## Summary Table of Study Protocol

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| **Title** | An Observational Study to Describe Women Exposed to Apremilast During Pregnancy and Infant Outcomes During the First Year of Life |
| **Protocol version identifier** | 20210218, 1.0 |
| **Date of last version of the protocol** | Not applicable (NA) |
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| **Active Substance** | Apremilast |
| **Medicinal Product** | Otezla |
| **Device** | NA |
| **Product Reference** | NA |
| **Procedure Number** | NA |
| **Joint PASS** | Yes |
| **Research Question and Objectives** | Among women exposed to Apremilast during pregnancy, to estimate the proportion of:<br>- pregnancy and maternal complications<br>- adverse events in the developing fetuses and neonates<br>- and among their infants, adverse events during the first year of life. |
| **Country(ies) of Study** | Global |
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**Marketing Authorization Holder**

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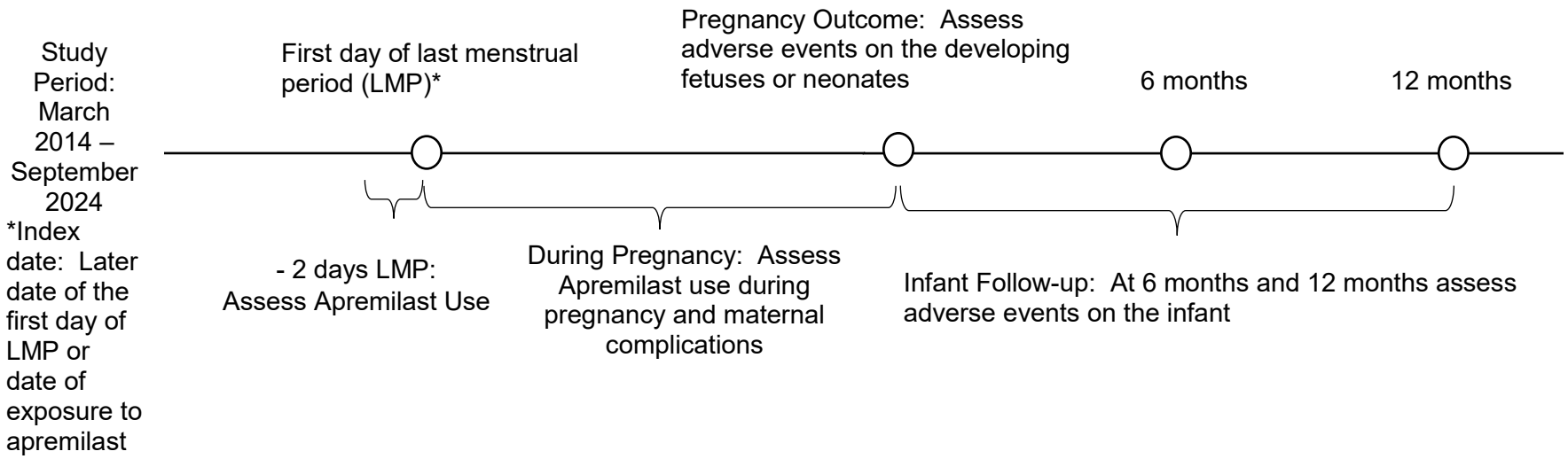
This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

**Proper Version Numbering and Dating**

VERSIONING:

| Protocol Version | Date of Protocol | Page Header Date |
|---|---|---|
| Original, Version 1.0 | 11 July 2023 | 11 July 2023 |

**Study Design Schema**



## 1. Table of Contents

**List of Appendices**

## 2. List of Abbreviations

| Acronym | Definition |
|---|---|
| AGS | Amgen Global Safety |
| ATC | Anatomical Therapeutic Chemical |
| cAMP | cyclic adenosine monophosphate |
| CDC | Center for Disease Controls |
| DALY | disability-adjusted life uears |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| GVP | good pharmacovigilance practices |
| HCP | healthcare provider |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HROoL | health-related quality of life |
| ICD | International Classification of Diseases |
| IEC | Independent Ethics Committee |
| IL | interleukin |
| IRB | Institutional Review Board |
| LMP | Last menstrual period |
| MAH | Marketing Application Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NA | not applicable |
| NNH | number needed to harm |
| OTC | Over the counter |
| OTIS | Organization of Teratology Information Specialists |
| PAS | Post-authorisation study |
| PASS | Post-authorisation safety study |
| PDE4 | phosphodiesterase 4 |
| PMR | postmarketing requirement |
| QALY | quality-adjusted life years |
| TNF-$\alpha$ | tumor necrosis factor alpha |
| US | United States |
| WHO | World Health Organization |

## 3. Responsible Parties

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## 4. Abstract

- Study Title

  An Observational Study to Describe Women Exposed to Apremilast During Pregnancy and Infant Outcomes During the First Year of Life

- Study Background and Rationale

  Study 20210218 is being conducted to complement the apremilast pregnancy registry (Study CC-10004-AID-001), which has enrolled a fewer number of apremilast-exposed pregnant women than expected. This study will estimate the proportion of pregnancy and maternal complications, adverse events reported in the developing fetuses and neonates, and adverse events reported in the infants through the first year of life using data from relevant cases in Amgen's Global Safety Database.

- Research Question and Objective(s)

| **Objectives** | **Endpoints** |
|---|---|
| **Primary** | |
| Among women exposed to apremilast during pregnancy, to estimate the proportion of:<br>• Pregnancy and maternal complications<br>• Adverse events in the developing fetuses and neonates<br>• And among their infants, adverse events during the first year of life. | • Number of cases reporting pregnancy and maternal complications.<br>• Pregnancy Outcomes: Number of cases reporting live full-term births, spontaneous abortion, elective abortion, fetal death/stillbirth, and premature delivery.<br>• Infant Outcomes: Number of cases reporting adverse events at 6 months and 12 months. |

  – Hypothesis(es)/Estimation

  This is an estimation study. No formal hypothesis will be tested.

