Summary Table of Study Protocol

Title	Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study
Protocol version identifier	20150338
Date of last version of the protocol	**01 March 2019** (Amendment **2**)
EU Post Authorization Study (PAS) Register No	TBD (Registration will occur after approval of the protocol and prior to commencement of first data capture)
NCT Number	**NCT02957604**
Active Substance	Evolocumab
Medicinal Product	Repatha®
Product Reference	AMG 145
Procedure Number	N/A
Joint PASS	No

Research Question and Objectives	This study is being conducted to collect more information on the use of evolocumab during pregnancy. Primary objective: To estimate the overall combined rate of major structural **birth** defects, as well as to evaluate any pattern of anomalies, in infants of women with atherosclerotic cardiovascular disease (ASCVD)**,** or **hypercholesterolemia associated with** familial hypercholesterolemia (FH) exposed to evolocumab during pregnancy. Secondary objectives are to evaluate the following outcomes: Pregnancy Outcomes: • Rate of spontaneous abortion • Rate of elective abortion • Rate of stillbirth • Rate of premature delivery Infant Outcomes: • Rate and pattern of ≥3 minor malformations • Rate of small for gestational age • Rate of postnatal growth deficiency • Rate of postnatal serious infections and hospitalizations • Rate of infant reactions to scheduled vaccinations • Adequacy of immune response (as measured by IgG-Tetanus antibody) • Rate of adverse neurodevelopmental outcomes Breastfeeding/lactation outcomes: • Proportion of women who report breastfeeding (at all) in the first 6 weeks post-delivery • Among women who breastfed in the first 6 weeks post-delivery, the proportion who breastfed exclusively for 2 weeks

Country(ies) of Study	United States, Canada
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Marketing Authorization Holder

Marketing authorization holder(s) (MAH)	Amgen Inc.
MAH Contact	PPD Global Development PPD Global Patient Safety

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Investigator's Agreement

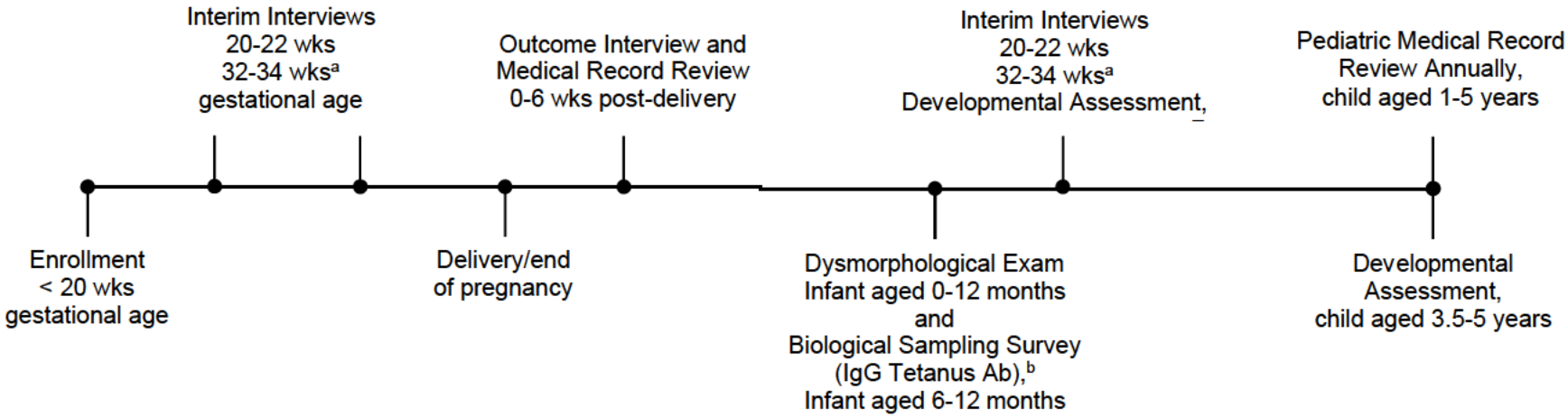
I have read the attached protocol entitled "Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study," dated **01 March 2019**, and agree to abide by all provisions set forth therein.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Study Design Schema



[a] A subject may have anywhere from 1 to 3 interviews during pregnancy, with a minimum of 4 weeks between interviews. If a subject enrolls at 18 weeks, the 20-week interview will be scheduled at 22 weeks. If a subject enrolls between 19 weeks and < 30 weeks, the next scheduled interview will be at 32 weeks. If a subject enrolls at 30 weeks, the 32-week interview will be scheduled at 34 weeks. If a subject enrolls after 30 weeks, no additional interviews will be scheduled during pregnancy.

[b] Immunoglobulin G Tetanus Antibody; Infant response to IgG-tetanus antibody as a biological marker to evaluate humoral immune response.

1. Table of Contents

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2. List of Abbreviations

Abbreviation	Meaning
Ab	antibody
ANOVA	analysis of variance
ASCVD	atherosclerotic cardiovascular disease
BASC-III	Behavioral Assessment Scale for Children
CDC	Centers for Disease Control and Prevention
CDI	Communicative Development Inventories
CES-D	**Center for Epidemiological Studies Depression Inventory**
CRF	Code of Federal Regulations
EDPS	**Edinburgh Postnatal Depression Scale**
EU PAS	European Union Post-Authorization Study
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
FSE	first subject enrolled
HoFH	homozygous familial hypercholesterolemia
HIPAA	Health Insurance Portability and Accountability Act
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	immunoglobulin
IQR	interquartile range
IRB	Institutional Review Board
LDL-C	low density lipoprotein cholesterol
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	marketing authorization holder
MCHAT-R	Modified Checklist for Autism in Toddlers
NIMH	National Institute of Mental Health
ORSR	Observational Research Study Report
OTC	over the counter
OTIS	Organization of Teratology Information Specialists
PCSK9	proprotein convertase subtilisin/kexin type 9

Abbreviation	Meaning
PSI	**Parent Stress Index**
RR	relative risk
US	United States
USPI	United States Prescribing Information
WASI-**II**	Wechsler Abbreviated Scale of Intelligence
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence-IV

3. Responsible Parties

Amgen Contacts

- PPD, Global Development
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Organization of Teratology Information Specialists (OTIS) Research Center

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4. Abstract

- Study Title: Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study
- Study Background, Rationale, **and Design**

  In the United States (US), evolocumab is indicated:

  (1) **In adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization; (2) As an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the 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 o**ther LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) **for the treatment of** patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C (**revised United States Prescribing Information [USPI], December 2017**). There are no data available on use of evolocumab in pregnant women to inform a drug-associated risk. In Section 8.1, the USPI for evolocumab states to "consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women". **Information on the pregnancy exposure registry was added to Section 8.1 of the USPI as well as to the US Patient Package Insert (December 2017)**.

This study is being conducted to address a requirement by the Food and Drug Administration (FDA) to conduct a prospective observational study of pregnant women exposed to evolocumab to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression.

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

    To estimate the overall combined rate of major structural **birth** defects, as well as to evaluate any pattern of anomalies, in infants of women with ASCVD, or **hypercholesterolemia associated with** familial hypercholesterolemia (FH) exposed to evolocumab during pregnancy.

  - Secondary Objective**(**s**)**

    To estimate the rate of study outcomes (other than major structural **birth** defects) in women or infants of women with ASCVD, or hypercholesterolemia associated with FH exposed to evolocumab during pregnancy.

  - Hypothes**is(es)/**Estimation

    The rate of overall major structural **birth** defects will be estimated in the Specific Evolocumab-Exposed cohort and Comparison Group I; and the relative risk (RR) of overall major structural **birth** defects will be estimated between these groups. A similar approach will be taken for the secondary outcomes and for comparing the Specific Evolocumab-Exposed cohort and Comparison Group II.

- Study Design/Type

  This is a prospective observational registry to evaluate fetal, infant, and childhood outcomes in women exposed to evolocumab during pregnancy.

- Study Population or Data Resource

  The Registry will be conducted by investigators at the University of California Research Center for the Organization of Teratology Information Specialists (OTIS), enrolling qualified subjects **who reside in** the US and Canada**. Subjects** will be enrolled on an ongoing basis through year 10 of the study and each will be followed from the time they enroll, through the 5-year postnatal follow-up period for an overall

study period of 15 years. **Study participants are consenting women/mothers and shall be referred to as "subjects" throughout this document.**

- Summary of Subject Eligibility Criteria

  Inclusion Criteria:

  (1) Specific Evolocumab-Exposed Cohort
    - Currently pregnant
    - Diagnosed with ASCVD, or hypercholesterolemia associated with FH
    - Exposed to evolocumab for any number of days, at any dose, and at any time from the first day of the last menstrual period (LMP) up to and including the end of pregnancy
    - Agree to the conditions and requirements of the study

  (2) Comparison Group I
    - Currently pregnant
    - Diagnosed with ASCVD, or hypercholesterolemia associated with FH
    - Unexposed to evolocumab during pregnancy or any time within 90 days prior to the first day of the LMP
    - Agree to the conditions and requirements of the study

  (3) Comparison Group II
    - Currently pregnant
    - Not diagnosed with ASCVD, or hypercholesterolemia associated with FH
    - Unexposed to evolocumab during pregnancy or any time within 90 days prior to the first day of the LMP
    - Unexposed to any known human teratogens as determined by the OTIS Research Center
    - Agree to the conditions and requirements of the study

  (4) General Evolocumab-Exposed Case Series
    - Women exposed to evolocumab during pregnancy (for any number of days, at any dose, and at any time from the first day of the LMP up to and including the end of pregnancy) who do not meet the criteria for cohort (1)

  Exclusion Criteria

  (1) Specific Evolocumab-Exposed Cohort
    - First contact the Registry after prenatal diagnosis of a major structural **birth** defect
    - Exposure to a different PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP
    - Enrollment in the Registry with a previous pregnancy

(2) Comparison Group I

- First contact the Registry after prenatal diagnosis of a major structural **birth** defect
- Exposure to **any** PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP
- Enrollment in the Registry with a previous pregnancy

(3) Comparison Group II

- First contact the Registry after prenatal diagnosis of a major structural **birth** defect
- Exposure to any PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP
- Enrollment in the Registry with a previous pregnancy

(4) General Evolocumab-Exposed Case Series

- None

- Follow-up

  Subjects will be enrolled on an ongoing basis through year 10 of the study and each will be followed from the time they enroll, through the 5-year postnatal follow-up period, for an overall study period of 15 years. Pediatric records will be requested 0-6 weeks after delivery and then on an annual basis. Subjects will be considered lost to follow-up if they completed the initial intake interview but subsequently fail to complete the outcome interview and medical records release despite repeated attempts within 1 year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.

