1. ABSTRACT

- **Title**

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

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- **Keywords**

Apremilast, pregnancy, infant outcomes, observational, postmarketing

- **Rationale and Background**

Study 20210218 was conducted to complement the apremilast pregnancy registry (Study CC-10004-AID-001), which enrolled fewer apremilast-exposed pregnant women than expected, in order to meet a postmarketing requirement in the United States. This study estimated 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 the Amgen Global Safety Database.

This final report provides the analysis of the data collected from the first marketing approval of apremilast in March 2014 through the data cutoff date of 30 September 2024.

- **Research Question and Objectives**

Primary Objectives: to estimate the proportion of pregnancy and maternal complications and adverse events in the developing fetuses and neonates among women exposed to apremilast during pregnancy, and adverse events during the first year of life among their infants.

- **Study Design**

This was a worldwide, single-arm, observational case-series study designed to collect retrospective and prospective data in women exposed to apremilast during pregnancy and their infants to assess 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 were assessed through the first year of life.

- **Setting**

The data collection for this study was retrospective and prospective. Retrospectively, data between March 2014 and the approval date of the study protocol (11 July 2023) were extracted from the Amgen Global Safety Database through existing reports for women exposed to apremilast during pregnancy, and their infants. Prospectively, data from 11 July 2023 through September 2024 were extracted from the Amgen Global Safety Database and were included in the final analysis.

- **Subjects and Study Size, Including Dropouts**

The study population included women worldwide exposed to apremilast during pregnancy or within 2 days before their last menstrual period, who consented to provide their information and that of their infants to Amgen. Case information was obtained through the Amgen Global Safety Database, which included data from postmarketing sources such as spontaneous reports (including regulatory authority and literature), cases solicited through patient support programs and market research, and

postmarketing noninterventional studies. The study size was dependent on the number of reports submitted to the Amgen Global Safety Database for women exposed to apremilast during pregnancy.

- **Data Sources and Methods**

The Amgen Global Safety Database contains reports of adverse event data for all Amgen products including apremilast including all serious cases from clinical studies and all postmarketing cases that were reported to Amgen. This database includes reports of pregnancy, birth outcomes (including potential congenital anomalies, spontaneous and elective abortions, fetal deaths/stillbirths, and premature birth), infant health information of women who have had direct exposure to apremilast before or during pregnancy, and data reported from postmarketing sources (including through spontaneous reporting, cases solicited through patient support programs, market research, from the literature, from regulatory authorities, or postmarketing noninterventional studies). Pregnant women may or may not provide consent for their and their children's health information to be recorded and followed up by Amgen. Pregnancy-exposure case reporting and follow-up through the infant's first year of life are voluntary and participants are free to withdraw their consent for such data to be collected and recorded at any time.

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 consent to obtain pregnancy and infant health information from the mother. Information requested includes, 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 healthcare provider names. The process includes a set number of follow up attempts performed as per Amgen's routine pharmacovigilance process over predefined intervals (post birth, when the infant is 6 months and 12 months) and adjusted accordingly depending on whether the mother is pregnant or has already delivered. 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.

- **Results**

This final report included 533 pregnancy cases that had maternal exposure to apremilast from March 2014 to September 2024 reported in the Amgen Global Safety Database. Of these, 376 cases were excluded because of unknown exposure time and 41 cases were excluded because of exposure occurring outside of the pregnancy window. Among the remaining 116 cases, 57 cases were excluded because of unknown pregnancy outcomes/lost to follow-up.

Of the 59 pregnancies included in the analysis cohort for this final analysis report, 54 (91.53%) pregnancies were medically confirmed (ie, those reported by healthcare providers or consumers with evidence of medical records). Medical history was reported in 22 (37.29%) pregnancies. A history of previous pregnancy was recorded in 16 women and included live birth (10 cases, 16.95%), unknown outcomes (4 cases, 6.78%), and spontaneous abortion (2 cases, 3.39%). The mean (SD) age of women at pregnancy was 31.96 (5.42) years; with age at pregnancy unknown for 10 (16.95%) cases. The indications for apremilast exposure were reported as psoriasis for 43 (72.88%) pregnancies, psoriatic arthropathy for 11 (18.64%) pregnancies, unknown for 4 (6.78%) pregnancies, Behçet's syndrome for 1 (1.69%) pregnancy, ulcerative colitis for 1 (1.69%) pregnancy, atopic dermatitis for 1 (1.69%) pregnancy, spondylitis for 1 (1.69%) pregnancy, and exposure during pregnancy for 1 (1.69%) pregnancy (some patients

reported more than 1 indications for apremilast use). Concomitant medications other than apremilast were reported in 28 (47.46%) pregnancies.