- Study Design/Type and Study Population
  This is a global retrospective and prospective observational case series study of pregnant women exposed to apremilast during pregnancy and their infants through the first year of life.

- Data Sources
  Case finding through the Amgen Global Safety Database, which includes other postmarketing sources such as spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing noninterventional studies. Retrospectively, data between March 2014 and the approval date of this protocol will be extracted from Amgen's Global Safety Database captured through existing reports for women exposed to apremilast during pregnancy, and their infants. Prospectively, data from approval date of this protocol through September 2024 will also be extracted from the Amgen Global Safety Database and collectively included in the analysis.

  The collected data extraction will cover a period from March 2014 until September 2024, in alignment with the end of the prospective pregnancy registry for apremilast (Study CC-10004-AID-001).

- Summary of Patient Eligibility Criteria
  Women exposed to apremilast during pregnancy who consent to provide their information and that of their infants to Amgen

- Follow-up
  If the pregnant women consent for follow-up, then Amgen will follow-up with the pregnant women from the time they are exposed to apremilast through the pregnancy outcome and their infants will be followed through the first year of life.

- Variables
  - Outcome Variable(s):
    The outcomes for the study include occurrence and dates of pregnancy and maternal complications, pregnancy outcomes, and infant outcomes based on self-report. Pregnancy outcomes include the number of cases reporting live full-term births, spontaneous abortion, elective abortion, fetal death/stillbirth, and premature delivery. Infant outcomes are the number of cases reporting adverse events including complications, medical problems, or congenital anomalies at birth and the number of cases reporting adverse events at 6 months and

12 months which may include whether they have not followed growth curves or met development milestones as expected for chronological age.

- Exposure Variable(s):
  The period defining exposure to apremilast during pregnancy will be any number of days, at any dose, and at any time from up to 2 days pre-LMP, through the first day of the last menstrual period (LMP) and up to and including the end of pregnancy. Identification of pregnancy will be via post-marketed reporting through Amgen's Global Safety Database.
- Other Covariate(s*):*
  Other covariates will be included which pertain to maternal information, exposure, and pregnancy and delivery. Maternal covariates include demographic information for the mother, pregnancy history; medical history; other relevant history that may impact the pregnancy (family history, mother's occupation). Variables related to exposure include current medical conditions; current medication (prescription and over the counter [OTC]) and dates of use; and occurrence and dates of current pregnancy complications. Characteristics of pregnancy and delivery such as maternal conditions, birth information, delivery details, and newborn complications.

- Study Sample Size
  This is an estimation study. The study size will depend on the number of reports submitted to the Amgen Global Safety Database for women exposed to apremilast during pregnancy.

- Data Analysis
  The cases of pregnant women exposed to apremilast identified from Amgen Global Safety Database for the study specified period constitute an exposed case series. Thus, line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes, and adverse events will be summarized along with tabulations of the numbers and frequencies of events by category of report: numbers who did not provide consent for follow-up, timing of exposure (pre-LMP, which trimester), and indication for use of the medication. The denominator is the number of pregnant women exposed to apremilast during pregnancy and the numerator is the number with the outcome. The proportion at birth with adverse events including complications, medical problems or congenital anomalies will be estimated in infants of women exposed to apremilast during pregnancy. The proportion of infants with

adverse events observed at 6 months and 12 months of age will be estimated. The proportion of mothers who have received apremilast at any time during the pregnancy with pregnancy and maternal complications and adverse events will be summarized. Corresponding 95% confidence intervals will also be presented, as appropriate.

To describe outcomes for the pregnancy in women exposed to apremilast during pregnancy, descriptive statistics such as the count and proportion of spontaneous abortions, elective abortions, feal deaths/stillbirths and premature delivery will be provided, along with corresponding 95% confidence intervals if appropriate.

If the available safety information relevant to exposure during pregnancy represents a safety signal, the signal will be further evaluated through the Amgen safety governance structure and, if deemed necessary, escalated for consideration of changes to the Reference Safety Information (eg, in labeling) as well as other forms of risk communication (eg, Dear Healthcare Provider Letters).

## 5. Amendments and Updates

None.

# 6. Rationale and Background

## 6.1 Diseases and Therapeutic Area

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4). By inhibiting PDE4, apremilast elevates intracellular cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn downregulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-$\alpha$), interleukin (IL)-23, IL-17, and other inflammatory cytokines, and increasing the production of anti-inflammatory mediators. Through targeted PDE4 inhibition, apremilast reduces the inflammatory response implicated in inflammatory and autoimmune disorders. Reference should be made to the Investigator's Brochure for further data on apremilast.

Apremilast has been developed for the treatment of several immune-mediated inflammatory disorders, including plaque psoriasis, active psoriatic arthritis, and Behçet's disease, and has marketing approval for these conditions in adults in multiple countries. As of 20 March 2023, an estimated 10 038 subjects (12 996.1 subject-years) have been exposed to apremilast in company-sponsored clinical studies, and 846 059 patients (746 987 patient-years) have been exposed to apremilast in the postmarketing setting in Amgen territories along with 2052 patients (2223 patient-years) exposed in Amgen's business partner territory. Reference should be made to the Periodic Benefit-Risk Evaluation Report for further data on apremilast.

There have been no adequate and well-controlled studies of apremilast in pregnant women. Available pharmacovigilance data with apremilast use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, however, these data are limited. Apremilast was not teratogenic in mice or monkeys. Other effects of apremilast on pregnancy included embryo-fetal loss in mice and monkeys and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure. Reference should be made to the Investigator's Brochure for further data on apremilast.

