A PHASE 3B, MULTI CENTER, OPEN-LABEL LONG-TERM EXTENSION STUDY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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PROTOCOL SUMMARY

Study Title

A Phase 3b, Multi Center, Open-label, Long-term Extension Study of Apremilast (CC-10004) in Pediatric Subjects from 6 Through 17 Years of Age with Moderate to Severe Plaque Psoriasis

Indication

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37%. European populations have a higher prevalence than African and Asian populations (Michalek, 2017). The prevalence of psoriasis in children in the United States (US) from birth to age 18 years is 1%, with an incidence of 40.8 per 100,000 (Tollefson, 2010). The most common form of the disease in both adults and children is plaque-type psoriasis that is characterized by erythematous plaques with silvery-white scales (Bronckers, 2015; Silverberg, 2010; Fan, 2007; Morris, 2001; Lebwohl, 2003). The nails and, less often, the mucous membranes may also be affected (Weinstein, 2003).

Most pediatric patients present with mild, localized psoriasis that can be treated primarily with topical medications. Phototherapy is not recommended for fair-skinned or younger children, and psoralens with long-wave ultraviolet radiation (PUVA) is not recommended for use in pediatric psoriasis patients, due to the increased risk of malignancies (Ståhle, 2010). Due to this risk, phototherapy is usually reserved for older children and adolescents with extensive areas of involvement or refractory plaque disease (Shah, 2013; Marqueling, 2013). Systemic medications are utilized for more extensive or refractory disease; however, approved therapies for moderate to severe psoriasis in children are limited. As of 2019, the only approved systemic medications in the US for pediatric patients with this indication are the injection-delivered anti-tumor necrosis factor (anti-TNF) biologic agents, etanercept (Enbrel) and the anti-p40 inhibitor ustekinumab (Stelara). In the European Union (EU), etanercept (Enbrel), adalimumab (Humira), and ustekinumab (Stelara) are approved for pediatric use. Fear of needles is common in both children and adults and can contribute to negative experiences with needle procedures and health care for patients, caregivers, and health professionals (McMurtry, 2016). Thus, there remains an unmet need for effective systemic therapies that offer oral convenient dosing and a favorable benefit/risk profile for the treatment of pediatric patients with moderate to severe plaque psoriasis.

Apremilast is an oral selective phosphodiesterase type 4 (PDE4) inhibitor marketed worldwide under the trade name OTEZLA®. Apremilast 30 mg twice per day (BID) received its first global marketing approval for the treatment of adult patients with moderate to severe plaque psoriasis in 2014. Clinical data from multiple Phase 2 and Phase 3 trials have consistently demonstrated that apremilast is an effective oral therapy with an acceptable safety profile for psoriasis. The safety profile of apremilast in the post-marketing setting has remained consistent with that seen in the clinical development program. Thus, the benefit/risk profile of apremilast continues to be favorable in adult psoriasis patients.

A recent Phase 2 study (CC-10004-PPSO-001) conducted in pediatric patients with moderate to severe psoriasis has demonstrated a safety profile during 50 weeks of apremilast treatment that is comparable to that seen in the adult population, while exploratory analyses have indicated an improvement in Psoriasis Area and Severity Index (PASI) score from baseline. Efficacy and

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safety of apremilast in pediatric subjects (ages 6 to 17) is also being evaluated in the Phase 3 study CC-PPSO-003. The Phase 3b study, PPSO-004, which is being conducted to evaluate the long-term safety of apremilast in the treatment of pediatric subjects, ages 6 through 17, with moderate to severe plaque psoriasis, is an extension of study PPSO-003.

Objectives

Primary Objective

- The primary objective of this study is to evaluate the long-term safety of apremilast in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis

Secondary Objective

- To evaluate maintenance of effect as measured by static Physician Global Assessment (sPGA)

Study Design

This is a Phase 3b, multi center, open-label, long-term safety study of subjects that have completed Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Pediatric subjects, ages 6 through 17 years, who have completed Week 52 (end of Apremilast Extension Phase) in study CC-10004-PPSO-003.

Length of Study

This study will have a duration of up to 216 weeks and consist of two phases.

- Long-term Extension Phase – up to 208 weeks
- Observational Follow-up Phase – 8 weeks

Subjects must withdraw from the study once the age of 18 is reached or if apremilast becomes commercially available for pediatric psoriasis in a subject's age group.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for data analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Apremilast will be provided in bottles throughout the entire study. Apremilast will be provided as 20 or 30 mg tablets, based on body weight category, by the study sponsor, Amgen Inc. and will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink.

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Overview of Key Safety Assessments

Safety Assessments will include:

- Adverse events (AE)
- Weight and height
- Physical examinations
- Vital signs
- Clinical laboratory tests
- Pregnancy test for females of childbearing potential (FCBP)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Tanner staging
- Psoriasis flare and rebound

Overview of Efficacy Assessments

Efficacy Assessment

- sPGA

Statistical Methods

Subjects previously enrolled in study CC-10004-PPSO-003 (core study) that complete Week 52 (end of Apremilast Extension Phase) of that study will have the option to enroll in this study and continue to receive uninterrupted apremilast therapy for up to an additional 4 years or until commercially available for pediatric psoriasis, or until a subject turns 18 years of age.

Evaluation of long-term safety is the primary objective for this study. The safety analyses will be performed using the long-term extension treatment population defined as all subjects who received at least one dose of IP in this extension study. Data from safety assessments in this extension study and the core study will also be analyzed for the Apremilast Exposure Period starting from the first apremilast dose date in the core study based on all subjects who received apremilast treatment in the core study. Assessments from Week 0 of the core study will be used as baseline for subjects who were treated with apremilast initially from Week 0 in the core study. Assessments from Week 16 of the core study will be used as baseline for placebo subjects who first received apremilast at Week 16 in the core study.

Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, height, weight, body mass index (BMI), Tanner staging, and C-SSRS. Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to investigational product (IP). TEAEs leading to death or to IP withdrawal and serious TEAEs will also be summarized and listed separately.

Long-term clinical efficacy will be evaluated in this study. Baseline for long-term clinical efficacy endpoints will be based on Week 0 of the core study. To evaluate the responses over

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time, the proportion of subjects achieving responses at the specified time points will be presented.