- Variables

  *Outcome Variable**(s)***

  - Primary Outcome
    - Rate of major structural **birth** defects, defined and classified by the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) 6-Digit Code Defect List coding manual (CDC, 2007)
  - Secondary Outcomes
    - Pregnancy Outcomes
      - Rate of spontaneous abortion, defined as non-deliberate fetal death which occurs prior to 19 completed weeks post-LMP
      - Rate of elective abortion, defined as deliberate termination of pregnancy at any time in gestation

- Rate of stillbirth, defined as non-deliberate fetal death anytime in gestation at or after 19 completed weeks post-LMP
- Rate of premature delivery, defined as live birth prior to < 37 completed weeks gestation as counted from LMP

- Infant Outcomes
  - Rate and pattern of > 3 minor structural **birth** defects, where a minor structural **birth** defect is defined as a structural anomaly which has neither cosmetic nor functional significance to the child (itemized on the study examination form), and a pattern is defined as the same 3 or more minor malformations in 2 or more children
  - Rate of small for gestational age, defined as birth size (weight, length, or head circumference) < 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants
  - Rate of postnatal growth deficiency, defined as postnatal size (weight, length, or head circumference) < 10th centile for sex and age using standard pediatric growth curves, and adjusted for postnatal age for premature infants if the postnatal measurement is obtained at < 1 year of age
  - Rate of postnatal serious infections and hospitalizations, as assessed throughout the 5-year postnatal follow-up period via pediatric records
  - Rate of infant reactions to scheduled vaccinations, as assessed throughout the 5-year postnatal follow-up period via pediatric records and a questionnaire designed to collect this information
  - Adequacy of immune response, as defined by an immunoglobulin (Ig)G-tetanus antibody assessment performed in the child between 6-12 months of age
  - Rate of adverse neurodevelopmental outcomes, as assessed in the child during 2 periods (between 16 months and 17 months 30 days of age and between 3.5-5 years of age) via standardized tests of performance
- Breastfeeding/Lactation Outcomes
  - Proportion of women who report breastfeeding (at all) in the first 6 weeks post-delivery; among women who breastfed in the first 6 weeks post-delivery, the proportion who breastfed exclusively for 2 weeks (both assessed via questionnaire administered between 0 – 6 weeks post-partum)

*Exposure Variable**(s)***

The period defining exposure to evolocumab during pregnancy will be any number of days, at any dose, and at any time from the first day of the LMP up to and including the end of pregnancy. The period defining non-exposure to evolocumab during pregnancy will be no exposure any time within 90 days prior to the first day of the LMP.

*Other Covariate**(s)** (refer to Stand Alone Documents listed in Appendix A)*

- Maternal intake form: pregnancy history; current health history; height and pre-pregnancy weight; socioeconomic and demographic information (occupation, education, race, ethnicity, income); current medication use (prescription and over the counter [OTC]); environmental and occupational exposures; alcohol, tobacco, caffeine, illicit drug use; current pregnancy complications; contact information of health care providers; history of onset and other characteristics of indications for evolocumab use; cholesterol test results prior to and during pregnancy
- Outcome interview for live born infants: date of delivery, hospital location and mode of delivery; ethnicity, sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview
- Outcome interview for spontaneous or elective abortions: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview
- Outcome interview for stillborn infants will include all of the above information for spontaneous abortion or elective termination plus information on sex, birth size, and autopsy results if available

- Study Sample Size

  A cohort sample size of 75 in the exposed group and 150 in each of the 2 comparison cohorts is estimated. Estimating 5% lost to follow-up resulting in a final analyzable sample size of 71 women enrolled in the Evolocumab-Exposed cohort, 142 women enrolled in Comparison groups I and II, at 80% power, alpha of 0.05, two-tailed tests of significance and each comparison group independently compared to the exposed group, a RR of 3.8 was calculated based on a baseline rate of major structural **birth** defects equal to 4%.

- Data Analysis

  Descriptive Analyses

  - Demographic and baseline characteristics will be summarized by cohort. Discrete variables will be summarized using numbers and percentages; continuous variables will be summarized using means and SD or medians and interquartile ranges (IQRs), as appropriate.

  Primary Analysis

  - Comparison of the primary outcome between the Specific Evolocumab-Exposed cohort and Comparison Group I

Secondary Analyses

- Comparison of all secondary outcomes between the Specific Evolocumab-Exposed cohort and Comparison Group I
- Comparison of the primary and all secondary outcomes between the Specific Evolocumab-Exposed cohort and Comparison Group II

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	**22 August 2016**	**See Summary of Changes**	**Update 1) clarify that exposure cut-off for evolocumab will be 90 days before the first day of the last menstrual period in accordance with the estimated half-life of 11 to 17 days (rather than 5 half-lives), 2) clarify that while the dysmorphological exam and immune response assessment should be scheduled to occur at the same visit (6 to 12 months after delivery), if the dysmorphological exam occurs 0 to 6 months after delivery, a separate visit will be scheduled to collect the immune response sample 6 to 12 months after delivery, 3) clarify that the study will enroll for the full 10 years, even if the minimum target sample size of 75/150 is reached prior to year 10, 4) increase the target sample size to 60 exposed live born infants and 60 for each comparison group (combined N of 120) in the immune function substudy, 5) add additional standalone form created for Cholesterol Study (02.B2) in order to capture cholesterol test results before and during pregnancy**	**See Summary of Changes**
2	**01 March 2019**	**See Summary of Changes**	**Update 1) language related to the disease/condition, 2) language related to the collection, recording, and reporting of safety information**	**See Summary of Changes**

6. Milestones

Milestone	Planned date
Start of data collection	Nov 2016
Registration in the EU PAS register	Before Nov 2016
Recruitment Reports	Annually on 01 Mar 2017 - 2026
Annual Reports submitted to FDA	Annually Oct 2017 - 2029
Study Completion	Oct 2030
Final ORSR of study results	April 2031

EU PAS = European Union Post-Authorization Study; FDA = Food and Drug Administration; ORSR = Observational Research Study Report.

7. Rationale and Background

In the US, evolocumab is indicated: (1) **In adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization;** (2) **As an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C**; **and** (3) **As an adjunct to diet and** other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) **for the treatment of** patients with HoFH who require additional lowering of LDL-C **(revised USPI**, **December 2017)**. There are no data available on use of evolocumab in pregnant women to inform a drug-associated risk. In Section 8.1, the USPI for evolocumab states to "consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women". **Information on the pregnancy exposure registry was added to Section 8.1 of the USPI as well as to the US Patient Package Insert (December 2017)**.

This study is being conducted to address a requirement by the FDA to conduct a prospective observational study of pregnant women exposed to evolocumab to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression.

In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from

organogenesis through parturition at dose exposures up to 12 times the exposure at the maximum recommended human dose of 420 mg every month (Amgen, 2017). However, in a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with evolocumab in infant monkeys (Amgen, 2017).

7.1 Diseases and Therapeutic Area

A serine protease expressed predominantly in the liver, kidney, and intestine (Seidah et al, 2003), PCSK9, plays an important role in the recycling and regulation of the LDL receptor (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 acts via direct binding to the LDL receptor, resulting in post-translational down-regulation of receptor expression on the hepatic cell surface. This in turn leads to increased levels of circulating LDL-C. Evolocumab is a fully human monoclonal IgG2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with the LDL receptor, thus lowering plasma LDL-C levels.

Based on modality, mechanism of action, published human data, and nonclinical studies, safety issues during pregnancy are not expected with evolocumab exposure. As a therapeutic monoclonal antibody, placental transfer during organogenesis in humans is likely to be low (DeSesso et al, 2012; ICH, 2009). Further, the conceptus derives at least 80% of its cholesterol needs from endogenous synthesis rather than from the maternal circulation (Bartels et al, 2012; Woollett, 2005). Independence from maternal sterol status indicates that normal fetal development would not be expected to be affected by the cholesterol lowering properties of evolocumab which are independent of effects on cholesterol synthesis. Across multiple species including humans, the rates of cholesterol synthesis in the fetus are much greater than in the adult (Dietschy et al, 1993). Consistent with this, low maternal cholesterol is not causally associated with adverse birth outcomes. Whether mediated by dietary intervention or by genetic mutations, normal embryo-fetal development has been observed in children born to mothers with low cholesterol throughout pregnancy (Homanics et al, 1993; McMurry et al, 1981; Connor et al, 1978).

Moreover, in animal and reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from organogenesis through parturition at exposures up to 12 times the

exposure at the maximal recommended human dose of 420 mg every month. However, in a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with evolocumab in infant monkeys (Amgen, 2016).

7.2 Rationale

The purpose of the Evolocumab Pregnancy Exposure Registry is to monitor planned and unplanned pregnancies exposed to evolocumab and to evaluate possible teratogenic effects of this medication on fetal, infant, and childhood outcomes. The lack of human fetal safety data for evolocumab from a controlled clinical study makes such a monitoring system an important component of epidemiologic research on the safety of this drug.

7.3 Statistical Inference

The rate of overall major structural **birth** defects will be estimated in the Specific Evolocumab-Exposed cohort and Comparison Group I, and the RR of overall major structural **birth** defects will be estimated between these groups. A similar approach will be taken for the secondary outcomes and for comparing the Specific Evolocumab-Exposed cohort and Comparison Group II.

8. Research Question and Objectives

8.1 Primary

To estimate the overall combined rate of major structural **birth** defects, as well as to evaluate any pattern of anomalies, in infants of women with ASCVD**,** or **hypercholesterolemia associated with** FH exposed to evolocumab during pregnancy.

This observational Registry will examine fetal, infant, and childhood outcomes among women in 4 study groups:

(1) Women diagnosed with ASCVD, or hypercholesterolemia **associated with** FH, who were exposed to evolocumab during pregnancy (Specific Evolocumab-Exposed cohort)

(2) Women diagnosed with ASCVD, or hypercholesterolemia **associated with** FH, who were not exposed to evolocumab during pregnancy (Comparison Group I)

(3) A general comparison group of pregnant women who have not been diagnosed with ASCVD, or hypercholesterolemia associated with FH, and who were not exposed to evolocumab during pregnancy (Comparison Group II)

(4) Women who were exposed to evolocumab but fail to fulfill eligibility criteria for study group (1) above (General Evolocumab-Exposed case series; see Section 9.2.3.1)

8.2 Secondary

To estimate the rate of study outcomes (other than major structural **birth** defects) in women or infants of women with ASCVD, or hypercholesterolemia associated with FH exposed to evolocumab during pregnancy.