Treatment with apremilast is contraindicated during pregnancy in some countries, such as in the European Union, but not in others including the United States. Where it is not contraindicated, apremilast should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No studies in the literature have reported the use of apremilast in pregnant women and hence the rates of maternal and infant outcomes among apremilast users are unknown.

Lower rates of congenital abnormality (0.8%) (Kimball AB et al, 2021) were reported among pregnant women with moderate to severe psoriasis than the US annual rate (3%) (Centers for Disease Control and Prevention [CDC] - Data & statistics on birth defects, 2023). The rates of spontaneous abortion (13.8%) (Kimball et al, 2021) were comparable with the general US population (10%) (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology, 2018); and preterm rates (9.1%) (Kimball et al, 2021) were comparable with US population (10.5%) (CDC - Preterm birth, 2023). A registry-based case control study reported an increased risk of ectopic pregnancy among women with psoriasis than in those without psoriasis (1.87% vs 1.50%; adjusted odds ratio [aOR], 1.34; 95% CI, 1.06-1.68) (Gangbe et al, 2022). The rates of gestational hypertension (aOR, 1.58, 95% CI 1.13-2.21) and small for gestational age (aOR, 2.42, 95% CI 1.49-3.93) (Gangbe et al, 2022) among pregnant women with psoriatic arthritis were higher than pregnant women without psoriatic arthritis. A meta-analysis demonstrated pregnant women with psoriasis or psoriatic arthritis were at increased risk of maternal complications such as preeclampsia, gestational diabetes, gestational hypertension, and preterm delivery compared to the general population (Xie et al, 2021). Pregnant women with Behcet's disease were at greater risk of preterm labor than pregnant women without Behcet's disease (12.50% vs. 7.15%; aOR,1.73; 95% CI 1.02–2.93); maternal venous thromboembolism was higher among pregnant women with Behcet's disease (4.86% vs. 0.26%; aOR,14.47; 95% CI 6.69-31.32) (Lee et al, 2019); pregnant women with Behcet's disease had a higher risk of cerebrovascular disorders (1.01% vs.0.07%; aOR,12.08; 95% CI 1.70–85.9), and pregnant women with Behcet's disease had a higher risk of gestational diabetes compared to pregnant women without Behcet's disease (13.13% vs. 5.39%; aOR,1.89; 95% CI 1.10–3.25) (Chan et al, 2021).

In the United States, Amgen has a postmarketing requirement (PMR 2135-1) to conduct a prospective, observational, controlled, pregnancy exposure registry study to monitor pregnancies exposed to apremilast with the primary objective to evaluate whether there is any increase in the risk of birth defects. Study CC-10004-AID-001 was initiated in October 2014 to address this PMR. The study is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to apremilast during pregnancy in the

United States and Canada. The study is conducted by the Organization of Teratology Information Specialists (OTIS) Research Group (PMR 2135-1). Enrollment in the registry was discontinued in April 2023 due to low enrollment in the apremilast-exposed cohort. As of 01 April 2023, a total of 225 subjects (out of a planned enrollment of 300 subjects with 100 subjects per cohort) have been enrolled with 15 subjects in the apremilast-exposed cohort, 106 subjects in the diseased comparison cohort, and 104 subjects in the non-diseased comparison cohort. An additional 8 subjects have been enrolled in the apremilast-exposed case series. Based on the limited data available, there is no evidence of a pattern of birth defects or other adverse outcomes. However, additional data are needed to adequately evaluate the safety of apremilast use during pregnancy.

### 6.2 Rationale

Study 20210218 is being conducted to complement the apremilast pregnancy registry (Study CC-10004-AID-001), which has enrolled a fewer number of apremilast exposed pregnant women than expected. This study will estimate the risk of pregnancy and maternal complications, adverse events reported in the developing fetuses and neonates, and adverse events reported in the infants through the first year of life using data from relevant cases in Amgen's Global Safety Database.

### 6.3 Statistical Inference (Estimation or Hypothesis)

This is an estimation study. No formal hypothesis will be tested.

## 7. Research Question and Objectives

### 7.1 Primary

Among women exposed to apremilast during pregnancy, to estimate the proportion of:

1. Pregnancy and maternal complications
2. Adverse events in the developing fetuses and neonates
3. And among their infants, adverse events during the first year of life.

## 8. Research Methods

### 8.1 Study Design

This is a worldwide, single-arm, observational case series study that is designed to collect retrospective and prospective data in women exposed to apremilast during pregnancy to estimate the proportion of pregnancy and maternal complications, adverse events in developing fetuses and neonates, and adverse events in infants in all exposed pregnancies. Infant outcomes will be assessed through the first year of life.

### 8.2 Setting and Study Population

The study population includes women worldwide exposed to apremilast during pregnancy, who consent to provide their information to Amgen, and their infants. Case information will be obtained through the Amgen Global Safety Database, which includes other postmarketing sources such as spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing non-interventional studies.

#### 8.2.1 Study Period

The data collection for this study is retrospective and prospective. Retrospectively, data between March 2014 and the approval date of this protocol will be extracted from Amgen's Global Safety Database, captured through existing reports for women exposed to apremilast during pregnancy, and their infants. Prospectively, data from approval date of this protocol through September 2024 will also be extracted from the Amgen Global Safety Database and collectively included in the analysis.

The data extraction will cover a period from March 2014 (the date of the first marketing approval of apremilast) until September 2024, in alignment with the end of the prospective pregnancy registry study (Study CC-10004-AID-001).

#### 8.2.2 Patient Eligibility

##### 8.2.2.1 Inclusion Criteria

Women exposed to apremilast during pregnancy who consent to provide their information and that of their infants to Amgen.

##### 8.2.2.2 Exclusion Criteria

None.

#### 8.2.3 Baseline Period

This study has no formal baseline period. Pregnant women exposed to apremilast for any number of days, at any dose, and at any time from up to 2 days prior to the last menstrual period (LMP) and up to and including the end of pregnancy will be identified through a search of Amgen's Global Safety Database.