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EDMS Doc. Number: 24696321 - 24085605

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 5
1. INTRODUCTION 15
1.1. Disease Background 15
1.2. Compound Background 15
1.3. Rationale 15
1.3.1. Study Rationale and Purpose 15
1.3.2. Rationale for the Study Design 16
1.3.3. Rationale for Dose, Schedule and Regimen Selection 16
2. STUDY OBJECTIVES AND ENDPOINTS 18
3. OVERALL STUDY DESIGN 19
3.1. Study Design 19
3.2. Study Duration for Subjects 20
3.3. End of Trial 20
4. STUDY POPULATION 21
4.1. Number of Subjects 21
4.2. Inclusion Criteria 21
4.3. Exclusion Criteria 22
5. TABLE OF EVENTS 24
6. PROCEDURES 26
6.1. Screening Period 26
6.2. Treatment Period 26
6.2.1. End of Treatment 27
6.3. Observational Follow-up Period 28
6.3.1. Observational Follow-up 28
6.4. Efficacy Assessment 28
6.5. Safety Assessments 29
6.5.1. Adverse Events 29
6.5.2. Contraception Education 29
6.5.3. Serum and Urine Pregnancy Tests for Females of Childbearing Potential 29
6.5.4. Complete Physical Examination 29

Approved

EDMS Doc. Number: 24696321 - 24085605

6.5.5. Abbreviated Physical Examination 30
6.5.6. Vital Signs, Height, Weight and Body Mass Index 30
6.5.7. Clinical Laboratory Evaluations 30
6.5.8. Hematology 30
6.5.9. Serum Chemistry 30
6.5.10. Urinalysis 31
6.5.11. Psychiatric Evaluation 31
6.5.12. Tanner Staging 31
6.5.13. Worsening of Psoriasis and Rebound Assessments 31
6.5.14. Unscheduled Visits 32
6.6. Subject Reported Outcomes 32
7. DESCRIPTION OF STUDY TREATMENTS 33
7.1. Description of Investigational Product(s) 33
7.2. Treatment Administration and Schedule 33
7.3. Method of Treatment Assignment 33
7.4. Packaging and Labeling 33
7.5. Investigational Product Accountability and Disposal 33
7.6. Investigational Product Compliance 34
8. CONCOMITANT MEDICATIONS AND PROCEDURES 35
8.1. Permitted Concomitant Medications and Procedures 35
8.2. Prohibited Concomitant Medications and Procedures 35
8.3. Required Concomitant Medications and Procedures 36
9. STATISTICAL CONSIDERATIONS 37
9.1. Overview 37
9.2. Study Population Definitions 37
9.3. Sample Size and Power Considerations 37
9.4. Background and Demographic Characteristics 37
9.5. Subject Disposition 38
9.6. Efficacy Analysis 38
9.7. Safety Analysis 38
9.8. Interim Analysis 38
9.9. Other Topics 39
9.9.1. Data Monitoring Committee 39

Approved

10. ADVERSE EVENTS....40
10.1. Monitoring, Recording and Reporting of Adverse Events....40
10.1.1. Seriousness....40
10.1.2. Severity/Intensity....41
10.1.3. Causality....42
10.1.4. Duration....43
10.1.5. Action Taken....43
10.1.6. Outcome....43
10.2. Abnormal Laboratory Values....43
10.3. Pregnancy....43
10.3.1. Females of Childbearing Potential – Collection of Pregnancy Information....44
10.3.2. Collection of Lactation Information....44
10.3.3. Male Subjects With Partners Who Become Pregnant....45
10.4. Reporting of Serious Adverse Events....45
10.4.1. Safety Queries....46
10.5. Expedited Reporting of Adverse Events....46
11. DISCONTINUATIONS....48
11.1. Treatment Discontinuation....48
11.2. Study Discontinuation....49
12. EMERGENCY PROCEDURES....50
12.1. Emergency Contact....50
12.2. Emergency Identification of Investigational Products....50
13. REGULATORY CONSIDERATIONS....51
13.1. Good Clinical Practice....51
13.2. Investigator Responsibilities....51
13.3. Subject Information and Informed Consent....51
13.4. Confidentiality....52
13.5. Protocol Amendments....52
13.6. Institutional Review Board/Independent Ethics Committee Review and Approval....52
13.7. Ongoing Information for Institutional Review Board/ Ethics Committee....53
13.8. Termination of the Study....53
14. DATA HANDLING AND RECORDKEEPING....54

Approved

14.1. Data/Documents 54
14.2. Data Management 54
14.3. Record Retention 54
15. QUALITY CONTROL AND QUALITY ASSURANCE 56
15.1. Study Monitoring and Source Data Verification 56
15.2. Audits and Inspections 56
15.3. Product Complaint 56
16. PUBLICATIONS 58
17. REFERENCES 59
18. APPENDICES 61
APPENDIX A. TABLE OF ABBREVIATIONS 61
APPENDIX B. STATIC PHYSICIAN GLOBAL ASSESSMENT (SPGA) 63
APPENDIX C. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) CHILDREN'S SINCE LAST VISIT 64
APPENDIX D. TANNER STAGING 67
APPENDIX E. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM 68
APPENDIX F. PREGNANCY NOTIFICATION FORM 71
APPENDIX G. LACTATION NOTIFICATION FORM 72

Approved

EDMS Doc. Number: 24696321 - 24085605

LIST OF TABLES

Table 1: Study Objectives....18
Table 2: Study Endpoints....18
[redacted]
Table 4: Abbreviations and Specialist Terms....61

Approved

LIST OF FIGURES

Figure 1: Overall Study Design.....20

Approved

EDMS Doc. Number: 24696321 - 24085605

1. INTRODUCTION

1.1. Disease Background

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37%. European populations have a higher prevalence than African and Asian populations (Michalek, 2017). The prevalence of psoriasis in children in the United States (US) from birth to age 18 years is 1%, with an incidence of 40.8 per 100,000 (Tollefson, 2010).

The first manifestation of psoriasis may occur at any age, with approximately one-third of cases reporting onset during childhood (Ståhle, 2010; Silverberg, 2010). Regardless of the timing of disease onset, the most common form of the disease in both adults and children is plaque-type psoriasis, characterized by erythematous plaques with silvery-white scales (Bronckers, 2015; Silverberg, 2010; Fan, 2007; Mallbris, 2005; Morris, 2001; Lebwohl, 2003). The nails and, less often, the mucous membranes may also be affected (Weinstein, 2003). One-third of patients present with the first signs and symptoms of psoriasis by the age of 20 years. (Tollefson, 2010; Benoit, 2007; Raychaudhuri, 2001).