9. Research Methods

9.1 Study Design

This is a prospective, observational, exposure cohort study (Registry) of fetal, infant, and childhood outcomes in women who have been diagnosed with ASCVD, or hypercholesterolemia associated with FH, and who have been exposed to evolocumab during pregnancy, compared to fetal, infant, and childhood outcomes in women with these same diseases/conditions who have not been exposed to evolocumab during pregnancy (disease-matched comparison group), and fetal, infant, and childhood outcomes in women not diagnosed with these same conditions (non-disease-matched comparison group) who have not been exposed to evolocumab during pregnancy.

The Registry cohort study will be conducted by investigators at the University of California Research Center for the Organization of Teratology Information Specialists (OTIS). OTIS is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout North America (Leen-Mitchell et al, 2000). These services receive spontaneous telephone inquiries from women who are pregnant or considering pregnancy as well as from healthcare providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the US and Canada will serve as a source of referrals not only for evolocumab-exposed pregnancies, but also for similarly ascertained pregnant women frequency-matched to the evolocumab-exposed pregnancies by disease indication who have not used evolocumab, and similarly ascertained pregnant women not diagnosed with ASCVD or hypercholesterolemia associated with FH who have not used evolocumab, nor any known human teratogen to serve as a general population comparator. In addition to the above-specified means of identification, Amgen will attempt to facilitate identification of potentially eligible women via its network of providers who are most likely to treat women of child-bearing age with an indicated condition (eg, women with FH).

Once women are in contact with the Registry Coordinating Center, enrollment in the Registry is voluntary and requires informed consent of the pregnant woman. The Registry encourages enrollment as early in the pregnancy as possible, before any prenatal testing results are known.

The OTIS Research Center will be responsible for verifying the subject selection criteria, enrolling each subject and securing informed consent (oral and/or written), providing all pregnancy follow-up interviews and medical record review, scheduling dysmorphological examinations, long-term follow-up of study **subjects** and developmental assessments, recording and storage of all data, and subsequent data analysis.

An overview of the timing of cohort enrollment, interviews, examination, and receipt of medical records is listed in Table 1.

Table 1. Timing of Enrollment, Interviews, Examinations, and Medical Records

	Anytime in Pregnancy[a]	20-22 Weeks Gestation	32-34 Weeks Gestation	0-6 Weeks After Delivery	0-12 Months After Delivery	6-12 Months After Delivery	Annually 1-5 Years After Delivery	16 Months-17 Months 30 Days and 3.5-5 Years After Delivery
Contact / Referral	X							
Enrollment and Consent	X							
Intake Interview	X							
Interim Interview I		X						
Interim Interview II			X					
Outcome Interview				X				
Medical Record Review					X		X	
Dysmorphological Examination					X[b]			
Pediatric Medical Record Review and Questionnaire For Growth, Infections, Vaccinations							X	
Adequacy of immune response (via biological sampling substudy of IgG tetanus Ab)						X[b]		
Developmental Assessment (for neurodevelopmental outcomes)								X

Ab = antibody; Ig = immunoglobulin.

[a] **A subject may have anywhere from 1 to 3 interviews during pregnancy, with a minimum of 4 weeks between interviews. If a subject enrolls at 18 weeks, the 20-week interview will be scheduled at 22 weeks. If a subject enrolls between 19 weeks and < 30 weeks, the next scheduled interview will be at 32 weeks. If a subject enrolls at 30 weeks, the 32-week interview will be scheduled at 34 weeks. If a subject enrolls after 30 weeks, no additional interviews will be scheduled during pregnancy**.

[b] The dysmorphology exam will be scheduled preferentially at or after 6 months of age to coincide with the adequacy of immune response assessment. In the case where an infant is examined prior to 6 months, an additional appointment will be scheduled in order to collect samples for the adequacy of immune response assessment 6 to 12 months after delivery.

9.2 Setting and Study Population

The study population includes pregnant women with ASCVD**,** or **hypercholesterolemia associated with** FH exposed to evolocumab during pregnancy when used to treat hypercholesterolemia, and 2 matching comparison groups (1 disease-matched group of women without exposure to evolocumab, and 1 non-disease-matched group of women without exposure to evolocumab nor to any known human teratogen during pregnancy) who reside in the US or Canada.

OTIS member services receive over 70,000 teratogen information telephone inquiries per year, OTIS members constitute a major, but not the only, source of identification and recruitment of exposed women and appropriate comparison women

(Chambers et al, 2001). Once women are in contact with the Registry Coordinating Center, enrollment in the Registry is voluntary and requires informed consent of the pregnant woman. The Registry encourages enrollment as early in the pregnancy as possible, before any prenatal testing results are known.

Although the Registry will follow up on all pregnancies exposed to evolocumab, the core of the Registry will be a prospective cohort study designed to ascertain and follow-up on pregnancy exposures to evolocumab and to compare these to 2 internally-generated comparison groups (Comparison Groups I and II) and 1 external comparison group (MACDP). Participating centers will be MotherToBaby Teratology Information Services or individuals who are members of OTIS in North America and who agree to the study protocol as established by the OTIS Research Committee and described herein.

9.2.1 Study Period

The study **started when the** first subject enrolled (FSE) in **December** 2016, and **is anticipated to** end in October 2030, with a final report submitted to the FDA in April 2031.

9.2.2 Subject Enrollment

Subject recruitment will continue for 10 years, even if the expected sample size of 75 exposed pregnancies is reached at an earlier time point. If after 10 years the minimum sample size of 75/150 is not reached, enrollment will cease with the FDA's agreement.

Spontaneous referrals from MotherToBaby/OTIS member services and sites will be a source of recruitment for the Registry. MotherToBaby/OTIS Pregnancy Studies have utilized repeated direct mailing campaigns to provide information to health care

professionals who are likely to treat women with the underlying conditions of interest, and this strategy will be continued with the Registry. Registry staff will participate in scientific meetings of professional organizations to initiate and maintain relationships that have been established with referring physicians. In addition, members of the Advisory Board will be asked to promote recruitment among colleagues. The existing Toll Free number for North American callers currently being utilized by all MotherToBaby Pregnancy Studies (877-311-8972) will be maintained and **has been** included in the product label for evolocumab.

The existing MotherToBaby/OTIS Pregnancy Studies contact and referral information is available on the web site and multiple methods are used to increase awareness through the website, social media, and print advertising. The FDA website lists the MotherToBaby/OTIS Pregnancy Studies including this Registry. The study **is** also listed on ClinicalTrials.gov. Additional venues for publicizing the Registry include advocacy groups and patient support networks for FH, and others such as Patients Like Me, BabyCenter.com, pharmacy groups, and professional practice organizations.

9.2.2.1 Subject Initiated Enrollment

Pregnant women can become enrolled into the study upon contacting the Registry at which time their eligibility will be evaluated. Pregnant women who contact the Registry and who do not meet the eligibility criteria for the cohort (cohort 1), but have had pregnancy exposure to evolocumab, will be consented, interviewed, medical records requested, and the outcome examination will be performed using the same protocol as cohort-eligible subjects. These subjects will not be included in the primary analysis for the cohort study, but will be included in the Evolocumab-Exposed Case Series (cohort 4). Collection of exposure and outcome information will follow the same time schedule to the extent this can be achieved as set forth in Table 1. Subjects enrolled in the Evolocumab-Exposed Case Series will not be asked to participate in neurobehavioral testing.

9.2.2.2 Health Care Provider Initiated Enrollment

If the Registry is initially contacted by the health care provider he or she will be asked to have the subject contact the Registry to learn more about the study, and consent to participate if desired. The MotherToBaby service fax referral form (see Appendix A, Form 01.A. *MotherToBaby Service Fax Referral*) or the online physician referral form (http://mothertobaby.org/healthcare-professional-referral-form/) can be utilized for health care provider initiated referrals.

9.2.2.3 Other Sources of Subjects

- Amgen will provide the Registry with the number of reports of pregnancy exposures to evolocumab from the US or Canada received through safety surveillance processes or studies in order to assist with evaluating potential for recruitment; Amgen will encourage exposed women or their Health Care Providers to contact the Registry directly. Amgen may also provide information about the Registry at appropriate professional and advocacy meetings and facilitate awareness among prescribers through Medical Science Liaisons.
- Relevant reports from the published literature will be included in the Registry Annual Interim Reports and reviewed by the Scientific Advisory Board.
- If other data sources (unpublished) on fetal, infant, or childhood outcomes following maternal exposure to evolocumab during pregnancy are available, they may be included in the Appendices to the Registry Annual Interim Reports.

9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

(1) Specific Evolocumab-Exposed Cohort

- Qualified subjects will be currently pregnant women (maternal report validated by medical records) diagnosed with ASCVD, or hypercholesterolemia associated with FH who have been exposed to evolocumab for any number of days, at any dose, and at any time from the first day of the LMP up to and including the end of pregnancy. If the date of the LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than 1 week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception.
- Qualified subjects will agree to the conditions and requirements of the study including the interview schedule, release of medical records, the physical examination of live born infants, and 5 years of follow-up.

(2) Comparison Group I

- Qualified subjects will be currently pregnant women (maternal report validated by medical records) diagnosed with ASCVD, or hypercholesterolemia associated with FH but who were not exposed to evolocumab during pregnancy or any time within 90 days prior to the first day of the LMP.
- Qualified subjects will agree to the conditions and requirements of the study including the interview schedule, release of medical records, the physical examination of live born infants, and 5 years of follow-up.

(3) Comparison Group II

- Qualified subjects will be currently pregnant women not diagnosed with ASCVD, or hypercholesterolemia associated with FH, who have not been exposed to evolocumab during pregnancy or any time within 90 days prior to the first day of the LMP, and who have no exposure to any known human teratogens as determined by the OTIS Research Center.
- Qualified subjects will agree to the conditions and requirements of the study including the interview schedule, release of medical records, the physical examination of live born infants, and 5 years of follow-up.

