widely thought to be under-diagnosed. However, it is unlikely that patients will be diagnosed with FH who do not have FH.

8.9.1.2 Selection Bias

We may have some selection bias in our pregnancy cohort, as we use a mother-to-child linkage algorithm to identify our pregnant women (see section 8.6.2). In MarketScan® and Optum the generation of mother-infant pairs is dependent on the infant being covered under the same insurer as the mother, and our mother-infant linkage algorithm could only link about 77% of live-born infants to their mothers (based on a completed exploratory analyses) and about 87% in Optum. For example, using 2011 Optum data, we identified 92,497 infants with a family ID that linked to a relative other than the mother. Additionally, in MarketScan®, the mothers that we were able to match with their infant were older (mean age=32.1 years) than the unmatched mothers (mean age= 27.2 years). It is likely that the younger mothers in this case are covered by their parents' health insurance. Other than age, we did find that the matched mothers were comparable to the unmatched mothers regarding geographic region, gestational age, and occurrence of pharmacy dispensation during pregnancy. In both Optum and MarketScan®, the generation of mother-infant pairs requires a common insurance provider between mother and infant via family ID (derived from the insurance policy holder) and the earliest delivery date year is required to match that of the infant's birth year. If the mother had a delivery in December 2014 for example, and the infant claim appeared in January of 2015, then those records would not be linked using this approach. It's possible that a live delivery occurred yet was captured by linkage to another relative via family ID. Additionally, for any EU analyses that examine FH, it is possible that a number of patients with FH diagnoses will not be identified. For example, CPRD is broadly representative of the UK general population, and has a policy of inviting

practices to participate based on providing representative demographic and socioeconomic inclusion. However, approximately 30% of GP practices do not contribute to CPRD, and it is likely that contributing and non-contributing practices may differ slightly in terms of geography, demographics, socioeconomics and clinical practice. At the time of writing, no publications evaluating the representativeness of CPRD for the entire UK general population were found.

8.9.2 External Validity of Study Design

Please see section 9.4 and 9.9.1.2. The findings of this study are fairly generalizable to insured individuals living in the United States (the source population) but may not be directly comparable to other countries where the use of Repatha is indicated differently. For the EU data analyses, the data may not be generalizable to countries not included in our analyses. However, we expect the findings to be fairly generalizable for assessing Repatha use among pregnant women.

8.9.3 Analysis Limitations

None. This study is descriptive.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Please see section 9.3.4, 9.7.2.2 and 9.9.1.1. As this study is descriptive, if there are missing codes (diagnoses, procedures, medications) we will not be able to report on that data. This could limit our ability to capture pregnant women, use of Repatha and/or accurately determine history of ASCVD. However, as our databases cover all claims from within their patient network, we anticipate missing/incomplete information to be minimal. For the EU databases, specifically CPRD, missing data should be limited due to the comprehensive representation of CPRD via GP practices throughout the UK. At the individual patient level, missingness on a significant scale is not anticipated; data points of interest in this study are basic demographic and health-related parameters, and such key information is likely to be captured in patient records.

8.10 Other Aspects

None.

9. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is analyzing secondary data from administrative healthcare claims and electronic health records and no safety data will be collected.

10. Administrative and Legal Obligations

10.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. Amgen also reserves the right to terminate the study at any time.

11. Plans for Disseminating and Communicating Study Results

The findings from this study will be included in the Repatha United States pregnancy registry three-year futility and feasibility report to be submitted to the FDA in September 2019.

11.1 Publication Policy

The results of this study will not be submitted for publication but will be submitted to regulatory authorities. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. 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 (e.g., 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.

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22. Appendices

Appendix A. Pregnancy Algorithm.

Estimated date of conception for live births

The EDC for live born (LB) infants will be determined using the ICD-10-CM weeks of gestation diagnosis codes (Z3A**) when available. If these codes are not available, a claims-based algorithm validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)[9] that flags pre- and post-term delivery codes which occurred within seven days of a live birth will be used to determine pregnancy duration. Lastly, if these codes are not available, a gestational period of 273 days will be assigned prior to the pregnancy outcome date. For births identified from between August 27, 2015 – September 31, 2015, the EDC for LB infants will be determined using the gestational age at the time of the live-birth delivery and the mother's live-birth delivery date (EDC = live-birth delivery date – gestational age (days)). ICD-9-CM claims-based diagnosis codes will be used to assign the gestational age at delivery in the order of preference listed in the table below.