1.2. Compound Background

Apremilast (CC-10004) is a specific phosphodiesterase type 4 (PDE4) inhibitor under development for use in the treatment of inflammatory conditions. PDE4 is one of the major phosphodiesterases expressed in leukocytes. PDE4 inhibition by apremilast elevates cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn down-regulates the inflammatory response by reducing the expression of pro-inflammatory cytokines, and increasing the production of anti-inflammatory mediators.

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA®) is approved in multiple countries worldwide for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and the treatment of adult patients with active psoriatic arthritis.

Apremilast remains under further clinical development for the treatment of inflammatory/autoimmune disorders. Further studies within the approved indications are also ongoing.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.3. Rationale

1.3.1. Study Rationale and Purpose

The treatment options for pediatric patients with plaque psoriasis remain limited. While most pediatric patients present with mild, localized psoriasis that can be treated primarily with topical medications, these therapies may be limited by their short treatment durations, poor treatment

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compliance and significant adverse effects (Chan, 2009; Kragballe, 2013). Phototherapy is not recommended for fair-skinned or younger children, and psoralens with long-wave ultraviolet radiation (PUVA) is not recommended for use in pediatric psoriasis patients, due to the increased risk of malignancies (Ståhle, 2010). Due to this risk, phototherapy is usually reserved for older children and adolescents with extensive areas of involvement or refractory plaque disease (Shah, 2013; Marqueling, 2013).

Systemic medications are utilized for more extensive or refractory disease; however, approved therapies for moderate to severe psoriasis in children are limited. Management of psoriasis in children can be challenging owing to a paucity of data and lack of standardized guidelines to the pediatric population (Vogel, 2012). As of 2019, the only approved systemic medications in the US for pediatric patients with this indication are the anti-tumor necrosis factor (TNF) biologic agent etanercept (Enbrel), and the anti-p40 inhibitor ustekinumab (Stelara), which is approved for use in adolescents aged 12 years and above. In the European Union (EU), etanercept (Enbrel), adalimumab (Humira) and ustekinumab (Stelara) are approved for pediatric use. Fear of needles is common in both children and adults and can contribute to negative experiences with needle procedures and health care for patients, caregivers, and health professionals (McMurtry, 2016). Thus, there remains an unmet need for effective systemic therapies that offer oral convenient dosing and a favorable benefit/risk profile for the treatment of pediatric patients with moderate to severe plaque psoriasis.

Apremilast is an oral selective PDE4 inhibitor marketed worldwide under the trade name OTEZLA®. Apremilast 30 mg twice per day (BID) received its first global marketing approval for the treatment of adult patients with moderate to severe plaque psoriasis in 2014. Clinical data from multiple Phase 2 and Phase 3 trials and in the post-marketing setting have consistently demonstrated that apremilast is an effective oral therapy with an acceptable safety profile in adults. Thus, the benefit/risk profile of apremilast continues to be favorable in adult psoriasis patients.

A recent Phase 2 study (CC-10004-PPSO-001) conducted in pediatric patients with moderate to severe psoriasis has demonstrated a safety profile during 50 weeks of apremilast treatment that is comparable to that seen in the adult population, while exploratory analyses have indicated an improvement in Protocol Area and Severity Index (PASI) score from baseline. Efficacy and safety of apremilast in pediatric subjects (ages 6 to 17) is also being evaluated in the Phase 3 study CC-10004-PPSO-003. This study was created to provide subjects who complete Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003 the option to continue to receive open-label uninterrupted apremilast therapy in an extension study.

1.3.2. Rationale for the Study Design

This Phase 3b, multi center, open-label, long-term extension study is designed to monitor long-term safety and efficacy of subjects that have completed Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

Two Phase 2 dose-finding studies have been conducted in adult subjects with moderate to severe plaque psoriasis. In study CC-10004-PSOR-005, a clear dose response was demonstrated with statistically significant improvement in the apremilast 20 mg BID and 30 mg BID, but not the

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apremilast 10 mg BID treatment groups, compared with placebo. Similar findings were observed in Study CC-10004-PSOR-011 which enrolled adult Japanese subjects with lower body weight and body mass index (BMI) than the subjects enrolled in study CC-10004-PSOR-005. The safety and tolerability profiles of the apremilast 20 mg BID and 30 mg BID treatment groups were acceptable with no clinically significant safety signals observed in either dose group. In both of these studies, the apremilast 30 mg BID treatment group provided a superior benefit/risk profile compared to apremilast 20 mg BID. The apremilast 30 mg BID dose was evaluated in two large pivotal Phase 3 studies (studies CC-10004-PSOR-008 and CC-10004-PSOR-009) and was subsequently approved for use in adult patients with moderate to severe plaque psoriasis.

Moderate to severe plaque psoriasis also occurs in children and adolescents ages 6 through 17 years. The pharmacokinetic (PK) profiles of two effective adult dosages, apremilast 20 mg BID and apremilast 30 mg BID, were evaluated in the pediatric Phase 2 study CC-10004-PPSO-001. The PK results from this study show that the apremilast exposure area under the plasma concentration-time curve (AUCtau) and peak observed plasma concentration of drug (C_{max}) on Day 14 in adolescents (12 to 17 years) treated with 30 mg BID, and children (6 to 11 years) treated with 20 mg BID appear to be comparable to the exposure observed in adult patients treated with 30 mg BID (Study CC-10004 PSOR-011). A population PK model was subsequently developed based on the data pooled from the pediatric study CC-10004-PPSO-001, and the adult studies CC-10004-PSOR-005 and CC-10004-PSOR-011. Based on modeling and simulation, the exposure of apremilast 20 mg BID in pediatric subjects weighing between ≥ 20 kg and < 50 kg is predicted to be similar to the exposure of apremilast 30 mg BID in adults (median of ratio within 0.8 and 1.25). The pediatric subjects weighing ≥ 50 kg are recommended to take the adult dose of 30 mg BID.

In study CC-10004-PPSO-001, the safety analyses showed a similar safety profile to that of adults but with higher incidence rates of adverse events, particularly of diarrhea, nausea and vomiting. These adverse events (AEs) were mostly mild to moderate, and of short duration with the majority of these AEs lasting < 3 days. It should be noted that dose titration, which has been shown to ameliorate gastrointestinal-related adverse events in the adult studies, was not implemented in CC-10004-PPSO-001. Exploratory efficacy analysis indicates that both apremilast doses (20 mg BID and 30 mg BID) may be efficacious in the treatment of moderate to severe plaque psoriasis in pediatric subjects.