(4) General Evolocumab-Exposed Case Series

- Qualified subjects will be women with exposure to evolocumab during pregnancy who do not meet the criteria for the Specific Evolocumab-Exposed cohort for reasons including (but not limited to): they do not have ASCVD**,** or hypercholesterolemia associated with FH (off-label use), they were exposed to evolocumab but the pregnancy has already completed, they enrolled in the cohort study with a previous pregnancy, or they already have a prenatal diagnosis of a major **structural** birth defect.

9.2.3.2 Exclusion Criteria

(1) Specific Evolocumab-Exposed Cohort

- Women who first contact the Registry after prenatal diagnosis of a major structural **birth** defect
- Women who were exposed to a different PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP
- Women who have enrolled in this Registry with a previous pregnancy

(2) Comparison Group I

- Women who first contact the Registry after prenatal diagnosis of a major structural **birth** defect
- Women who have enrolled in this Registry with a previous pregnancy
- Women who were exposed to **any** PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP

(3) Comparison Group II

- Women who first contact the Registry after prenatal diagnosis of a major structural **birth** defect
- Women who were exposed to any PCSK9 inhibitor during their current pregnancy or at any time within 5 half-lives prior to the first day of the LMP
- Women who have enrolled in this Registry with a previous pregnancy

(4) General Evolocumab-Exposed Case Series

- None

9.2.4 Matching

Not applicable

9.2.5 Baseline Period

This study has no formal baseline period. However, for each eligible and consenting subject, a structured maternal intake telephone interview will be conducted by a trained Research Associate at the Research Center. This interview will include questions on the following: pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education, ethnicity, and income category; current medication use, both

prescriptive and OTC; other environmental or occupational exposures including alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; names and addresses of health care providers; cholesterol test results prior to and during pregnancy; and history of onset and other characteristics of hypercholesterolemia, ASCVD, and/or FH, if applicable (see Appendix A, Forms 02.B. Personal Information Interview Form, 02.B1. Demog Med Hist Interview Form, 02.B2. Cholesterol Study Form, 02.C. Exposure Interview Form).

9.2.6 Study Follow-up

Subjects will be enrolled on an ongoing basis through year 10 of the study and each will be followed from the time they enroll, through the 5-year postnatal follow-up period, for an overall study period of 15 years. Pediatric records will be requested 0-6 weeks after delivery and then on an annual basis. Subjects will be considered lost to follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview despite repeated attempts within 1 year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.

9.3 Variables

9.3.1 Exposure Assessment

The period defining exposure to evolocumab during pregnancy will be any number of days, at any dose, and at any time from the first day of the LMP up to and including the end of pregnancy. Pregnancy will be assessed via maternal report validated by medical records. If the date of the LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than 1 week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception.

The period defining non-exposure to evolocumab during pregnancy will be any time within 90 days prior to the first day of the LMP.

9.3.2 Outcome Assessment

9.3.2.1 Primary Outcome

- Rate of major structural **birth** defects, where a major structural **birth** defect will be defined and classified using the CDC coding manual (CDC, 2007). This method has been previously described by the study investigators and the OTIS Research Group (Chambers et al, 2001) and has been used in previous studies conducted by this group.
  - Time Period: Major structural **birth** defects identified up to 1 year of age by the mother, the health care provider, or identified in the dysmorphological examination will be included in the primary analysis. Defects identified after 12 months to 5 years of age will be described and considered separately in the context of a possible pattern.
  - Confirmation: Independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect that is ascertained by the examining dysmorphologist will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted in the dysmorphological examination will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies, and in accordance with the CDC coding manual referenced above.
  - Adjudication: A co-Investigator physician with expertise in teratology, pediatrics, and dysmorphology will act as the primary adjudicator of defects classified using the CDC coding system. Verification of classifications in question are performed in 2 ways: (1) by consultation with a Medical Director for the MACDP, who has an ongoing agreement with the MotherToBaby OTIS studies to consult on classification of cases in question, and (2) through a member of the Scientific Advisory Board who has expertise in this area. At annual meetings of the Board, cases classified with major defects are reviewed and where questions arise regarding appropriate classification, primary records are reviewed by one of the members of the Advisory Board with the relevant qualifications.

9.3.2.2 Secondary Outcomes

9.3.2.2.1 Pregnancy Outcomes

- Rate of spontaneous abortion where spontaneous abortion is defined as non-deliberate fetal death which occurs prior to 19 completed weeks post-LMP
- Rate of elective abortion where elective abortion is defined as deliberate termination of pregnancy at any time in gestation
- Rate of stillbirth where stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 19 completed weeks post-LMP
- Rate of premature delivery where premature delivery is defined as live birth prior to 37.0 weeks gestation as counted from LMP (or ultrasound adjusted date)

9.3.2.2.2 Infant Outcomes

- Rate and pattern of minor structural **birth** defects where a minor structural **birth** defect is defined as a structural anomaly (itemized on the study examination form) which has neither cosmetic nor functional significance to the child, and a pattern is defined as the same 3 or more minor structural **birth** defects in 2 or more children (see Appendix A, 04.E. Dysmorphology Exam Form). Due to the large variability in the sensitivity and specificity of identification of minor defects, in this study, minor defects are tabulated only in those infants who receive the study-related physical examination. This approach of assessment for clusters is based on prior studies that suggest 3 or more minor malformations is a meaningful cut point (Leppig et al, 1987; Méhes et al, 1973; Marden et al, 1964).
- Rate of small for gestational age where small for gestational age is defined as birth size (weight, length, or head circumference) $\leq$ 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (NCHS, 2000; **Olsen** et al, **2010**).
- Rate of postnatal growth deficiency where postnatal growth deficiency is defined as postnatal size (weight, length, or head circumference) $\leq$ 10th centile for sex and age using standard pediatric growth curves, and adjusted for postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age.
- Rate of postnatal serious infections (see Appendix D) and hospitalizations as assessed throughout the 5-year postnatal follow-up period. Pediatric records will be requested after delivery and then on an annual basis with specific requests for documentation of serious infections and hospitalizations
- Rate of infant reactions to scheduled vaccinations as assessed throughout the 5-year postnatal follow-up period. Pediatric records and a questionnaire regarding vaccine administration according to recommended schedule and any vaccine-related adverse events will be obtained on an annual basis (see Appendix A, 08.12. Vaccine Information Form).
- Infant response to IgG-tetanus antibody as a biological marker to evaluate humoral immune response. To be performed via a heel stick **or venipuncture** and standardized assay test between 6-12 months of age in a subset of infants in each of the study groups, conditional on the consent of the mother.
- Adverse neurodevelopmental outcomes as assessed during 2 periods (between 16 months to 17 months 30 days of age and between 3.5-5 years of age) via standardized tests of performance (further described in Section 9.4.5).

9.3.2.2.3 Breastfeeding/Lactation Outcomes

Both assessed via questionnaire administered between 0–6 weeks postpartum

(see Appendix A, 02.F. Outcome Delivery and Birth Interview Form):

- Proportion of women who breastfed (at all) in the first 6 weeks after delivery
- Among women who breastfed (in the first 6 weeks after delivery), the proportion who breastfed exclusively during the first 2 weeks of life

9.3.3 Covariate Assessment

9.3.3.1 Maternal Intake Form

(At enrollment) Variables collected include demographic and socioeconomic information (occupation, education, race, ethnicity, income); pregnancy history; pre-pregnancy weight and height; family history; medical history (including history of onset and other characteristics of indications for evolocumab use)**;** cholesterol test results prior to and during pregnancy (see Appendix A, 02.B1. Demog Med Hist Interview Form and 02.B2. Cholesterol Study Form).

9.3.3.2 Exposure Interview Form

(At scheduled time points during pregnancy and post-delivery) Variables collected include current medication use (prescription and OTC); environmental and occupational exposures; alcohol, tobacco, caffeine, illicit drug use; current pregnancy complications; contact information of health care providers (see Appendix A, 02.C. Exposure Interview Form).

9.3.3.3 Pregnancy and Delivery Outcome Interview

(Upon pregnancy ending) Data collected on this form include details regarding pregnancy and delivery such as maternal conditions, birth information, delivery details, and newborn complications (see Appendix A, 02.F. Outcome Delivery and Birth Interview Form).

9.3.4 Validity and Reliability

For the primary exposure variable regarding evolocumab, maternal report will be confirmed by medical records abstraction. In cases of discrepancy, the mother will be queried to help resolve. For the primary outcome variable of major **structural** birth defects, maternal report is validated through medical record review and expert study investigator classification; external validation is performed by consultants and the Advisory Board as described above. For other outcome variables, standard methods are used to classify the outcome, and data management procedures are in place to confirm reliability of data capture, data entry and classification. The neurobehavioral testing instruments that have been selected for this study have been validated in the age groups for which they will be used. Reliability procedures are in place for test administration and scoring and are overseen by the study psychologist.

9.4 Data Sources

Standard study interview and data collection forms are listed in Appendix A and summarized below.

9.4.1 Initial Intake Interview

Upon enrollment, **subjects** will be interviewed using the Maternal Intake Form (see Appendix A, 02.B. Personal Information Interview Form, 02.B1. Demog Med Hist Interview Form, 02.B2. Cholesterol Study Form, and 02.C. Exposure Interview Form) the purposes of which are to collect information on demographic and socioeconomic characteristics, pregnancy history, family history, and medical history.

9.4.2 Interim Interviews

Following the initial intake interview, **subjects** will be sent a pregnancy diary in which they will be asked to record any additional exposures or events as the pregnancy progresses (see Appendix A, 03.D**. Patient** Exposure Diary)**, as well as the obstetric medical record release form.**

A subject may have 1 to 3 interviews during pregnancy, with a minimum of 4 weeks between interviews. If a subject enrolls at 18 weeks, the 20-week interview will be scheduled at 22 weeks. If a subject enrolls between 19 weeks and < 30 weeks, the next scheduled interview will be at 32 weeks. If a subject enrolls at 30 weeks, the 32-week interview will be scheduled at 34 weeks. If a subject enrolls after 30 weeks, no additional interviews will be scheduled during pregnancy (see Table 1, and Appendix A, 02.C. Exposure Interview Form and 02.F. Outcome Delivery and Birth Interview Form). The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, to remind women to maintain the exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

9.4.3 Outcome Interview

At any of the interim interview points, if the pregnancy has ended, the outcome interview will be conducted at this time or at the earliest convenient time for the mother (see Appendix A, 05.G. Adverse Outcome Delivery and Birth Form or 02.F. Outcome Delivery and Birth Interview Form). For women who are still pregnant at the 32-34 week interview, the outcome interview will be conducted within 0 to 6 weeks after the expected due date (see Appendix A, 02.F. Outcome Delivery and Birth Interview Form).