#### 8.2.4 Study Follow-up

If pregnant women consent, they will be followed from the later date of the first day of their LMP or the date of their exposure to apremilast (index date) through the pregnancy and birth. A postpartum follow-up will occur when the infant is 6 and 12 months of age.

If there is no response to the follow-up attempts, the due diligence process is considered complete and the case is categorized as lost to follow-up.

## 8.3 Variables

### 8.3.1 Exposure Assessment

The period defining exposure to apremilast during pregnancy will be any number of days, at any dose, and at any time from 2 days prior to the first day of the LMP up to and including the end of pregnancy. Identification of pregnancy will be via post-marketed reporting through Amgen's Global Safety Database.

### 8.3.2 Outcome Assessment

Pregnancy outcomes include the number of women reporting pregnancy or maternal complications, as well as the number reporting:

- Live full-term births
- Spontaneous abortion defined as non-deliberate fetal death which occurs prior to 20 completed weeks post-LMP
- Elective abortion defined as deliberate termination of pregnancy at any time in gestation
- Fetal death/stillbirth defined as non-deliberate fetal death anytime in gestation at or after 20 completed weeks post-LMP
- Premature delivery defined as live birth prior to 37 weeks gestation as counted from the LMP (eg, ultrasound adjusted date or Ballard's score)

Outcomes related to pregnancy and maternal complications (eg, preeclampsia, placenta previa, gestational diabetes, gestational hypertension) will be assessed with an Initial Pregnancy Questionnaire (a sample form included in Appendix C). Outcomes for live births will be assessed with a Post Due Date Questionnaire (a sample form included in Appendix D) from the Amgen Global Safety Database.

The number of infants with adverse events including complications, medical problems or congenital anomalies at birth will be assessed with a Post Due Date Questionnaire (a sample form included in Appendix D) from the Amgen Global Safety Database.

The Initial Pregnancy Questionnaire and the Post Due Date Questionnaire will capture the indications for all the medications that were taken 3 months prior to and during pregnancy. The Initial Pregnancy Questionnaire captures relevant comorbidities that may affect the pregnancy outcomes.

Major malformations or birth defects are defined as abnormalities incompatible with life or requiring medical/ surgical intervention. The term minor birth defect generally refers

to minor physical anomalies with less clinical importance that represent deviations from what is considered normal and do not have obvious medical, surgical, or cosmetic consequences. Major birth defects identified up to 1 year of age by the mother or the healthcare provider (HCP) will be included in the primary analysis. Major structural birth defects may be reported by the mother, a family member or her child's HCP via medical records. If a major malformation is reported the medical record will be adjudicated by a physician with expertise in teratology, pediatrics, and dysmorphology. Defects will be classified using the Center for Disease Controls (CDC) criteria (CDC 2023 - https://www.cdc.gov/ncbddd/birthdefects/macdp.html).

Infant outcomes are the number of cases reporting adverse events at 6 months and 12 months and may include whether they have not followed growth curves or met development milestones as expected for chronological age. These outcomes will be assessed with an Infant Questionnaire (a sample form included in Appendix E).

### 8.3.3 Covariate Assessment

#### 8.3.3.1 Pregnancy Information

Variables related to pregnancy such as demographics (age); pregnancy history; medical history; current medical conditions; current medication (prescription and over the counter [OTC]) and dates of use; other relevant history (family history, mother's occupation), and occurrence and dates of current pregnancy complications.

#### 8.3.3.2 Post Due Date Birth Information

Variables related to pregnancy and delivery such as maternal conditions, newborn complications, birth information, and delivery details.

### 8.3.4 Validity and Reliability

The primary exposure variable, exposure during pregnancy, is based on maternal, other family member, or HCP report. The outcome variable of adverse events at birth including complications, medical problems, or congenital anomalies is based on maternal or HCP report. Adverse events reported at 6 months and 12 months are based on follow-up received from the pregnant woman or HCP. For major congenital malformations, adjudication will be conducted to verify the outcome. For other outcome variables, standard methods are used to classify the outcome, confirm reliability of data capture, data entry, and classification.

### 8.4 Data Sources

The Amgen Global Safety Database is a comprehensive pharmacovigilance database that contains reports of adverse event data for all Amgen products including apremilast and all relevant cases from clinical and postmarket sources. Amgen performs follow-up on adverse events reported for all products including apremilast as per Amgen's due diligence process. The Amgen Global Safety Database includes reports of pregnancy, birth outcome, and infant health information of women who have had direct exposure to apremilast prior to or during pregnancy. Pregnant women may or may not provide consent for their health and their children's health information to be obtained by Amgen. The database contains positive and negative pregnancy outcome data, including congenital anomalies, spontaneous and elective abortions, fetal death/stillbirths, and premature birth.

All apremilast pregnancy cases (which may include multiple pregnancies from the same woman), of which Amgen becomes aware, reported from postmarketing source(s) (including through spontaneous reporting, cases solicited through patient support programs, market research, from the literature, from regulatory authorities, or postmarketing non-interventional studies) are entered into the Amgen Global Safety Database. Pregnancy exposure case reporting and follow-up through the infant's first year of life is voluntary and participants are free to withdraw at any time.

Amgen does not provide compensation for participation in the follow-up process. Participants are required to provide verbal or written consent that allows Amgen to collect relevant pregnancy, birth outcome, and infant health information.