Of the 59 cases with known pregnancy outcomes, there were 32 (54.24%) live births, 13 (22.03%) spontaneous abortions, 10 (16.95%) elective abortions, 4 (6.78%) fetal deaths/stillbirths, and 3 (5.08%) therapeutic abortions (pregnancy outcome categories are not mutually exclusive). Multiple outcomes of pregnancy were reported for some cases because of insufficient information to make a delineation between potential pregnancy outcomes. One pregnancy resulted in both spontaneous abortion and fetal death/stillbirth, 1 pregnancy resulted in both therapeutic abortion and fetal death/stillbirth, and 2 pregnancies resulted in both elective abortion and therapeutic abortion; follow up was ongoing for 1 reported pregnancy case at the time of this final report. Four (6.78%) pregnancies resulted in premature deliveries, of which 1 had fetal death/stillbirth and 2 had infants born with congenital anomalies, with 1 infant observed with a neurological disorder and 1 infant with multiple disorders (cardiac/vascular, ear/labyrinthine, congenital and hereditary disorders not elsewhere classified). None of the mothers responded to 6-month and 12-month follow-up questionnaires on infants outcomes. There were no spontaneous reports (for example by physicians) of abnormal screening tests, abnormal growth curves, delayed developmental milestones, or illnesses/persistent health problems for the infants at ≤ 6 and ≤ 12 months postdelivery in the safety database. Six cases had maternal or pregnancy complications recorded in the database including pre-eclampsia/eclampsia (1 case [1.69%]), gestational diabetes (1 case [1.69%]), and other complications (4 [6.78%] cases) such as blood sugar dropped, low pregnancy hormones, pain and morning sickness, and perinatal depression.

- **Discussion**

In this final analysis, maternal and pregnancy complications/adverse outcomes were assessed only among patients with known pregnancy outcomes. Of the 116 pregnant women who reported apremilast exposure within the pregnancy window, 50.86% of cases were excluded because of unknown outcomes/lost to follow-up. The dataset examined was limited due to missing information and other limitations inherent to the study design.

For pregnancy outcomes, there were 32 (54.24%) live births, 13 (22.03%) spontaneous abortions, 10 (16.95%) elective abortions, 4 (6.78%) fetal deaths/stillbirths, and 3 (5.08%) therapeutic abortions (pregnancy outcome categories are not mutually exclusive). Four (6.78%) pregnancies resulted in premature deliveries, of which 1 had fetal death/stillbirth and 2 had infants born with congenital anomalies. Maternal/pregnancy complications were reported for 6 cases (1 reported complication per case). Overall, few outcomes of maternal and pregnancy complications and fetal defects were reported. No pattern was observed for major malformations at birth and there were no findings for infant outcomes at 6 months and 12 months post birth in the reported results, though assessment of the latter was limited due to lack of responses to infant follow-up questionnaires. Selection and information bias and inability to validate pregnancy outcomes in some of the cases could have impacted the proportions of adverse outcomes reported in this study. Based on the descriptive nature of the study and the limitations with respect to missing data and potential bias, the results of this study are not sufficient to warrant a change in the risk profile for apremilast.

- **Marketing Authorization Holders**

Amgen Europe B.V., located at Minervum 7061, 4817 ZK Breda, The Netherlands, holds the marketing authorization for apremilast in the European Union.

Amgen Inc., located at One Amgen Center Drive, Thousand Oaks, CA 91320, holds the marketing authorization for apremilast in the United States.

- **Names and Affiliations of Principal Investigators**

Not applicable.