The outcome interview for live born infants will be a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; ethnicity, sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names

and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

The outcome interview for spontaneous or elective abortions will also be structured and information will be elicited on the following: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview. The outcome interview for stillborn infants will include all of the above plus information on sex, birth size, and autopsy results, if available.

9.4.4 Medical Records, Pediatric Evaluations

Upon completion of the outcome interview, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician **(if the release form has not been received)**, pediatrician, internist, cardiologist or other specialty physician if applicable (see Appendix A, Form 09.J. Sample OB Medical Records Release Form). For women whose pregnancies have ended in spontaneous or elective abortion or stillbirth, records release forms will be mailed for the specialty physician's evaluation, if applicable, and if prenatal diagnosis, pathology or autopsy reports are available. Each woman will be asked to sign the forms and to return them along with the **patient** exposure diary. Specific information on maternal cholesterol levels obtained prior to and during pregnancy will be requested for women in the Evolocumab-Exposed group and Comparison Group I.

Upon receipt of the signed medical records release forms, a standard physical evaluation form (see Appendix A, 06.H. Birth Info and Private Pediatrician Form) will be mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and questions about postnatal complications and congenital anomalies. After delivery, at 1 year of age, and annually thereafter until the child's fifth birthday, a medical records release form for the pediatrician or health care provider caring for the child will be sent to the mother for signature. The signed form along with a standard questionnaire about infant/child growth, congenital malformations, serious infections (see Appendix D for list of conditions qualifying as serious infection), hospitalizations, and adverse reactions to vaccinations administered is sent to the health care provider (see Appendix A, 07.I. Pediatric One Year Follow-up Form, and 08.I2. Vaccine Information Form).

9.4.5 Developmental Behavioral Assessments

9.4.5.1 Phase I – Maternal Questionnaires at Infant Age 16 Months to 17 Months 30 Days

The developmental behavioral assessments consist of mail-out questionnaires completed by all mothers/primary caregivers when the child is 16 months to 17 months 30 days of age. The measures are described in Table 2.

All mothers or primary caregivers in each of the 3 study groups will be asked to complete questionnaires about the development of their child when the child is 16 months to 17 months 30 days of age. These scales include the Ages and Stages Questionnaire, the MacArthur-Bates Communicative Development Inventories (CDI)**, and the** Modified Checklist for Autism in Toddlers (MCHAT**-R**) will be mailed when the child is 15 months of age and the mothers or primary caregiver will be asked to complete it when the child is between 16 months and 17 months 30 days of age. The mothers/primary caregivers will also complete 2 questionnaires about their own functioning, the Center for Epidemiological Studies Depression Inventory **(CES-D)**, and the Parent Stress Index **(PSI)** Short Form. This will allow for the preliminary evaluation of the child's motor skill, general mental ability, language development, and social and emotional development. Interpretation of these data will be aided by an understanding of the mother's social and emotional adjustment and stress context. Although a window is provided to allow the mother to complete the questionnaires, scoring for these questionnaires is standardized to the month of age of the child so comparisons between groups will appropriately be age-adjusted.

9.4.5.2 Phase II – Face-to-Face Developmental Testing at 3.5-5.0 Years of Age

When the children are at least 3.5 years of age but not yet 5.0 years of age, a subset will then be evaluated through a single set of direct assessments completed in the **subject's/child's** home setting, as well as an age appropriate set of maternally completed questionnaires. Preference will be given to the assessment of children exposed prenatally for the longest durations and children in each of the comparison groups who are of similar age. Longer duration exposures should improve the ability to assess risks because brain development continues throughout prenatal development and may be vulnerable to drug exposure beyond the first trimester. Direct assessment will be conducted using the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV). This standardized (Z-score), norm-referenced measure provides an evaluation of the child's general mental ability, verbal and non-verbal abilities, as well as

processing speed. The mother or primary caregiver will complete 1 questionnaire about the child's development, the Behavioral Assessment Scale for Children (BASC-II**I**), and questionnaires about her own functioning, the **CES-D,** the **PSI, and the Edinburgh Postnatal Depression Scale (EDPS)**. These questionnaires will provide additional information about the child's social and emotional development in the family context. Additionally, a direct evaluation of the mother or primary caregiver's cognitive functioning will be made using the Wechsler Abbreviated Scale of Intelligence (WASI**-II**). Understanding the cognitive level of the mother will facilitate accuracy of interpretation of children's scores and any group differences.

Face-to-face assessments will be made until a sample size of 40/group (cohorts 1-3) has been reached. At this sample size, statistical power (0.80) will allow confidence in judgments of group differences of SD in primary score endpoints.

Table 2. Postnatal Developmental Screening and Evaluation, Phase I (16 Months and 17 Months 30 Days of Age) & Phase II (3.5-5.0 Years)

Age	Measure	Description
16 months – 17 months 30 days	Ages and Stages Questionnaire **(ASQ-3)** (Squires, 2009)	Used to screen infants and young children for developmental delays during the first 5 years of age. Parents complete an illustrated 30-item questionnaire that covers 5 key developmental areas: communication, gross motor, fine motor, problem solving, and personal-social areas of functioning.
16 months – 17 months 30 days	The MacArthur-Bates Communicative Development Inventories (CDI) (Fenson, 2007)	Used to assess the development of expressive and receptive language abilities during 2 early age periods. The CDI Words and Gestures is used for children 8-16 months of age and the CDI Words and Sentences is used for children 16-30 months of age.
16 months – 17 months 30 days	Modified Checklist for Autism in Toddlers (MCHAT-**R**) (Robins et al. 2001)	Used to screen for autism spectrum disorders in toddlers over the age of 16 months.
3.5-5 years	Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV) (Wechsler and Psychological Corporation, 1989)	Provides an evaluation of the child's general mental ability, verbal and non-verbal abilities, as well as processing speed. Completed via direct assessment.
3.5-5 years	Behavioral Assessment Scale for Children (BASC-II**I**) (Reynolds and Kamphaus, 2004)	Completed by the mother or primary caregiver regarding the child's development with respect to behavioral, emotional, and social characteristics.

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Table 2. Postnatal Developmental Screening and Evaluation, Phase I (16 Months and 17 Months 30 Days of Age) & Phase II (3.5-5.0 Years)

Age	Measure	Description
16 months – 17 months 30 days and 3.5-5 years	The Center for Epidemiological Studies Depression Inventory **(CES-D)** (available through public domain; National Institute of Mental Health [NIMH])	Evaluation of the caregiver: Used as a screening tool for depression in adults. The mother or primary caregiver completes this 20 item questionnaire with respect to her/his own status.
16 months – 17 months 30 days and 3.5-5 years	The Parent Stress Index **(PSI)** Short Form (Abidin, 2012)	Evaluation of the caregiver: Used for the identification of parenting and family characteristics that fail to promote normal development in children as well as to detect children with behavioral and emotional problems.
3.5-5 years	Wechsler Abbreviated Scale of Intelligence (WASI-**II**) (Wechsler and Psychological Corporation, 1999)	Done via direct evaluation of the mother or primary caregiver. Designed for ages 6 to 89 years, used to better understand the cognitive level of the mother/primary caregiver.
3.5-5 years	**Edinburgh Postnatal Depression Scale (EPDS) (Cox et al, 1987)**	**Evaluation of the caregiver: Used as a screening tool for "perinatal" depression. The mother or primary caregiver completes this 10-item questionnaire with respect to her own status.**

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9.4.6 Dysmorphology Evaluation

All live born infants will be examined by one of a team of study-dedicated dysmorphologists, led by a co-investigator from the University of California, San Diego. All members of the team are licensed pediatricians with subspecialty fellowship training in dysmorphology and/or genetics. This team of physicians has been functioning as the specialist examiners for the current MotherToBaby/OTIS Pregnancy Studies and have completed examinations for well over **1400** infants throughout North America as part of this protocol using the same standard procedures as are incorporated in this Registry. The physical examinations evaluate infants for both major and minor structural **birth** defects which provide increased sensitivity for detecting a specific pattern of malformation should one exist. All infants will be examined as soon as is practical, and optimally within the first year of life. The Research Center will group and schedule these follow-up examinations to maximize physician blinding as to exposure status, and to minimize travel time and expense for these types of investigations.

Infant examinations will be conducted using a standard checklist of approximately 130 minor malformations included in a dysmorphology exam form (see Appendix A, 04.E. Dysmorphology Exam Form). In addition, digital photographs of the infant will be taken to aid in validating any diagnoses.

9.4.7 Biological Assessment of Child Immune Function

To supplement the information obtained on serious infections and hospitalizations and vaccination experience over the 5-year follow-up period for all live born children in the study, a biological sample sub-study will be offered to **subjects** in all 3 cohorts, to be overseen by a co-investigator. Eligible infants will be **at least** 6 **months of age, and preferably by** 12 months of age and will have had up to 3 diphtheria, tetanus, and pertussis scheduled immunizations. A small blood sample via heel stick **or venipuncture** will be collected in enrolled infants and sent to a single laboratory for analysis of IgG-tetanus antibody. Results of the test will be measured both continuously as well as classified as negative, indeterminate, or positive.

OTIS will communicate the result to the mother, and in those situations where the result is negative or indeterminate, the mother will be advised to share this result with her pediatrician, and OTIS will recommend repeating the test in approximately 1 year. The expectation is that near 100% of children in all 3 groups will test positive for immunity.

As this sample collection is most efficiently accomplished at the **contracted laboratory, the study will work with subjects to identify a local laboratory location for sample collection. If the subject is unable or unwilling to have the sample taken at the contracted laboratory, the sample may be taken at the** time of the dysmorphology examination. **T**he study physicians will be tasked with collecting samples from infants whose mothers have consented. The dysmorphology exam for this study will be scheduled preferentially at or after 6 months of age and should coincide with the adequacy of immune response assessment. In the case where the dysmorphology exam is scheduled prior to 6 months, an additional appointment **may** be scheduled in order to collect samples for the adequacy of immune response assessment 6 to 12 months after delivery. **If it is not possible for the subject to have the sample taken by the contracted laboratory or the study dysmorphologist, the study will work with the subject to coordinate with the child's pediatrician or the laboratory associated with the pediatrician's office to collect the sample.**

While it is anticipated that not all mothers will agree to this sub-study, a sample size of 60 in each group will be targeted, with preference given to recruiting exposed pregnancies that represent the distribution of length of exposure.