As per Amgen's due diligence process, upon notification of an apremilast exposure during pregnancy (with or without an adverse event), Amgen Global Patient Safety follows up with the reporter to request informed consent to obtain pregnancy and infant health information from the mother. Follow-up will be performed as per Amgen's routine pharmacovigilance process at predefined intervals and adjusted accordingly depending on whether the mother is pregnant or has already delivered. Information requested may include, but is not limited to, alternate contact information for the mother, such as contact information of a close relative or friend, pregnancy/delivery details, medical history, laboratory and diagnostic tests, and HCP names. The process includes a set number of follow-up attempts over predefined intervals (post birth, when the infant is 6 months and 12 months). If there is no response to the follow-up attempts, the due diligence process is considered complete and the case is categorized as lost to follow-up. An exception to

this process is when the reporter explicitly states they are not prepared to provide any further information, did not provide consent to follow-up, or refused to provide any additional information about the pregnancy or infant. If this occurs, follow-up is not conducted.

**Migration of the Celgene Otezla (apremilast) Safety Database to the Amgen Global Safety Database**

Amgen acquired worldwide rights to apremilast from Celgene Corporation in connection with its merger with Bristol-Myers Squibb Company (BMS). Celgene Corporation was the Marketing Authorization Holder of apremilast until the product was acquired by Amgen in the third quarter of 2019. The Celgene Safety Database for apremilast was not transferred to Amgen until May of 2020, therefore, any/all reports collected prior to May of 2020 were processed by Celgene, as per Celgene's conventions.

In May of 2020, the cases/reports present within the Celgene Safety Database for apremilast were imported to the Amgen Global Safety Database "as is". Amgen Global Patient Safety did not retrospectively re-process the individual cases to align with current Amgen conventions.

All cases/reports following the Safety Database Transfer in May of 2020 were processed by Amgen utilizing Amgen's routine pharmacovigilance processes as outlined above.

### 8.5 Study Size

Sample size will not be pre-determined. This is a descriptive study which will identify the pregnant women exposed to apremilast through the Amgen Global Safety Database. The study size will depend on the number of reports submitted to the Amgen Global Safety Database for women exposed to apremilast during pregnancy.

### 8.6 Data Management

As per Amgen's due diligence process, hard copy questionnaire forms are mailed to women exposed to apremilast who have provided consent. Completed forms may be mailed, faxed, or emailed back to Amgen Global Safety (AGS). The forms are processed in the Amgen Global Safety Database in accordance with Amgen policies, processes and practices. Attempts to obtain additional information are performed if consent is provided. If further details are made available to Amgen, the Amgen Global Safety Database is updated.

## 8.7 Data Analysis

### 8.7.1 Planned Analyses

#### 8.7.1.1 Interim Analysis/Analyses

Interim report(s) of analyses performed for this study will be submitted to the FDA with the annual Periodic Benefit-Risk Evaluation Reports/Periodic Safety Update Reports for apremilast.

#### 8.7.1.2 Primary Analysis

The primary analysis for both annual reports and final analysis (at the end of the study) will be performed for primary outcomes.

### 8.7.2 Planned Method of Analysis

#### 8.7.2.1 General Considerations

All analyses will be descriptive. We will analyze the exposed cases overall, and, where possible, will group cases by whether outcomes were known when the exposure was reported (retrospectively) or whether the exposure was reported prior to occurrence of outcomes (prospectively). Pregnancy and infant outcomes will be summarized overall and separately for cases identified retrospectively and prospectively. These data constitute a case series, thus line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes and adverse events will be summarized along with tabulations of the numbers and proportions of outcomes based on timing of exposure (first, second, or third trimester), and indication for use of the medication.

Missing or Incomplete Data and Lost to Follow-up

Pregnancy and infant outcomes will be described among women exposed to apremilast during pregnancy. All available data will be included in the reporting. Missing and incomplete data will not be imputed. This may affect the overall description of the population and outcomes. Due to voluntarily self-reporting of the information, a proportion of cases may be lost to follow-up, and women with adverse events may be more likely to report than women without. This may result in overestimation of the proportion of exposed pregnancies with adverse outcomes.

#### 8.7.2.2 Descriptive Analysis

##### 8.7.2.2.1 Description of Study Enrollment

Descriptive results will be presented in each annual interim report.

#### 8.7.2.2.2 Description of Patient Characteristics

This study includes pregnant women exposed to apremilast during pregnancy. Demographic characteristics of subjects will be summarized using descriptive statistics. Continuous variables will be summarized using the mean, standard deviation, median, and range. Categorical variables will be summarized using counts and frequencies.

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

All analyses will be descriptive. The cases included in this study constitute a case series, thus line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes, and adverse events will be summarized along with tabulations of the numbers and frequencies of events by category of report: numbers who did not provide consent for follow-up, timing of exposure (first, second, or third trimester), and indication for use of the medication. The denominator is the number of pregnant women exposed to apremilast during pregnancy and the numerator is the number with the outcome.

The proportion of infants with adverse events including complications, medical problems or congenital anomalies at birth will be assessed in infants of women exposed to apremilast during pregnancy with corresponding 95% confidence intervals, as appropriate. The proportion of infants with adverse events at 6 months and 12 months of age will be assessed. All adverse events among mothers who have received apremilast at any time during the pregnancy will be summarized including the proportion with pregnancy and maternal complications. To assess events in the developing fetuses and neonates in women exposed to apremilast during pregnancy, the proportion of pregnancies resulting in spontaneous abortions, elective abortions, fetal death/stillbirths and premature delivery will be presented, along with corresponding 95% confidence intervals if appropriate.

If the available safety information relevant to exposure during pregnancy represents a safety signal, the signal will be further evaluated through the Amgen safety governance structure and, if deemed necessary, escalated for consideration of changes to the Reference Safety Information (eg, in labeling) as well as other forms of risk communication (eg, Dear Healthcare Provider Letters).

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

This study includes data of pregnant women exposed to apremilast and their infants through the first year of life. All outcomes in this study are safety endpoints including pregnancy and maternal complications, pregnancy outcomes, infant outcomes, and adverse events reported through the Amgen Global Safety Database.