Based on these Phase 2 results, the Phase 3 studies will evaluate the efficacy and safety of apremilast 20 mg BID for subjects < 50 kg and apremilast 30 mg BID for subjects ≥ 50 kg, compared to placebo, in the treatment of children and adolescent subjects with moderate to severe plaque psoriasis. As in the adult Phase 3 studies, dose titration is being implemented in study CC-10004-PPSO-003 in order to mitigate potential gastrointestinal-related adverse events. Subjects will enter study CC-10004-PPSO-004 directly from CC-10004-PPSO-003, therefore dose titration will not be included.

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the long-term safety of apremilast in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis.
Secondary Objective(s)
The secondary objective of the study is to evaluate the maintenance of effect as measured by static Physician Global Assessment (sPGA).

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Adverse Events: Type, frequency, severity, and relationship to apremilast	Week 0 (Visit 1) through end of Observational Follow-up	Study duration
	Columbia-Suicide Severity Rating Scale (C-SSRS)	Questionnaire to monitor depression, suicidal thoughts and behavior	Study duration
	Tanner Staging	Assessment of sexual maturity	Week 0 (Visit 1) and then every 52 weeks. Also Early Termination visit
	Body weight, height and BMI: Monitor growth	Height and body weight are measured at each visit	All visits
Secondary	sPGA	Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	All visits

BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; sPGA = static Physician Global Assessment.

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3. OVERALL STUDY DESIGN

3.1. Study Design

This study was created to provide subjects who complete Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003 the option to continue to receive open-label uninterrupted apremilast therapy. In study CC-10004-PPSO-004 treatment will be assigned by weight category at Visit 1 with subjects 20 kg to < 50 kg receiving apremilast 20 mg BID and subjects ≥ 50 kg receiving apremilast 30 mg BID. Treatment assignment will change during the study once the subject's weight reaches 50 kg.

The study will consist of up to 208 weeks of long-term treatment followed by an 8-week observational follow-up phase.

- Long-term Extension Phase – up to 208 weeks
- Observational Follow-up Phase – 8 weeks
  - Subjects who complete all 208 weeks of treatment or discontinue the study early, should return for observational follow-up visits 4 and 8 weeks after the last dose of apremilast

An external, independent Data Monitoring Committee (DMC) will review available safety and efficacy data approximately semi-annually for the first year and then annually or on an ad-hoc basis throughout the remainder of the study. The DMC consists of 4 external independent members (3 independent clinical trialists and 1 independent biostatistician) with voting privileges. All members are selected by Amgen with consideration for their respective expertise in the subject matter and/or in their experience in convening or participating in a DMC.

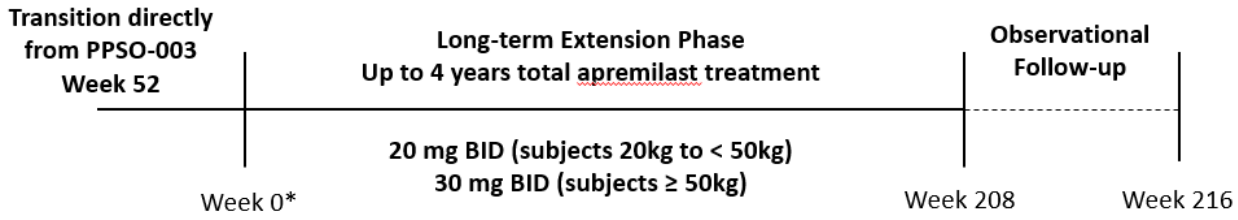
Treatment administration and schedule are discussed in Section 7.2.

At this time, there are no consistent AEs or laboratory findings that would generally constitute a reliable stopping rule for this study. Subjects will be monitored for AEs, vital signs, and laboratory assessments. All AEs, clinically significant changes in laboratory measures and clinically meaningful changes in vital signs will be recorded. Clinically meaningful changes that increase the risk to the subject, as assessed by the Investigator or Sponsor, may result in discontinuation of the subject from the study. Subjects who have psoriasis disease flare at any time during the period of the study and require additional psoriasis medication including systemic therapies such as methotrexate, systemic corticosteroids, or biologics, will be discontinued from the study and treated according to local treatment guidelines.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

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Figure 1: Overall Study Design



* Data and study assessments scheduled to be collected for Visit 1 (Week 0) will be populated with information collected at Visit 16 (Week 52) of study PPSO-003 with the exception of consent/assent forms and eligibility criteria.

3.2. Study Duration for Subjects

The study will last for up to a total of 216 weeks which includes 208 weeks of open-label apremilast treatment and an 8-week observational follow-up period.

Subjects must withdraw from the study once the age of 18 is reached or if apremilast becomes commercially available for pediatric psoriasis in a subject's age group.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

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4. STUDY POPULATION

4.1. Number of Subjects

An estimate of 140 subjects in North America, the EU, and rest of world may choose to be enrolled in this study. This is an estimate of the number of subjects from study CC-10004-PPSO-003 that may complete Week 52 and choose to continue receiving apremilast in study CC-10004-PPSO-004.

4.2. Inclusion Criteria

Subject must satisfy the following criteria to be enrolled in the study:

1. Subject is male or female 6 to 17 years of age, inclusive, at the time the informed consent document is signed by the legal guardian.
2. Subject must have a weight of ≥ 20 kg.
3. Subjects must have an age and sex specific BMI value no lower in range than the 5th percentile on the Centers for Disease Control (CDC) growth chart for children and adolescents (CDC, 2000).
4. Subject must have completed Week 52 (Apremilast Extension Phase) of Study CC-10004-PPSO-003.
5. Subject is able to sign an assent with a legal guardian/s who understand/s and voluntarily sign/s an informed consent prior to any study-related assessments/procedures being conducted.
6. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
7. All female subjects of childbearing potential (FCBP) must either practice abstinence* from heterosexual contact or use one of the approved contraceptive options as described below while on apremilast and for at least 28 days after administration of the last dose of apremilast. For the purpose of this study, a female subject is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first.

   At the time of study entry, and at any time during the study when a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

   Females of childbearing potential must have a negative pregnancy test at each visit or whenever else tested. All FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

   Option 1: Any one of the following effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

   OR

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Option 2: Male or female condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

NOTE: Option 2 may not be acceptable as a contraception option in all countries per local guidelines/regulations.

*Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has a condition, including the presence of laboratory abnormalities, or psychiatric illness, that would place the subject at unacceptable risk if he/she were to participate in the study.
2. Subject has a condition that confounds the ability to interpret data from the study.
3. Subject has evidence of skin conditions, other than psoriasis, that would interfere with clinical assessments.
4. Subject is pregnant or breastfeeding.
5. Subject has guttate, erythrodermic, or pustular psoriasis.
6. Subject has active tuberculosis (TB) or a history of incompletely treated TB.
7. Subject answers "Yes" to any question on the Columbia-Suicide Severity Rating Scale at Visit 16 of study CC-10004-PPSO-003.
8. Subject plans concurrent use of the following therapies that may have a possible effect on psoriasis.
    a) Conventional systemic therapy for psoriasis (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters)
    b) Biologic therapy:
        i. Etanercept (or biosimilar) treatment
        ii. Adalimumab (or biosimilar) treatment
        iii. Other TNF or interleukin (IL)-17 blockers (such as infliximab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, or their biosimilars)
        iv. Anti-IL-12 or anti-IL-23 treatment (such as ustekinumab, guselkumab, or tildrakizumab)
    c) Use of any investigational drug other than apremilast

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9. Subject has prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources.
10. Children in Care: a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation.

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EDMS Doc. Number: 24696321 - 24085605

5. TABLE OF EVENTS

Table 3: Table of Events

	Long-term Extension Phase (Year 1)					Long-term Extension Phase (Year 2)		Long-term Extension Phase (Year 3)		Long-term Extension Phase (Year 4)		Observational Follow-up[a]		UNS[b]	ET[c]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Week	**0**	**13**	**26**	**39**	**52**	**78**	**104**	**130**	**156**	**182**	**208**	**212**	**216**		
Informed consent/Assent[d]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Mass Index (BMI)	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Complete physical examination	X	-	-	-	X	-	X	-	X	-	X	-	-	-	X
Abbreviated physical[f] examination	-	X	X	X	-	X	-	X	-	X	-	X	X	-	-
Tanner Staging Assessment[g]	X	-	-	-	X	-	X	-	X	-	X	-	-	-	X
Pregnancy test and contraception education (FCBP only)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations	X	-	X	-	X	X	X	X	X	X	X	-	X	-	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psoriasis flare/rebound	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral Dose Apremilast[j]	X	X	X	X	X	X	X	X	X	X	X	-	-	-	-
Apremilast Drug Accountability	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X
Drug Dispensation	X	X	X	X	X	X	X	X	X	X	-	-	-	X	-

Abbreviations: BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; FCBP = females of childbearing potential; sPGA = static Physician Global Assessment; UNS = unscheduled visit.
Note: Data and study assessments scheduled to be collected for Visit 1 (Week 0) will be populated with information collected at Visit 16 (Week 52) of study PPSO-003 with the exception of consent/assent and eligibility.

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EDMS Doc. Number: 24696321 - 24085605

Footnotes:

[a] Subjects who discontinue the study early, should return for observational follow-up visits 4 and 8 weeks after the last dose of apremilast. Subjects who discontinue early should be encouraged to come back for an Early Termination Visit within 4 days of last intake of IP.

[b] Refer to Section 6.5.14 for details.

[c] Subjects who discontinue early should be encouraged to come back for an Early Termination Visit within 4 days of last intake of apremilast.

[d] Written informed consent from subject's legal guardian and subject assent will be obtained by the Principal Investigator or designee prior to entering data at Visit 1 and performing any study assessments thereafter.

[e] Vital signs will be obtained after the subject has been in the supine position for at least 5 minutes.

[f] An abbreviated physical examination may be performed at the discretion of the Investigator, if clinically needed.

[g] Tanner Staging assessment will be performed once every 52 weeks or at the Early Termination visit for subjects that do not complete the study.

[h] Urine pregnancy testing will be required for all FCBP. Urine pregnancy testing will be performed at each visit and the early termination (ET) visit (if applicable). If a urine test is positive, a serum test will be done for confirmation. In addition to the scheduled pregnancy tests in the clinic, monthly urine pregnancy tests should be performed by the subject between scheduled visits up to Visit 11. If a urine test is positive, the investigator will instruct the subject to suspend further apremilast dosing. The subject should then come into the site as soon as possible for a confirmatory serum pregnancy test.

[i] Any subject that answers 'Yes' to any question on the Columbia-Suicide Severity Rating Scale, at any time during the study (up to completion or early withdrawal) will be immediately withdrawn from study treatment and must be referred immediately for a psychiatric evaluation.

[j] Apremilast will be administered orally twice daily from Visit 1 to Visit 11 (if a subject remains eligible for study continuation).

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6. PROCEDURES

The following administrative/demographic procedures will be conducted as outlined in the Table of Events, Section 5.

Informed Consent and Subject Assent

Both an age-specific assent (by the study subject) and an informed consent form (ICF) by subject's legal guardian must be signed before any study-related assessments are performed. This process must be repeated with new signatures if a subject fails Screening for any reason and chooses to return and rescreen for a second attempt to meet study entrance.

Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study. Inclusion and exclusion criteria will be assessed at Visit 1.

Demographic Data

The demographic data will include the subject's year of birth (or as allowed by local regulations), age, gender, and race/ethnic origin. The demographic profile recorded in the source documents and electronic data record of study CC-PPSO-003, with the exception of age, will be copied directly into the CC-PPSO-004 database.

Medical and Disease History

Relevant medical history, as defined in the electronic case report form (eCRF) Completion Guidelines, will be copied into the CC-PPSO-004 database directly from the records collected in study CC-10004-PPSO-003. Disease history should include history of plaque psoriasis.

6.1. Screening Period

There will be no screening period in this study since subjects are rolling in directly from study CC-10004-PPSO-003 after confirmation of eligibility.

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. An administrative window of ± 2 weeks will be permitted throughout the Long-term Extension Phase. The permitted administrative window for the Observational Follow-up will be ± 4 days.

During the Long-term Extension Phase, the efficacy assessment may be performed by the Investigator or qualified designee at any time during a study visit. The Investigator performing an efficacy assessment shall make independent observations at a given study visit and shall not review previous assessments in advance of conducting an assessment.

The following evaluations will be performed at the frequency specified in the Table of Events, Section 5.