9.5 Study Size

An enrollment total of 75 in the exposed group and 150 in each of the 2 comparison groups after 10 years is anticipated. Given that these numbers assume the prevalence of exposure is sufficient to support recruitment of these numbers, the feasibility of achievement will be re-evaluated at each annual interim review of the data.

Based on previous experience with MotherToBaby/OTIS Pregnancy Studies, we estimate that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion/stillbirth rate is 10%, the estimated elective abortion rate is 5%, and the estimated lost to follow-up rate is 5%. This results in an estimated 71 observable pregnancies of which 60 are estimated to result in live births in cohort 1 (exposed group), and an estimated 142 observable pregnancies of which 120 are estimated to result in live births in cohorts 2 and 3 (control groups).

Baseline rates of major structural **birth** defects, spontaneous abortion, premature delivery, and small for gestational age, as well as the standard deviation for mean birth weight of full-term infants were based on previous MotherToBaby/OTIS studies and on general population data (Table 3). With the sample size estimated above, at $\geq$ 80% power, alpha of 0.05, two-tailed tests of significance (except as noted below for pattern of minor structural **birth** defects), and each comparison group independently compared to the exposed group, the minimum effect sizes detailed in Table 3 will be detectable.

With respect to the evaluation of minor malformations, the strength of this study design is in the ability to examine the data for a pattern of minor and/or major structural **birth** defects, given that the known human teratogens are typically associated with a pattern as opposed to isolated major **structural** birth defects. A baseline prevalence estimate of 1% has been used for a specific pattern of minor **structural birth** defects. The RR detectable with this sample size is 10.0. This represents a 10% birth prevalence of a specific pattern (ie, approximately 6 children in the exposed sample), which is comparable to the birth prevalence of a specific pattern in other known human teratogens of moderate risk such as the anticonvulsant medications.

For the primary outcome, the study is powered to detect that the Evolocumab-Exposed group has a 3.8-fold (or greater) risk of all major **structural** birth defects combined relative to the risk in the primary comparison group. This level of risk for teratogenicity is below that observed for other, but not all, agents deemed teratogenic. Importantly, known human teratogens tend to be associated with increased risks for specific patterns of birth defects and are not associated with increased risks for any and all major **structural birth** defects. For this reason, the analysis of the primary outcome, combined with evidence of a cluster or pattern of defects, provides the best ability for evaluation of teratogenic risk.

Table 3. Sample Size and Power for a Specified Effect Size Based on Minimal Sample Size[a]

Outcome	N in Cohort 1	N in Cohort 2 or 3	Baseline Rate	RR	Power[b]
Major structural **birth** defects[c]	71	142	4%[d]	3.8	84%
Specific pattern of 3 or more minor structural **birth** defects	60	120	1%[e]	10.0	71%[f]
Spontaneous abortion/stillbirth	71	142	10%[g]	2.5	88%
Preterm delivery	60	120	9%[h]	2.8	85%
SGA	60	120	10%[i]	2.6	80%
Small for age (postnatal growth deficiency)	46	108	10%	2.8	82%
Neurodevelopmental outcomes (Phase II)	40	40	--	0.5 SD[j]	80%
Inadequate immune response (via IgG tetanus antibody status)	60	120[k]	20%[l]	2	82%

Definitions: Ig = immunoglobulin; RR = relative risk; SGA = small for gestational age.
[a] Software used to calculate power and effect size: OpenEpi v3 (Dean et al, 2015).
[b] Based on Fisher's Exact Test or chi-square, two-tailed, alpha 0.05, except for specific pattern of 3 or more minor anomalies as noted below.
[c] Primary endpoint.
[d] Baseline rate in comparison group based on 4.1% in statin exposed (Winterfeld et al, 2013).
[e] Baseline rate in comparison group expected to be 0-1% based on no evidence of a pattern.
[f] Based on one-tailed Fisher's Exact Test, alpha 0.05.
[g] Baseline rate based on 13.6% in statin exposed (Winterfeld et al, 2013) and 4.4% (Chambers et al, 2013) (rate influenced by gestational time of enrollment).
[h] Baseline rate based on 16.1% (Winterfeld et al, 2013) and 6.2% (Toleikyte et al, 2011).
[l] Baseline rate based on 5.0□ for low birth weight defined as < 5th centile which translates to 10□ for SGA defined as < 10th centile (Toleikyte et al, 2011).
[j] Minimum detectable difference calculated for neurodevelopmental outcomes as a continuous variable (instead of RR for categorical variables).
[k] Estimating 60 infants per cohort.
[l] Baseline rate based on Marshall et al (2010).

9.6 Data Management

Interview, medical record, examination, neurodevelopmental and biological sample sub-study data will be recorded on hard copies of forms and these records will be retained in the Research Center. Data from these forms will be extracted and entered into a customized database located in the Research Center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. Access to the database will be controlled by password. Hard copies of patient files and subject signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis/Analyses

No formal interim analyses are planned. However, the appropriate regulatory authorities will receive:

- Annual reports of analyses performed during the study for the advisory board.
- A feasibility/futility report 3 years after study commencement, and annually thereafter, summarizing the number of subjects enrolled, any exposure to evolocumab, and describing primary and secondary outcome data.

9.7.1.2 Primary Analysis

The primary analysis will be conducted at the end of the study. The objective of the primary analysis is to compare the rates of the primary and secondary outcomes in the evolocumab-exposed and diseased comparison group.

9.7.1.3 Final Analysis

The final analysis will be conducted at the end of the study observation period (currently scheduled to occur 15 years after study commencement) or when the study is determined to have been completed based on other criteria (eg, FDA agreement).

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The analysis of the cohort dataset will be hypothesis testing. The analysis of the exposed case series will be descriptive only. Significance testing at the alpha level of 0.05 will be utilized for the cohort analysis as well as 95% confidence intervals for rate ratios. Due to the small sample size, no adjustment for multiple testing is planned.

9.7.2.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort. Discrete variables will be summarized using numbers and percentages; continuous variables will be summarized using means and SD or medians and IQR, as appropriate. When making comparisons between cohorts, discrete variables will be compared using chi-square tests. If $\geq$ 25% of categories have expected counts less than 5, Fisher's Exact tests will be used. Continuous variables will be analyzed using analysis of variance (ANOVA).

9.7.2.3 Missing or Incomplete Data and Lost to Follow-up

Pregnancies enrolled in the cohort study for which outcome information is unobtainable within 1 year after the estimated date of delivery are considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the lost to follow-up may have on any analysis of the cohort study. Should lost to follow-up numbers be substantial, however, efforts at comparing some of the characteristics of each group will be made in an attempt to address this potential source of bias. However, the OTIS Research Center prior experience has been that lost to follow-up is extremely low, typically < 5%.

9.7.2.4 Descriptive Analysis

Descriptive results will be presented in each annual report.

Results for the fourth group (Evolocumab-Exposed Case Series) will be summarized separately from other cohorts. All analyses of this cohort will be descriptive and no comparisons to the other cohorts will be made. These cases constitute an exposure series, thus line listings of major malformations, pattern of minor malformations, serious infections, hospitalizations, and any neonatal deaths will be summarized along with tabulations of the frequencies of events by category of report: reasons for exclusion, timing of exposure, and indication for use of the medication. Although select, and likely biased, collection of exposure and outcome information in this group is important for providing additional evidence on the safety of evolocumab use during pregnancy.

9.7.2.4.1 Description of Study Enrollment

Outcome	Analysis Subset
Major Structural Birth Defect Among Live Births	All pregnancies ending in at least 1 live born infant
Major Structural Birth Defects Among All Pregnancies Excluding Lost to Follow-Up	All pregnancies excluding lost to follow-up
Spontaneous Abortion	Pregnancies enrolled prior to 20 weeks' gestation
Stillbirth	Pregnancies enrolled excluding lost to follow-up
Preterm Delivery	Pregnancies enrolled prior to 37 completed weeks' gestation, excluding pregnancies ending in twin or higher order multiple births
Minor Structural Birth Defects	Live born infants who have received the dysmorphology examination
Small for Gestational Age Infants	Live born infants excluding twin or higher order multiple births
Breastfeeding	Pregnancies ending in at least 1 live born infant
Postnatal Growth	Live born infants followed up to 1 year postpartum, excluding twin or higher order multiple births
Serious or Opportunistic Infections	Live born infants followed up to 1 year postpartum
Immune Function	Live born infants who received the tetanus titer testing
Response to vaccines	Live born infants who received at least one vaccine
Neurodevelopment	Live born infants for whom developmental screening questionnaires were completed or face-to-face testing was completed

9.7.2.4.2 Description of Subject Characteristics

Not applicable

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

9.7.2.5.1 Primary Analysis

Comparison of the primary outcome between the Specific Evolocumab-Exposed cohort and Comparison Group I will serve as the primary analysis.

Comparison of the prevalence of major structural **birth** defects between the Specific Evolocumab-Exposed cohort and Comparison Group I will be among all live births and, separately, among all pregnancies excluding those lost to follow-up.

Outcomes that are adjudicated as not associated with drug exposure will be excluded from the primary analysis, but included in a sensitivity analysis **(**Section 9.7.2.6**).**

9.7.2.5.2 Secondary Analysis

The following will comprise the secondary analyses:

1. Comparison of all secondary outcomes between the Specific Evolocumab-Exposed cohort and Comparison Group I
2. Comparison of the primary and all secondary outcomes between the Specific Evolocumab-Exposed cohort and Comparison Group II

The comparison of the prevalence of the total proportion of major structural **birth** defects between the Specific Evolocumab-Exposed cohort and Comparison Group II will be among all live births and, separately, among all pregnancies excluding those lost to follow-up. The comparison of the prevalence of $\geq$ 3 minor malformations between the Specific Evolocumab-Exposed cohort and each of the 2 comparison groups will be among children who receive the dysmorphological examination. The comparison of IgG-tetanus antibody status (test negative or indeterminate vs test positive) by group (Exposed, Comparison Group I, Comparison Group II) among those in the biological sample sub-study.

In each cohort we will separately calculate the proportion of all pregnancies ending in live birth, spontaneous abortion, stillbirth, elective termination, and lost to follow-up; crude comparisons will be made between cohorts.