### 8.7.4 Quality Control

See Section 8.6.

### 8.7.5 Limitations of the Research Methods

#### 8.7.5.1 Internal Validity of Study Design

##### 8.7.5.1.1 Measurement Error(s)/Misclassification(s)

Identification of pregnant women exposed to apremilast depends upon the accuracy of the incoming information received by Amgen's Global Safety Database. Amgen has a comprehensive system to detect these events and a process to verify the data. However, the postmarket data may have missing information which could lead to not classifying the report as a pregnancy case.

Misclassification of outcomes due to poor patient recall should be reduced in this retrospective and prospective study design. For those women exposed to apremilast during pregnancy that are identified retrospectively, they are likely to accurately recall any maternal complications, pregnancy outcomes, adverse infant outcomes, and events that may have occurred. However, exposed pregnant women that do not experience complications or adverse events may be less likely to consent to follow-up or may be lost to follow-up which would affect the denominators for aggregate outcomes.

A limitation of the study design relates to the evaluation of spontaneous abortion rates. As the study does not include women without recognition of pregnancy, cases of early spontaneous abortion (ie, at 7 to 9 weeks post-LMP or less) will likely not be captured. Underreporting of spontaneous abortions ranges from 25% to 30% (Johansen et al, 2022). In that case, the study results with respect to spontaneous abortion will potentially be limited to cases of late first-trimester and early second-trimester pregnancy loss.

Also, the calculation of frequency of birth defects excludes fetal losses (spontaneous abortions, elective abortions, or fetal deaths) for which no birth defects have been detected. This may introduce a misclassification bias as there is no uniform evaluation of embryos or fetuses that do not survive. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or structural defects. Amgen Global Safety will attempt to obtain information on structural defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. Therefore, defects reported in these groups will be considered separately from the primary analysis.

#### 8.7.5.1.2 Information Bias

Not applicable.

#### 8.7.5.1.3 Selection Bias

Pregnant women exposed to apremilast during pregnancy who consent to share their information with Amgen may be different from those who do not and may affect the accuracy of our estimates as discussed in Section 8.7.2.2. Due to voluntary self-reporting of the information, a proportion of cases may be lost to follow-up, and women with adverse events may be more likely to report than women without. This may result in overestimation of the proportion of exposed pregnancies with adverse outcomes.

#### 8.7.5.1.4 Confounding

Since this is a descriptive study and there is no comparison group, confounding will not be assessed in the study.

### 8.7.5.2 External Validity of Study Design

The pregnant women who consent to give their information may be different from women who do not share their information and hence limiting its generalizability to larger population of pregnant woman exposed to apremilast.

### 8.7.6 Analysis Limitations

None. The study is descriptive.

### *8.7.7* Limitations Due to Missing Data and/or Incomplete Data

Some patients may be lost to follow-up resulting in missing data. Patients that are lost to follow-up may differ from those that remain in the study and this could be an issue in this study.

## 8.8 Other Aspects

None.

## 9. Protection of Human Subjects

This study will be conducted in compliance with the protocol and protections in place during the collection of safety data through the AGS system, 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).

### 9.1 Informed Consent

Informed consent is required to perform follow-up for pregnancy, birth, and health information of the mother and infant.

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

There is not an IRB/IEC for this study.

### 9.3 Subject Confidentiality

No personal identifiers will be included in the data analyses or reporting from the Amgen Global Safety Database for this study.

### 9.4 Subjects Decision to Withdraw

All exposed women are identified from postmarketing reports to the Amgen Global Safety Database. Consent for follow-up is the responsibility of Amgen Global Safety. Subjects are free to withdraw consent at any time.

## 10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This is a retrospective and prospective observational study analyzing pre-existing data and the corresponding follow-up data within the Amgen Global Safety Database for women exposed to apremilast during pregnancy. Collection, recording, and reporting of safety information and product complaints is not applicable for this study because all data reported for the study either has been previously received or will further be captured in the Amgen Global Safety Database and reported as required in accordance with local requirements to regulatory authorities, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

## 11. Administrative and Legal Obligations

### 11.1 Protocol Amendments and Study Termination

If Amgen plans to amend the protocol, a proposed protocol amendment will be sent to the FDA for review and agreement before initiating any changes to the study conduct. Amgen will not terminate the study early unless agreement to do so has been given by the FDA.

## 12. Plans for Disseminating and Communicating Study Results

### 12.1 Publication Policy

These analyses will not be submitted for publication. However, if the study produces information that is informative to the benefit/ risk profile for apremilast as determined by Amgen Safety or the FDA, then the team will seek to publish the results from this study.

## 13. References

Apremilast Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

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American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: early pregnancy loss. *Obstet Gynecol*. 2018;132(5):e197-e207.

Centers for Disease Control and Prevention. Preterm birth. October 2019. Accessed 06 June 2023. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm.

Centers for Disease Control and Prevention. Data & statistics on birth defects. Accessed 06 June 2023. https://www.cdc.gov/ncbddd/birthdefects/macdp.html.

Chan TM, Chiou MJ, Kuo CF. Adverse pregnancy outcomes in women with Behçet's disease: population-based registry linkage study in Taiwan. *Clin Rheumatol*. 2021;40(10):4135-4142.

Gangbe EM, Badeghiesh A, Baghlaf H, Dahan MH. Pregnancy, delivery, and neonatal outcomes among women with psoriatic arthritis, a population-based study. *J Perinat Med*. 2022;50(5):581-586.

Johansen CB, Egeberg A, Jimenez-Solem E, Skov L, Thomsen SF. Psoriasis and adverse pregnancy outcomes: A nationwide case-control study in 491,274 women in Denmark. *JAAD International*. 2022;7:146-155.