- Execution of the informed consent and assent forms
- Review of the inclusion and exclusion criteria

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- Adverse event evaluation (continuously)
- Concomitant medications and procedures evaluation
- Physical examination (Complete or abbreviated as indicated in Table 3)
- Vital signs (including blood pressure, temperature, respiratory rate and pulse)
- Body weight, height and BMI
- Hematology and chemistry panels as well as urinalysis
- Columbia-Suicide Severity Rating Scale
- Tanner Staging
- Psoriasis flare/rebound assessment
- Efficacy assessment (sPGA)
- Investigational product dispensation and accountability
- Urine pregnancy test is required at all visits for all female subjects of childbearing potential as defined in Section 6.5.3 along with counselling about pregnancy precautions and the potential risks of fetal exposure. In addition to the scheduled pregnancy tests in the clinic, monthly urine pregnancy tests should be performed by the subject between scheduled visits up to Visit 11.

6.2.1. End of Treatment

An Early Termination visit will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. The Investigator should make every attempt possible to have the subject evaluated at the Early Termination Visit within 4 days of the last intake of IP.

At the Early Termination Visit, the efficacy assessment may be performed by the Investigator or qualified designee at any time during a study visit. The Investigator performing an efficacy assessment shall make independent observations at a given study visit and shall not review previous assessments in advance of conducting an assessment.

The following evaluations will be performed at the frequency specified in the Table of Events, Section 5.

- Adverse event evaluation
- Concomitant medications and procedures evaluation
- Physical examination (Complete)
- Vital signs (including blood pressure, temperature, respiratory rate and pulse)
- Body weight, height and BMI
- Hematology and chemistry panels as well as urinalysis
- Columbia-Suicide Severity Rating Scale
- Tanner Staging

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- Psoriasis flare/rebound assessment
- Efficacy assessment (sPGA)
- Investigational product accountability
- Urine pregnancy test is required at all visits for all female subjects of childbearing potential as defined in Section 6.5.3 along with counselling about pregnancy precautions and the potential risks of fetal exposure.

6.3. Observational Follow-up Period

6.3.1. Observational Follow-up

All subjects will be followed for 56 days after the last dose of IP for AE reporting, as well as all serious adverse events made known to the Investigator at any time following the protocol-required reporting period or after end of study, as described in Section 10.1. The follow up period consists of two visits, one 4 weeks after last dose of apremilast and one 8 weeks after last dose of apremilast.

During the follow-up period, efficacy assessments may be performed by the Investigator or qualified designee at any time during a study visit.

The following evaluations will be performed at both Observational Follow-up Visits as specified in the Table of Events, Section 5.

- Adverse event evaluation
- Pregnancy testing for FCBP subjects
- Concomitant medications and procedures evaluation
- Abbreviated physical examination
- Vital signs (including blood pressure, temperature, respiratory rate and pulse)
- Body weight, height and BMI
- Hematology and chemistry panels as well as urinalysis (Visit 13 only)
- Columbia-Suicide Severity Rating Scale
- Psoriasis flare/rebound assessment
- Efficacy assessment (sPGA)
- Drug accountability at 4-week follow up visit

6.4. Efficacy Assessment

The following assessments will be conducted as outlined in the Table of Events, Section 5.

- **static Physician Global Assessment (sPGA)**

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and

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plaque elevation. When making the assessment of overall severity, the Investigator should factor in areas that have already been cleared (ie, have scores of 0 and not just evaluate remaining lesions for severity, ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions.

In the event of different severities across disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. See details in Appendix B.

6.5. Safety Assessments

6.5.1. Adverse Events

Safety assessments will be performed as outlined in the Table of Events, Section 5. Details of AE reporting can be found in Section 5.

6.5.2. Contraception Education

There are no adequate and well controlled studies of apremilast in pregnant women.

All females of childbearing potential (FCBP) must practice abstinence or use one of the approved contraceptive options as described in Section 4.2 while on apremilast and for at least 28 days after administration of the last dose of apremilast.

When a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes at the time of study entry or at any time during the study, the Investigator will educate the subject regarding options, including abstinence, and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

More information regarding the effects of apremilast on reproduction in animal and in vitro studies can be found in the Investigator's Brochure.

6.5.3. Serum and Urine Pregnancy Tests for Females of Childbearing Potential

Urine pregnancy testing will be performed on all FCBP at each planned study visit, including the two Observational Follow-up Visits and the Early Termination Visit (if applicable). In addition to the scheduled pregnancy tests in the clinic, monthly urine pregnancy tests should be performed by the subject between scheduled visits up to Visit 11. A serum pregnancy test with a sensitivity of ≤ 25 mI U/mL will be performed as confirmation of any positive urine test. A urine pregnancy test kit will be provided by the central laboratory. Pregnancy testing should be performed if the FCBP has missed a menstrual period or the contraception method has changed.

For the purposes of this study, a female subject is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first.

6.5.4. Complete Physical Examination

A complete physical examination including evaluations of general appearance, skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal (GI), neurological, and musculoskeletal systems will be performed at Visit 1 and then at 52-week intervals. A complete physical examination will also be performed at any Early Termination Visit.

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6.5.5. Abbreviated Physical Examination

An abbreviated physical examination including evaluation of the general appearance, respiratory, cardiovascular and GI systems may be performed at any visit after Visit 1 at the discretion of the Investigator, if clinically needed.

6.5.6. Vital Signs, Height, Weight and Body Mass Index

Vital signs, including temperature, respiratory rate, pulse, and blood pressure, will be taken during the visits indicated in the Table of Events (Section 5). Vital signs will be obtained after the subject has been in the supine position for at least 5 minutes. Height (using stadiometer) and weight and body mass index will be measured and recorded as indicated in the Table of Events (Section 5).

Blood pressure will be obtained after the subject has been in the supine position for at least 5 minutes. Since drinking hot or cold beverages (including water) has a significant impact on recorded oral body temperature, no beverages should be ingested within 15 minutes when using an oral thermometer.

Investigators are to report any clinically significant abnormal findings as AEs.

6.5.7. Clinical Laboratory Evaluations

A central laboratory will be used for this study. Clinical laboratory evaluations will be performed as indicated in the Table of Events (Section 5). The Principal Investigator (PI) or medically-qualified designee will review and assess all clinical laboratory data. The laboratory reports should be initialed and dated by the PI or medically-qualified designee, and the clinical or nonclinical significance of any abnormal laboratory results should be indicated. Abnormal laboratory results may be repeated to rule out laboratory errors. Any clinically significant abnormal laboratory result should be reported as an AE and should be followed to resolution (ie, stabilizes, returns to baseline or becomes clinically insignificant).