The evaluation for a pattern of minor structural **birth** defects will be conducted using the following steps:

1. A comparison among groups of the proportion of infants with any 3 or more minor structural **birth** defects will be made without regard to pattern
2. Among infants with 3 or more minor **structural birth** defects, the Evolocumab-Exposed group will be examined for evidence of a specific pattern of 3 or more defects in any 2 or more children. If such a pattern is identified, Comparison Groups I and II will be evaluated for any evidence of the same pattern.

In each cohort among all live born infants we will separately calculate the proportion of premature delivery, small for gestational age on weight, length or head circumference, and rates of serious infections, hospitalizations, adverse vaccine reactions, and adverse neurodevelopmental outcomes; crude comparisons will be made between cohorts.

Mean birth weight, length and head circumference for full-term live born infants will be compared between cohorts. Postnatal growth parameters will be compared using the proportion of infants $\leq$ 10th centile for sex and age with respect to weight, height, or head circumference.

Among the subset of live born infants who participate in the IgG-tetanus antibody assessment at 6-12 months of age, adequacy of immune response will be compared between groups.

Among mothers who give birth to live born infants, the proportion who breastfeed in the first 6 weeks post-delivery will be compared; also among those who breastfeed, the proportion who breastfed exclusively during the first 2 weeks of life.

At the end of the study or as deemed appropriate in consultation with the Scientific Advisory Board, unadjusted and adjusted comparisons between cohorts will be made. Potential confounders will be examined, and adjusted estimates of exposure effects (along with 95% confidence intervals) will be made using Cox proportional hazards, logistic regression, or linear regression techniques as appropriate. Propensity score methods will be considered for adjusted analyses when more than 1 confounder is identified.

9.7.2.6 Sensitivity Analysis

Because early prenatal diagnostic testing is prevalent in the US and increasingly performed prior to the second trimester, it is not feasible to exclude all pregnancies with prior prenatal testing from the analysis. Thus, the Registry will include pregnancies that are enrolled prior to outcome but after a prenatal test has been performed, as long as the test does not indicate a major structural **birth** defect. Because of the possibility that this practice could potentially bias the results, analyses for the primary outcome of major **structural** birth defects will be stratified by use of prenatal testing and on gestational timing of enrollment (prior to prenatal testing).

The intention of the primary endpoint is to analyze pregnancies with evolocumab exposure occurring in the first trimester. In the event that there are exposures in the second and third trimester, sub-analyses will be conducted based on length of exposure and timing of exposure, when feasible.

Outcomes that can be adjudicated as not associated with drug exposure will not be included in the primary analysis. Those outcomes, such as chromosomal and genetic abnormalities, that cannot be adjudicated as not associated with drug exposure will be analyzed in the primary analysis as well as in multiple sensitivity analyses that will be designed to address the specific outcomes observed and are impractical to fully pre-specify. However, they will be in keeping with other ongoing studies, advice received from experts, and current and evolving FDA registry guidance.

9.7.2.6.1 Subgroup Analysis

Subgroup analyses by timing and length of evolocumab exposure as feasible.

9.7.2.6.2 Stratified Analysis

Stratified analysis by prenatal diagnosis testing prior to versus after enrollment is planned for the primary endpoint of major structural birth defects.

9.7.2.6.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable

9.7.2.6.4 Other Sensitivity Analysis

Sensitivity analysis excluding chromosomal anomalies is planned.

9.7.2.7 External Comparisons

The overall rate/proportion of major structural **birth** defects in the Specific Evolocumab Exposed group will be compared to the most recently available rate/proportion from the MACDP, a population-based tracking system for birth defects established in 1967 in the US with careful follow-up and classification of major structural **birth** defects identified up to 1 year of age (CDC, 2007). This particular program is considered appropriate for external comparisons because it is population-based and includes a relatively high level of validation of reported defects identified in children up to 6 years of age. However, comparisons are considered secondary because there is no potential to control for differences in the MACDP methods for ascertainment of defects as well as differences in the characteristics of the source population relative to the cohort **subjects** in the Registry.

9.7.3 Analysis of Safety Outcomes

Apart from the primary and secondary analyses, no other Safety analyses are planned as part of this study.

9.8 Quality Control

Outside of the Quality Control measures outlined in Section 9.3.4 (Validity and Reliability) and Section 9.6 (Data Management), the Registry will make use of a scientific advisory board external to Amgen. The primary objective of the advisory board is to review the accumulating summary data reports from the study to evaluate the possible risks to the pregnancy, paying particular attention to the risk for major structural birth defects in infants whose moms were exposed to evolocumab. The advisory board makes recommendations regarding the conduct of the study in order to safeguard the interests of registry **subjects** while preserving the integrity and credibility of the study.

Specifically, the advisory board is responsible for evaluating the accumulated summary data and determining whether there are any safety concerns. The advisory board can recommend that the conduct of the study should be altered. Members of the advisory board are also responsible for maintaining confidentiality regarding the data that are provided to the board in interim and annual reports from OTIS and data from the Registry presented at board meetings by teleconference or face-to-face.

The advisory board is also available for ad hoc consultation, data review, and advice, and is typically composed of external experts in the field of obstetrics, dysmorphology/ genetics, epidemiology, and a physician who specializes in the condition/disease that is being treated (eg, FH). Sponsor representatives can also be included as non-voting members of the advisory board.

9.9 Limitations of the Research Methods

The primary limitation of a cohort study utilizing volunteer subjects is selection bias. The use of comparably selected comparison women will address this concern to some extent, and support internal validity of the results. The use of a volunteer sample may not be representative of the entire population of evolocumab-exposed pregnancies. However, use of a disease-matched comparison group will allow for internal validity of comparisons.

It is likely that women prescribed evolocumab will be more severely diseased than the women in Comparison Group I (disease-matched control group), leading to confounding by indication. In addition, subjects in the Evolocumab-Exposed group are more likely to be exposed to additional medications to lower their LDL-C levels (including multiple medications and higher doses). Confounding by indication may also vary over time with increased awareness and access to the drug. In order to attempt to mitigate biases associated with confounding by indication, the Registry proposes to collect careful measurements of comorbidities including maternal cholesterol levels and comorbidities including cardiovascular disease history that are likely to differ across cohorts. Additionally, methods such as propensity scores may be utilized in attempts to balance covariates between comparison groups. Nonetheless, unmeasured confounding remains a limitation of the observational study design and should be recognized when interpreting results.

It is unknown to what extent women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies. However, the study results will be strictly applicable to women fitting the profile of the sample of women who enroll.

The overall sample size is expected to be modest and limits the statistical power to detect differences on the primary and secondary endpoints. However, given the necessity and value of the study questions, we will capitalize on getting the most complete data possible regardless of the expected low frequency of pregnancy exposure to evolocumab.

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion (ie, at < 6-7 weeks post-LMP) will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion will be limited to hazards of late first-trimester and early second- trimester pregnancy loss.

Because early prenatal diagnostic testing is prevalent in the US and Canada and increasingly performed prior to the second trimester, it may be difficult to achieve adequate numbers of subjects if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the Registry will include pregnancies in the cohort study that are enrolled prior to outcome but after a prenatal test has been performed, as long as the test does not indicate a major structural **birth** defect. The FDA guidance document acknowledges that such an approach may be necessary to accrue adequate numbers (FDA, 2002). However, this practice could potentially bias the results by lowering the overall incidence of birth defects. The data analysis will address this by stratifying on use of prenatal testing and on gestational timing of enrollment (prior to prenatal testing). In addition, women who are excluded from the cohort portion of the study due to prenatal diagnosis of a major **structural birth** defect prior to enrollment will be eligible for enrollment in the Registry General Evolocumab-Exposed case series; thus these data will be captured.

It is expected that some exposures to evolocumab will occur in unintended pregnancies and unplanned pregnancy may be risk factor for adverse outcomes, for example, because the mother does not start taking prenatal vitamins until after recognition of pregnancy. Although more than half of all pregnancies in the US are unintended (Henshaw, 1998), it is possible there could be imbalances among comparison groups. This factor will be taken into consideration in the recruitment of comparison groups using the results from the interim analysis as a guide for correcting imbalances in the future. However, differences between groups will also be addressed in the statistical analysis.

The study design has relative strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on

a variety of factors which may be related to exposure and to pregnancy outcome, such as maternal cholesterol levels and comorbidities including cardiovascular disease history, obesity, diabetes, and hypertension. The use of a disease-matched comparison group addresses to some extent the issue of confounding by indication.

Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this. In addition, each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias regarding outcome is minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol.

Another strength of the study design is the anticipated minimal lost to follow-up rate. Based on previous experience of the investigators in the MotherToBaby/OTIS Pregnancy Studies, and the frequent subject contact, lost to follow-up is typically < 5% and therefore is not expected to pose a threat to the validity of study results. A subject meeting the criteria for enrollment is considered "lost to follow-up" if follow-up information on the outcome (live birth, fetal loss) is not obtainable, or for a live birth if the birth defect status is designated as "unknown" as of 12 months following the estimated due date. Before a **subject** is designated as lost to follow-up, the subject or reporter receives at least 3 reminder telephone calls (documented in database) followed by written correspondence; alternative contact information that is requested upon enrollment is also utilized. All follow-up attempts are documented. Losses to follow-up are tallied in the Registry Interim Reports. No imputation of missing data is planned.

Finally, the primary strength of the cohort study portion of the Registry is its sensitivity for detection of a pattern of malformation. As the known teratogens are associated with specific patterns of malformation, this study design, by virtue of providing study-related dysmorphological evaluation of prospectively ascertained and exposed infants, has the unique capability of detecting within reasonable limits such a pattern if it exists.

10. Protection of Human Subjects

This Registry will be conducted in compliance with the protocol, International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the US, US FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995), and the Health Insurance Portability and Accountability Act (HIPAA) (US Department of Health and Human Services, 2003; US Department of Health and Human Services, 2002; International Society for Pharmacoepidemiology, 1996).

10.1 Informed Consent

10.1.1 Oral and Written Consent

The pregnant woman must agree to the oral consent form at the time of enrollment and before completing the intake interview. She must sign an informed consent in order to **complete the dysmorphology exam and the face-to-face neurodevelopmental testing**. Each **subject** will be sent 2 copies of the written informed consent document following the initial intake interview and requested to sign and return 1 copy. She must also sign for release of medical information to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the subject's obstetrician, the hospital of delivery, and any health care specialist, and for the infant from the infant's pediatrician.