Kimball AB, Guenther L, Kalia S, DeJong EMGJ, Lafferty KP, Chen DY, Langholff W, Shear NH. Pregnancy Outcomes in Women With Moderate-to-Severe Psoriasis From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Deramatol*. 2021;157(3):301-306.

Lee S, Czuzoj-Shulman N, Abenhaim HA. Behcet's disease and pregnancy: obstetrical and neonatal outcomes in a population-based cohort of 12 million births. *J Perinat Med*. 2019;47(4):381–387.

Xie W, Huang H, Ji L, Zhang Z. Maternal and neonatal outcomes in pregnant women with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Rheumatology*. 2021;60 (9):4018-4028.

## 14. Appendices

## Appendix A. List of Stand-alone Documents

None.

## Appendix B. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

### ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 section number 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

| |
|---|
| Study title: An Observational Study to Describe Women Exposed to Apremilast During Pregnancy and Infant Outcomes During the First Year of Life |

| |
|---|
| **EU PAS Register® number:** |
| **Study reference number (if applicable): 20210218** |

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 8.2.1 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 8.2.1 |
| 1.1.3 Progress report(s) | ☐ | ☒ | ☐ | |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | 8.7.1.1 |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 8.2.1 |

Comments:

| |
|---|
| Need to add EU PAS Register information |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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) | ☒ | ☐ | ☐ | 6.2 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 7.1 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized) | ☒ | ☐ | ☐ | 8.2 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no a priori hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| No hypotheses will be tested in the study. |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 8.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection? | ☒ | ☐ | ☐ | 8.2 |

[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 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence) | ☒ | ☐ | ☐ | 8.3.2 |
| 3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm [NNH]) | ☐ | ☒ | ☐ | |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 8.3.2 |

Comments:

| |
|---|
| There is no comparison group so no measures of association. |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 8.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 8.2.1 |
| 4.2.2 Age and sex | ☒ | ☐ | ☐ | 8.2 |
| 4.2.3 Country of origin | ☒ | ☐ | ☐ | 8.2 |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 6.1 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 8.2.4 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 8.2.3.1 |

Comments:

| |
|---|
| |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 8.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 8.3.4 |
| 5.3 Is exposure categorized according to time windows? | ☒ | ☐ | ☐ | 8.3.1 |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 8.3.1 |
| 5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 8.3.1 |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| This is a single arm study with no comparators. |

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 8.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 8.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☒ | ☐ | ☐ | 8.3.4 |
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☒ | ☐ | |

Comments:

| |
|---|
| These outcomes are not relevant for this study. |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☐ | ☐ | ☒ | 8.7.5.1.4 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☐ | ☐ | ☒ | 8.7.5.1.3 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☐ | ☐ | ☒ | 8.7.5.1.2 |

Comments:

| |
|---|
| There is no comparison group so measurement of bias and confounding is not applicable to this study |

| **Section 8: Effect measure modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| Effect measure modification is not applicable to this study. |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 8.4 |
| 9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 8.4 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.4 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 8.3.1 |
| 9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 8.3.2 |
| 9.2.3 Covariates and other characteristics? (eg. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 8.3.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical [ATC] Classification System) | ☐ | ☐ | ☒ | |
| 9.3.2 Outcomes? (eg, International Classification of Diseases [ICD], Medical Dictionary for Regulatory Activities [MedDRA]) | ☐ | ☒ | ☐ | |
| 9.3.3 Covariates and other characteristics? | ☐ | ☒ | ☐ | 8.3.3 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| Exposure coding is not applicable because all women in the study are exposed to apremilast. Outcomes, covariates and other characteristics are based on report from the mother or HCP and will be reported descriptively. No linkage will be performed. |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 8.7.2 |
| 10.2 Is study size and/or statistical precision estimated? | ☐ | ☒ | ☐ | 8.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 8.7.2.3 |
| 10.4 Are stratified analyses included? | ☐ | ☒ | ☐ | |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | 8.7.5.1.4 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☒ | ☐ | ☐ | 8.7.5.1.1 |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 8.7.7 |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| There is no comparison group so confounding will not be measured. Due to the descriptive nature of the study, no sensitivity analyses will be conducted. |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 8.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 8.6 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☒ | ☐ | |

Comments:

| |
|---|
| |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☐ | ☐ | ☒ | 8.7.5.1.3 |
| 12.1.2 Information bias? | ☐ | ☐ | ☒ | 8.7.5.1.2 |
| 12.1.3 Residual/unmeasured confounding? | ☐ | ☐ | ☒ | |
| (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | | | | 8.7.5.1.4 |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| This is a single arm study so bias and confounding will not impact the results. This is a case series so study feasibility is not applicable. |

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☐ | ☐ | ☒ | 9.2 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 9.3 |

Comments:

| |
|---|
| Cases for this study are drawn from the Amgen Global Safety Database. |

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 11.1 |

Comments:

| |
|---|
| |

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12.1 |

Comments:

| |
|---|
| |

Name of the main author of the protocol: PPD

Date: dd/Month/year

Signature: _____

## Appendix C. Initial Pregnancy Questionnaire – Mother

AMGEN

**Safety Database #** _____

**INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)**

*You may return completed form to Amgen Office Fax or Email:
Fax: (888) 814-8653 Email: svc-ags-in-us@amgen.com

### Section 1 – Reporter Information

**Reporter:** ☐ Mother ☐ Health Care Professional ☐ Other _____ Parent exposed to product? ☐ Mother ☐ Father

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the Authorization for Release of Medical Information? ☐ Yes ☐ No

In the event your contact information changes, please provide a back-up contact (for example a close relative or friend who does not live with you) who we may reach in an effort to contact you.