Additional clinical safety laboratory evaluations should be performed if judged clinically appropriate by the Investigator or by a medically qualified designee, or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is warranted.

The amount of blood taken from subjects at each visit and cumulatively over the course of the entire study is within the safety limits as described in a bulletin published by the World Health Organization (WHO) (Howie, 2011). The volume of blood drawn will not exceed 6 mL at any visit.

6.5.8. Hematology

Hematology laboratory evaluations will include red blood cells (RBCs), hemoglobin, hematocrit, white blood cells (WBCs), absolute and differential and platelet count. Approximately 2 mL of blood will be taken to complete hematology evaluations at each visit as designated in Table 3.

6.5.9. Serum Chemistry

Serum chemistry laboratory evaluations will include sodium, potassium, chloride, carbon dioxide, calcium, blood urea nitrogen, creatinine, glucose, albumin, total protein, alkaline

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phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamate pyruvic transaminase (ALT/SGPT), gamma-glutamyl transpeptidase, lactate dehydrogenase, phosphate, and magnesium. Approximately 3.5 mL of blood will be taken to complete serum chemistry evaluations at each visit as designated in Table 3.

6.5.10. Urinalysis

Urinalysis, completed as designated in Table 3, will include specific gravity, pH, glucose, protein, ketones, and hemoglobin/blood. A microscopic examination (eg, casts, RBCs, and WBCs) will be performed in the event of a positive result.

6.5.11. Psychiatric Evaluation

Psoriasis has been associated with an increased risk of developing psychiatric disorders, including depression and anxiety in pediatric patients (Kimball, 2012). Apremilast prescriber information (eg, Summary of Product Characteristics, Package Insert) includes a warning regarding depression and suicidal thoughts. The Investigators should advise subjects, their caregivers, and families of the need to be alert for the emergence or worsening of depression or other mood changes, and if such changes occur, to contact the Investigator.

All subjects will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix C) assessment. This questionnaire is suitable for assessment of suicidal ideation and behavior in clinical and research settings (Posner, 2011). The C-SSRS questionnaire will be administered at all study visits. Any subject that answers 'Yes' to any question on the C-SSRS at any time during the study will be immediately withdrawn from study treatment and must be referred immediately for a psychiatric evaluation. The subject should return for the Observational Follow-up Visits at 4 and 8 weeks after Early Termination.

A copy of the psychiatric evaluation report, if available, should be in the subject's source document.

6.5.12. Tanner Staging

Assessments of sexual maturity (Tanner Staging) will be performed at Visit 1 and then every 52 weeks thereafter. A Tanner Staging assessment will also be completed at the Early Termination visit for subjects that do not complete the study. A description of each Tanner stage is provided in Appendix D (WHO, 2010).

6.5.13. Worsening of Psoriasis and Rebound Assessments

Psoriasis flare is an AE (and will be recorded as an AE) and represents an atypical or unusual worsening of disease during treatment (Carey, 2006). It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. A more typical, gradual worsening of plaque psoriasis will not be recorded as an AE.

Rebound is an AE and is defined as a severe and sudden worsening of disease or a new generalized pustular, erythrodermic, or more inflammatory psoriasis that occurs after treatment had been discontinued (Gordon, 2005).

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6.5.14. Unscheduled Visits

Unscheduled visits may be necessary during the course of the study to capture a subject's status between regularly scheduled visits. Examples include, but are not limited to, a worsening of psoriasis symptoms, occurrence of an AE, or follow-up to a previously reported AE.

The following assessments will be performed at these visits:

- Assess vital signs (temperature, respiratory rate, pulse, and blood pressure), height and weight
- Record concomitant medications/procedures and AEs
- Drug accountability and dispensation if needed
- sPGA
- Psoriasis flare or rebound
- C-SSRS questionnaire

The following assessments may also be performed at the discretion of the Investigator, if clinically needed:

- Obtain blood sample and/or urine sample for any necessary laboratory test indicated in the Table of Events (Table 3)
- Perform abbreviated physical examination

6.6. Subject Reported Outcomes

Not Applicable

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7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

The chemical name of apremilast (CC-10004) is acetamide, N[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl].

Apremilast will be provided in bottles throughout the entire study. Apremilast will be provided as 20 or 30 mg tablets and will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink.

7.2. Treatment Administration and Schedule

At Visit 1, subjects who meet entry criteria will continue to receive apremilast. Subjects with a weight between 20 kg to < 50 kg will receive apremilast 20 mg BID and subjects with weight ≥ 50 kg at Visit 1 will receive apremilast 30 mg BID. Subjects that begin the study receiving apremilast 20 mg BID and later record a body weight ≥ 50 kg, will be switched to apremilast 30 mg BID. Additional dose adjustments will be allowed for issues of tolerability or safety.

Overdose for this protocol, on a per dose basis, is defined as ingestion of greater than 100 mg of apremilast tablets in any 24-hour period whether by accident or intentionally. On a schedule or frequency basis, an overdose is defined as dosing more than 4 times during any 24-hour period.

Subjects will be dispensed apremilast in bottles which will contain a sufficient number of tablets to last up to the next scheduled study visit.

7.3. Method of Treatment Assignment

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense apremilast in accordance with the number assigned by the centralized interactive response technology (IRT).

7.4. Packaging and Labeling

The label(s) for apremilast may include, but may not be limited to, Sponsor name, address and telephone number, the protocol number, apremilast name, dosage form and strength (where applicable), amount of apremilast per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5. Investigational Product Accountability and Disposal

The Investigator(s) or a qualified designee(s) is/are responsible for taking an inventory of each shipment of apremilast received and comparing it with the accompanying apremilast accountability form. The Investigator(s) or designee(s), will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and record the information in the IRT.

At the study site, all apremilast will be stored in a secure, locked area to prevent unauthorized access. Apremilast must be stored as directed on the bottle label(s).

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The Investigator(s) or qualified designee(s) is responsible for the accountability of all apremilast issued to the site during the course of the study.

Amgen (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Amgen (or designee).

7.6. Investigational Product Compliance

The study staff will maintain an ongoing record of the dispensing and administration of apremilast for each subject via an accountability record or equivalent document that will be verified by Amgen's study monitor.