Table 1. ICD-9-CM diagnosis codes for pre-term and post-term birth and completed weeks of gestation, and their use in the gestational age algorithm*

Hierarchy	ICD 9 CM Diagnosis code	Definition	Algorithm-derived gestational age	
			Weeks	Days
	Pre-Term Birth Codes			
1	765.21	Less than 24 completed weeks of gestation	24	168
2	765.22	24 completed weeks of gestation	24	168
3	765.23	25–26 completed weeks of gestation	26	182
4	765.24	27–28 completed weeks of gestation	28	196
5	765.0–765.09	Extreme immaturity	28	196
6	765.25	29–30 completed weeks of gestation	30	210
7	765.26	31–32 completed weeks of gestation	32	224
8	765.27	33–34 completed weeks of gestation	34	238
9	765.28	35–36 completed weeks of gestation	36	252
10	765.1–765.19	Other preterm infants	35	245
11	765.20	Preterm with unspecified weeks of gestation	35	245
12	644.21	Onset of delivery before 37 completed weeks of gestation	35	245
	Post-Term Birth Codes			
13	645.1x	Post-term pregnancy, delivered, with or without mention of antepartum condition (over 40 weeks to 42 completed weeks gestation)	41	287

14	766.21	Post-term infant (gestation period over 40 weeks to 42 completed weeks)	41	287
15	645.2x	Prolonged pregnancy delivered (pregnancy which has advanced beyond 42 completed weeks gestation)	42	294
16	766.22	Prolonged gestation of infant (gestation period over 42 completed weeks)	42	294
	Normal Term Codes			
17	NA	Without any of the codes for pre-term or post-term	40	273

*Adapted from Andrade et al. Surveillance of Medication Use During Pregnancy in the Mini-Sentinel Program. Matern Child Health J 08 (2015).

Estimated date of conception for non-live births

For spontaneous abortion and stillbirth, the actual date of death of the fetus may be unknown to both the mother and the medical provider. ICD-10-CM diagnosis weeks of gestation codes (Z3A**) will be used when available or the ICD-9-CM priority list above in Table 1. If these codes are not available, anchoring on the pregnancy outcome date, we will impute random gestational times using a triangular probability distribution (described in a protocol by GlaxoSmithKline[10]), which includes the minimum, maximum, and median of the gestational age specific to the non-live pregnancy outcome observed. The triangular approach is advantageous because the distribution patterns of these pregnancy outcomes are not normal (rather skewed), and the gestational age is expected to fall between the minimum and maximum values of the triangular distribution (high containment probability). Both the minimum and maximum gestational age of pregnancies terminating in non-live outcomes are well-understood and identifiable using national statistics. By generating random variables using this distribution pattern, the variability of the pregnancy episode duration can be simulated among pregnancies terminating in non-live outcomes. This is dissimilar to the alternative approaches, which assign a national average gestational estimate specific to either the pregnancy outcome[11] or screening[3] identified during the episode.

A published algorithm for estimating median gestational age for non-live births assumes a median of 12 weeks for spontaneous abortion outcomes, and 38 weeks for stillbirth outcomes[11,12]. For spontaneous abortion, we will use the triangular probability distribution with minimum 5 weeks (since spontaneous abortions before that time are usually not detected), maximum 20 weeks, and median at 12 weeks[13,14]. For stillbirth, the input figures will be minimum 20 weeks, maximum 43 weeks, and mode at 38 weeks[15]. The median is typically utilized to identify central tendency in skewed distributions, therefore the median was substituted for the mode in the triangular distribution for spontaneous abortion and stillbirth.

To ascertain spontaneous abortion and stillbirth in claims, first, the earliest available claim specific to the pregnancy outcome (spontaneous abortion and stillbirth) is flagged as the outcome date. An eligibility window of 280 days of continuous enrollment in medical and pharmaceutical benefits is required prior to the outcome date. Once the outcome is flagged, the triangular

distribution parameters will be set and plotted in SAS®. Depending on the outcome flagged (spontaneous abortion and stillbirth), random gestational times (in weeks) will be generated using the distribution parameters specified above (minimum, median, maximum). The imputed gestational weeks will be subtracted from the outcome date to determine the EDC for each spontaneous abortion and stillbirth pregnancy episode

End of pregnancy

Pregnancy end will be defined by the date of delivery for live births and non-live outcomes; and by date of admission with an abortive outcome for pregnancies ending in an abortive outcome.