The original oral and signed informed consent documents will be maintained by the Registry Office. Original copies of medical record release documents will be retained at the Registry office as well, and the copies will be sent to the institution or physician from whom records are being requested.

Pregnant women under the age of 18 who are eligible for the study and who wish to participate will require written consent of their parent or guardian prior to the initial intake interview and written assent from themselves.

Consent/assent forms and study participation will be available in English and Spanish.

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

The Registry will be run under a protocol currently approved by the OTIS Research Group and the IRB of the University of California, San Diego. Notification of the Board's approval of the study will be provided to Amgen prior to initiation of participation in the Registry.

10.3 Subject Confidentiality

The Registry makes every effort to assure subject confidentiality within the Registry. When information is distributed to Advisory Board members, no contact information or direct subject identifiers are included. Mother and infant names are obtained as part of the informed consent and linked to pregnancy history, exposure and outcome data from maternal interview, medical records, physical and neurodevelopmental examinations. This personally identified information is maintained securely at the Research Center and is not shared with Amgen, the Advisory Board, or any external parties other than what is required by law.

Care will be taken to ensure that a subject is not identifiable in the data tables published in the Annual Reports, or other publications. No protected health information is included in any published information. Ad hoc requests for Registry information are reviewed and approved by the Registry Investigators with the advice of the Advisory Board.

10.3.1 Access to the Registry Data

Registry Staff: The Registry Investigators, data collection and management staff reside at the MotherToBaby/OTIS Pregnancy Studies Research Center located at the University of California, San Diego. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data.

Sponsor: Amgen representatives through the Registry Advisory Board have access to de-identified summary data as part of the periodic annual review. In addition, Amgen will receive de-identified reports of major **structural** birth defects, spontaneous abortion, stillbirth, and neonatal or infant deaths identified in **evolocumab-exposed subjects and their children** through the MedWatch form (see Section 11.2, Safety **Collection, Recording, and Submission to Amgen** Requirements, below) regardless of attribution.

Advisory Board: The Registry Advisory Board will receive information on pregnancy outcomes obtained. Contact information is not included in any listings provided. The Advisory Board, in preparation for the annual meeting, reviews the listings and summary tables. At the meeting, interpretation of results will be discussed and decisions made on the appropriate updates to the Annual Report.

10.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

No new data will be collected after the subject withdraws.

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

11.1 Definition of Safety Events

11.1.1 Adverse Events

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 unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), 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 responsibility **of the Registry Coordinating Center to ensure that** adverse event**s that are attributed by the enrolled woman or her physician to exposure to evolocumab are reported** to Amgen.

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**/patient** at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other **medically important serious event**" that does not meet any of the above criteria

A hospitalization 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 **medically important serious events**" refer to important medical events that may not be immediately life threatening or result in death or hospitalization 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 event) 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 authorized 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), device(s)**, or combination products** provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

11.2 Safety Collection, Recording, and Submission to Amgen Requirements

This study is collecting information from subjects enrolled prospectively or retrospectively, during pregnancy or after pregnancy outcome. For this Pregnancy Registry the primary outcomes of interest are **major structural** birth defects occurring in the offspring of a pregnant woman exposed to evolocumab during pregnancy. All major **structural** birth defects, spontaneous abortions, stillbirths, neonatal or infant deaths, **and maternal death occurring in pregnancies exposed to evolocumab** are considered serious adverse events and will be reported to Amgen **irrespective of attribution of causality**. **These serious adverse** events must be submitted as individual case safety reports to Amgen via the applicable MedWatch Form within 1 business day of the Registry Coordinating Center's awareness. In order to facilitate this reporting, the Registry Coordinating Center will request information from the reporter about the details of the event and will provide information to Amgen using the MedWatch Form format (FDA, 2016).

The Registry Coordinating Center is responsible for ensuring that other **serious and non-serious** safety events (adverse drug reactions, product complaints, and other

safety findings) **that are reported during the interview and** attributed to evolocumab by the subject/patient **or are reported in subject/patient's medical records by the provider and attributed to evolocumab are** reported to Amgen using the MedWatch Form within 1 business day of the Registry Coordinating Center's awareness. See Appendix C for sample Safety Report Form (MedWatch Form). **The Registry Coordinating Center is responsible for ensuring that the specified serious adverse events listed in Section 11.2 and any other safety events attributed to evolocumab by the enrolled subject or her provider that occur from informed consent through the end of study (last subject's study contact) are recorded in the subject/patient's appropriate study documentation.**

The Registry Coordinating Center may be asked to provide additional information for any event submitted.

Protocol Exempted Events

Pregnancy and lactation exposure **to evolocumab events** will not be **reported** for this study as other safety information as this is the actual patient population and the Registry Coordinating Center will be following these subjects/patients for pregnancy and child outcomes.

If the Registry Coordinating Center is contacted by a provider or patient who is not enrolled in the study and who wishes to report a serious or non-serious adverse event that they attribute to evolocumab, the Registry Coordinating Center will refer the provider or patient to Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) in the US or 1-866-512-6436 in Canada.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required **in accordance with local requirements** 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.**

Amgen will report adverse events to regulatory authorities in accordance with 21 Code of Federal Regulations (CFR) 314.80, FDA Guidance to Industry, Establishing Pregnancy Registries (FDA, 2002) and other regulations. For this Registry the primary outcomes of interest are **major structural** birth defects occurring in the offspring of a pregnant

subject exposed to evolocumab during pregnancy. Major **structural** birth defects, spontaneous abortions, stillbirths, and neonatal or infant deaths are considered serious adverse events and will be reported to Amgen **using the MedWatch Form within 1 business day of the Registry Coordinating Center's awareness. Other serious and non-serious safety events that are reported during the interview and attributed to evolocumab by the subject/patient or are reported in subject/patient's medical records by the provider and attributed to evolocumab will also be reported to Amgen using the MedWatch Form within 1 business day of the Registry Coordinating Center's awareness.** Other **secondary** outcomes, including but not limited to, low birth weight and preterm delivery will be included in periodic annual reporting to Amgen.

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 must be informed of all amendments **that require a change to the research plan** and give approval. The Investigator must send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen 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 in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The Registry will initiate presentations at scientific and professional meetings, and will publish results at interim points, if appropriate, and at the completion of the Registry. The Registry will use these and several other strategies to raise awareness of the Registry. However, the Registry never identifies individual subjects or shares its list of providers.

A publication plan for submissions of abstracts to scientific meetings regarding evolocumab exposure in pregnancy will be planned and drafts of abstracts will be provided to Amgen for comment at least 14 days prior to submission. Manuscripts to be submitted for publication regarding evolocumab exposure in pregnancy will be provided to Amgen for comment at least 30 days prior to planned submission for publication.

13.1 Publication Policy

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.

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15. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number.	Date	Title
1	*01.A*	*NA*	*MotherToBaby service Fax referral*
2	*02.B*	*08/18/2014*	*Personal Information Interview Form*
3	*02.B1*	***10/10/2017***	*Demog Medical Hist Interview Form*
4	*02.B2*	***06/13/2018***	***Additional Questions for*** *Cholesterol Study*
5	*02.C*	***05/11/2018***	*Exposure Interview Form*
6	*02.F*	***05/11/2018***	*Outcome Delivery and Birth Interview Form*
7	*03.D*	***03/28/2013***	***Patient*** *Exposure Diary*
8	*04.E*	*06/04/2013*	*Dysmorphology Exam*
9	*05.G*	***06/20/2018***	*Adverse Outcome*
10	*06.H*	*12/04/2014*	*Birth Info and Private Pediatrician*
11	*07.I*	*04/14/2015*	*Pediatric One Year Follow-up*
12	*08.12*	*04/14/2015*	*Vaccine Information*
13	*09.J*	*NA*	*Sample OB Medical Records Release*

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study

Study reference number:
20150338

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:
Note: need to EU PAS milestone to Section 6 before finalizing this form

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	7.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9.3.2
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.2
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.2.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:
There are no co-morbidities or seasonality under study

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.3
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	9.2.3

Comments:

Exposure to Repatha is defined as any number of days, at any dose, and at any time from the first day of the last menstrual [period up to and including the end of pregnancy.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	9.3.2
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.4

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	9.3.3
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Effect measure modification is not applicable to this study

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.3.1
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.3.2
8.1.3 Covariates?	☒	☐	☐	9.3.3
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3.3

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	9.3.1
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9.3.2
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Exposure coding is not applicable because Repatha (evolocumab) is the only exposure. Covariates and concomitant medication use other than Repatha will be reported descriptively; it is not anticipated that analyses by covariate subgroups will be performed. No linkage will be performed.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	9.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	9.7.2.2
10.2 Is the choice of statistical techniques described?	☒	☐	☐	9.7.2
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.4
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2.3
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	9.7.2.3
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.3 Are methods of quality assurance described?	☒	☐	☐	9.6
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	9.8
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:
Study will utilize a scientific advisory board

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	9.9
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9
12.3 Does the protocol address other limitations?	☒	☐	☐	9.9

Comments:
A report on study feasibility is planned at 3 years post-initiation and annually thereafter

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:
No ethical review has yet taken place

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD

Date: 8/17/2018

Signature: PPD

ENCePP Checklist for Study Protocols (Revision 2) 5

Appendix C. Sample Safety Reporting Form(s)

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event, or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*
4. Date of this Report *(mm/dd/yyyy)*

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1
#2

2.	Dose or Amount	Frequency	Route
#1			
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. Diagnosis or Reason for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Expiration Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER ***(See confidentiality section on back)***

1. Name and Address

Phone #
E-mail

2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Appendix D. Conditions Considered Serious or Opportunistic Infections

- Any infection resulting in hospitalization or extended hospitalization
- X-ray proven pneumonia (requiring antibiotic treatment and/or hospitalization)
- Neonatal sepsis
- Meningitis (asceptic or culture proven)
- Osteomyelitis
- Bacteremia Septic
- Arthritis Abscess (deep tissue)
- Mycobacteria infection (including but not limited to tuberculosis)
- Invasive fungal infection (biopsy proven) including histoplasmosis, coccidiomycosis, candidiasis, aspergillosis, blastomycosis
- Pneumocystis jirovecii infection
- Systemic Cytomegalie Virus, Herpes zoster, and Herpes simplex infection
- Listeria infection
- Legionella infection