Relationship to patient: _____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

### Section 2 – Mother Current Pregnancy Information

**Mother's Initials:** _____

**Age:** _____years

**Number of fetuses:** _____

**Date of birth:** (if permitted to provide by local laws) _____ Day Month Year

**Date of last menstrual period:** _____ Day Month Year

**Estimated date of delivery:** _____ Day Month Year

**Relevant Laboratory Tests & Procedures**

| Test Name | Test Date (dd/mm/yr) | Test Result |
|---|---|---|
| | | |
| | | |
| | | |

### Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

| Amgen Product Used | Dose | Route (e.g. oral, subcutan.) | Frequency (e.g. daily, weekly) | Date Drug Started (dd/mm/yy) | Date Drug Stopped (dd/mm/yy) | Weeks of Pregnancy When Drug Taken (e.g. wk 28–wk 32) | Indication for Treatment |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Resumed (if applicable) | | | | | | | |
| Amgen Product Lot Number _____ ☐ Lot Number Not Known | | | | | | | |

AMGEN Safety Database #

List any other medications used within 3 months prior to or during the pregnancy

| Medications/Drugs | Dose | Route (e.g. oral, subcutaneous) | Frequency (e.g. daily, weekly | Date Drug Started (dd/mm/yy) | Date Drug Stopped (dd/mm/yy) | Indication for Treatment |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

## Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

| Pregnancy Complication or Adverse Event | Date the Complication or Event Started (dd/mm/yy) | Date the Complication or Event Resolved (dd/mm/yr) | Outcome (for example: resolved, not resolved, unknown, other, etc.) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

## Section 5 – Mother Relevant Medical History

**Please provide pertinent medical history:**

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other _____

**Please describe any additional factors that may have an impact on the outcome of this pregnancy**, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

## Section 6 – Mother Previous Obstetrical (Pregnancy) History

**Please provide the number of pregnancies after treatment with an Amgen product was initiated and the pregnancy outcome for each of these pregnancies and any additional relevant details:**

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____
☐ Stillbirth: _____
☐ Baby with birth defect: _____
☐ Outcome unknown: _____
☐ Miscarriage: _____
☐ Abortion (induced for medical reason): _____

AMGEN **Safety Database #** _____

☐ Abortion (induced for non-medical [voluntary] reason): _____

_____

☐ Other (specify outcome) or any significant additional information:

## Section 7 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

**Pregnancy Outcome (please check the appropriate box below):**

☐ Live birth
☐ Number of infants_____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below.)

**If live birth:** Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight _____gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)?

☐ Yes

☐ No

If yes, please provide specific information below.

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify): _____

_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐Yes ☐No
If yes, please provide the details below.

**Additional information** on pregnancy outcome:

AMGEN Safety Database #

**Section 8 – Reporter Signature**

Signature of person completing questionnaire _____ Date _____

Please print name _____

Title and specialty if HCP _____

***For consumers/patients only. Please provide contact information for your and your child's HCPs***
***May Amgen contact your HCP?*** ☐ ***Yes*** ☐ ***No***

**Health Care Provider for the pregnancy/delivery:**

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

**Health Care Provider who is prescribing the Amgen product:**

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

**Health Care Provider for the child:**

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

## Appendix D. 6 to 8 Weeks Post Due Date Questionnaire – Mother

Safety Database # [case_id]

You may return completed form to Amgen Office Fax or Email:

### 6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

**Section 1 – Reporter Information**

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

**Section 2 – Mother Prenatal Medication History**

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

| Medications/Drugs | Dose | Route (e.g. oral, subcutaneous) | Frequency (e.g. daily, weekly) | Date Drug Started (dd/mm/yy) | Date Drug Stopped (dd/mm/yy) | Indication for Treatment |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

**Section 3 – Mother Pregnancy Complications and/or Adverse Event Information**

| Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes) | Date the Complication or Event Started (dd/mm/yy) | Date the Complication or Event Resolved (dd/mm/yr) | Outcome (for example: resolved, not resolved, unknown, other, etc.) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

AMGEN Safety Database # [case_id]

## 6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

### Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

**Pregnancy Outcome (please check the appropriate box below)**

☐ Live birth
☐ Number of infants _____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify):_____

**If live birth**: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____ cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

**Additional Information** on pregnancy outcome:

### Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

***For consumers/patients only. Please provide contact information for your and your child's HCPs***
***May Amgen contact your HCP? ☐ Yes ☐ No***

**Health Care Provider for the pregnancy/delivery:**

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

**Health Care Provider who is prescribing the Amgen product:**

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

**Health Care Provider for the child:**

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

## Appendix E. 6-month and 12-month Infant Questionnaire

| | |
|---|---|
| Mother Safety Database # | |
| Infant Safety Database # | |

**SIX AND TWELVE MONTH INFANT QUESTIONNAIRE**

| | |
|---|---|
| **From:** [Title] [First Name] [Last Name]<br>[Company Name] [Country] | [today] |
| | |
| To:[reporter_first_name:corresp_contact]<br>[reporter_last_name:corresp_contact] | |

| | |
|---|---|
| **Event:**<br>Pregnancy | **Product:**<br>[product_name]:[1] |
| **AERA:**<br>[case_id] | **Reply Due By:**<br>[Due Date] |

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **SIX AND TWELVE MONTH INFANT QUESTIONNAIRE**

Respectfully Yours,

[Title] [First Name] [Last Name]
[Company Name] [Country]
Email: [email]
Fax: [fax]
Phone: [phone]

Mother Safety Database #

Infant Safety Database #

You may return completed form to Amgen Office Fax or Email:

AMGEN

# SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

## Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

## Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone (  ) _____ Fax (  ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

## Section 3 – Infant Medical Health Information

**List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)**

| Medications/Drugs | Dose | Route (e.g. oral, subcutaneous) | Frequency (e.g. daily, weekly | Date Drug Started (dd/mm/yy) | Date Drug Stopped (dd/mm/yy) | Indication for Treatment |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

## Section 4 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____ Title and specialty if HCP_____