Multiple pregnancies

To adjust for multiple overlapping pregnancy episodes (e.g., a spontaneous abortion claim followed by a live birth claim three days later), once a pregnancy outcome is flagged, there will be a standard 15-day period following the pregnancy outcome where no claims will be assessed (e.g., a subsequent live birth claim will be ignored). See Hornbrook et al[11] for windows to assess pregnancy episodes. Additionally, based on the Hornbrook et al. method a fixed window between subsequent pregnancies based on the first and subsequent outcomes will be applied, regardless if it is a live or non-live outcome. If there are multiple spontaneous abortion or stillbirth events in proximity to one another, the end of pregnancy (EOP) date will be determined using the hierarchy defined below:

1. MarketScan indicators (emergency department, birthing center, ambulance)
2. EOP Procedure Codes (ICD-10-CM & CPT)
3. Diagnostic Related Groups codes defining EOP
4. Other Procedure codes indicating EOP
5. Other Diagnosis codes defining EOP

In the event of non-live and live pregnancy claims reported on the same date, the non-live outcomes take priority over the live birth claims. If a spontaneous abortion claim occurs on the same date as the stillbirth claim, the stillbirth claim will take precedence. In such cases, a hierarchy is required to select the most relevant claim for any given pregnancy episode. Subsequent live pregnancy outcomes will be assessed in this manner: apply a specific gap period for preterm and post-term pregnancies (using ICD-10-CM and ICD-9-CM specific diagnosis codes), and a 280-day gap (normal pregnancy duration) preceding any full-term live pregnancy outcome to avoid overlapping episodes. The 280-day gap or ICD-10-CM or ICD-9-CM specific gap also applies in the event of the last live pregnancy event occurring during the baseline period. In this case, a gap period is necessary to evaluate the first pregnancy episode. Given that the live pregnancy gap period should be similar to the pregnancy period for the live birth outcome, we would not expect to miss capturing any non-live birth outcomes during this period. Any non-live birth outcomes occurring during this time period should be noted, but not counted in the analysis.

Feasibility and Methods for Timing of Exposure Assessment During Pregnancy

Administrative databases can be useful in the assessment of prenatal drug exposure, and estimation of the conception date is necessary to classify exposure. Incorrect gestational age information can lead to misclassification of medication exposure during specific periods of pregnancy. Since there are no definitive diagnosis codes that clearly indicate the last menstrual period, pregnancy duration, or gestational age, diagnosis and other procedure codes have been recommended and utilized to determine the estimated date of conception (EDC). Approaches to arrive at the EDC in patients with live birth outcomes has been thoroughly studied in administrative claims data and have been shown to accurately identify most of these pregnancies[6,12,16,17]. Alternatively, there are no validated approaches for identifying pregnancies ending in non-live outcomes. Therefore, our team has previously tested the feasibility of three approaches using the MarketScan® databases to identify the EDC among pregnancies resulting in fetal death[3,10,11].

To test the first approach[11], we assigned outcome-specific gestational age estimates based on national averages from the literature[18]. Assigning a fixed estimate (e.g. patients with stillbirths were assigned a gestational period of 28 weeks) yielded no variability in the gestational age assignment among patients with identical outcomes, which did not accurately reflect the true date of conception. However, the approach provided solutions to address pregnancy durations that were incompatible with the respective pregnancy outcomes, overlapping pregnancy episodes, and subsequent pregnancy episodes.

To test the second approach[3] we flagged prenatal screening claims prior to the pregnancy outcome date to arrive at the EDC. This method was developed under the assumption that the prenatal screenings were expected to occur at specified time points during the pregnancy episodes (e.g., nuchal screenings are generally 12 weeks from the EDC). Significantly fewer prenatal screenings were recorded during pregnancy episodes terminating in non-live outcomes than live births, particularly among those ending in spontaneous abortion. This is likely due to shorter pregnancy episodes characteristic to mothers with non-live outcomes. Additionally, the frequency of screenings was dependent on the outcome, and the relative timing between screenings (e.g., from nuchal screen to triple screen) in the MarketScan® database was inconsistent with the assumptions specified by the authors.

Lastly, we tested the third approach by implementing a triangular distribution (described in a protocol from GlaxoSmithKlein[10], which included predefined distribution parameters (minimum, median, and maximum) specific to the outcome in efforts to estimate the pregnancy episode duration. This was the preferred approach to estimate the date of conception.

Appendix B. Pregnancy-Related CPRD codes.

Table 1. CPRD diagnosis codes for pregnancy and pregnancy-related outcomes

Medcode
974
1214
1825
2267
2353
3030
4264
4543
5253
8104
8295
8776
8906
10719
11152
11966
13287
13586
14899
15359
16675
16727
17354
18369
20573
22426
23330
24480
26589
28446
28726
30209
31203
35511
37693
37878
39150
40633
41050
41718
42336
43595
44069
45870
47338
53310
56962
58821
67000
69665
70813
72025
72552
89152
94586
95044
97703
100230
101463
101857
104143
107956
110099
110211
110245
111253
111793