For apremilast dispensed to the subject/guardian for outpatient administration, study personnel will review the instructions printed on the package with the study subject and/or legal guardian prior to dispensing apremilast in tablet form. Investigational product will be dispensed as noted in the Table of Events, Section 5. The subjects will be instructed to return the apremilast bottles, including any unused medication, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their apremilast as instructed at each study visit. Any problems with apremilast compliance will be reviewed with the subject. If a subject misses four or more consecutive days of dosing, Amgen should be contacted to decide whether dosing should resume or whether the subject should be terminated from the study.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with Amgen. Overall compliance with the study treatment regimen is defined as taking between 75% and 120% of the expected doses during a subject's participation while in the Long-term Extension Phase of the study.

Accurate recording of all apremilast administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

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EDMS Doc. Number: 24696321 - 24085605

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression.

For information regarding other drugs that may interact with apremilast and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

Subjects may take any medication that is not restricted by the protocol, is not expected to interfere with the conduct of the study and will not affect study assessments. Chronic medication should be dosed on a stable regimen and continued through the 208-week Long-term Extension Phase.

All medications (prescription and non-prescription), treatments and therapies taken by the subject from Visit 1 throughout the Long-term Extension Phase, the 4- and 8-week follow-up periods, including those initiated within 30 days prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The name of the medication/treatment, dose, unit, frequency, route, indication, the date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. The recording of any permitted topical medications taken for psoriasis should also include the area of the body to which they are applied.

The following topical therapy will be permitted*:

- Low-potency or weak corticosteroids (such as hydrocortisone, desonide, alclometasone dipropionate) will be allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study.
- An unmedicated skin moisturizer (eg, Eucerin®) will also be permitted for body lesions only.

* Subjects should not use these topical treatments within 24 hours of a study visit.

8.2. Prohibited Concomitant Medications and Procedures

The following psoriasis medications cannot be administered while subjects are receiving apremilast:

- Topical therapy unless otherwise specified (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol)
- Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters
- Phototherapy including UVB and PUVA

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- Biologic agents such as etanercept, infliximab, adalimumab, certolizumab pegol, guselkumab, tildrakizumab, ixekizumab, brodalumab, or ustekinumab
- Use of tanning booths or other ultraviolet light sources
- Use of an investigational drug

Subjects who need to be treated with protocol-prohibited medication will be withdrawn from the study.

8.3. Required Concomitant Medications and Procedures

Not Applicable

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9. STATISTICAL CONSIDERATIONS

9.1. Overview

Subjects previously enrolled in study CC-10004-PPSO-003 (core study) that complete Week 52 (end of Apremilast Extension Phase) of that study will have the option to enroll in this long-term extension study (CC-10004-PPSO-004) and continue to receive uninterrupted apremilast therapy for up to an additional 4 years or until commercially available for pediatric psoriasis, or until a subject turns 18 years of age.

Key elements of the statistical analyses for this study are described in this section. The statistical analyses for this study will be the responsibility of the Sponsor or its designee.

9.2. Study Population Definitions

For the long-term extension study, the safety and efficacy analyses will be performed using the long-term extension treatment population defined as all subjects who received at least one dose of apremilast in the extension study.

For the Apremilast Exposure Period, the safety analysis will use data from the core study and the long-term extension study. The safety analyses will be based on the apremilast subjects as treated population, which includes all subjects who received apremilast treatment in the core study who may or may not have enrolled in the long-term extension study.

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9.3. Sample Size and Power Considerations

Approximately 140 subjects in North America, the EU, and rest of world may become eligible and choose to be enrolled in this study. This is an estimate of the number of subjects from study CC-10004-PPSO-003 that may complete Week 52 and choose to continue receiving apremilast in study CC-10004-PPSO-004. For a common adverse event with subject incidence rate of 5%, 10% or 15% in this extension study, the two-sided 95% confidence intervals will be (1.4%, 8.6%), (5.0%, 15.0%), or (9.1%, 20.9%) respectively.

Assuming two years as the average for subjects receiving apremilast treatment in the extension study, the overall apremilast exposure in the extension study will be estimated as 280 subject-years. For a common adverse event with the exposure adjusted incidence rate (EAIR) of 3.0, 5.0 or 7.0 per 100 subject-years in the extension study, the two-sided 95% confidence interval for EAIR ranges are (0.9, 5.1), (2.2, 7.8) or (3.7, 10.3) respectively, using a normal approximation approach based on the Poisson distribution assumption.

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

The summaries will be based on data collected by date of randomization in the core study. When appropriate, summaries will also be provided using data collected by the first visit of the extension study.

EDMS Doc. Number: 24696321 - 24085605

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

The efficacy endpoints will be summarized descriptively.

Missing data will be handled by non-responder imputation (NRI) and data as observed (DAO) for binary endpoints.

Baseline for long-term clinical efficacy endpoints will be based on Week 0 of the core study. To evaluate the responses over time, the proportion of subjects achieving the response at the specified time points will be presented.

9.7. Safety Analysis

Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, height, weight, BMI, Tanner staging, and C-SSRS. No inferential testing for statistical significance will be performed.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to apremilast. TEAEs leading to death or to apremilast withdrawal and serious TEAEs will also be summarized and listed separately. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory, vital signs, weight, height, BMI, Tanner staging, and C-SSRS data will be summarized descriptively by time point. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges at baseline versus postbaseline will be provided for laboratory tests.

The safety analyses will be performed using the long-term extension treatment population defined as all subjects who received at least one dose of apremilast in this extension study. Data from safety assessments in the extension study and the core study will also be analyzed for the Apremilast Exposure Period starting from the first apremilast dose date in the core study based on all subjects who received apremilast treatment in the core study. Assessments from Week 0 of the core study will be used as baseline for subjects who were treated with apremilast initially from Week 0 in the core study. Assessments from Week 16 of the core study will be used as baseline for placebo subjects who first received apremilast at Week 16 in the core study.

9.8. Interim Analysis

No formal interim analysis will be conducted. However, safety and efficacy data of this extension study may be analyzed before study completion.

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9.9. Other Topics

9.9.1. Data Monitoring Committee

Monitoring will also be performed by an independent, external Data Monitoring Committee (DMC) that will assess safety as outlined in the DMC charter (available upon request). The DMC is comprised of three independent external clinical trialists and one independent external biostatistician for whom there is no identified conflict of interest. The DMC will meet as outlined in the DMC charter. The DMC scope, conduct, processes, and accountabilities are prespecified in its charter. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension.

Approved

EDMS Doc. Number: 24696321 - 24085605

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.2), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the case report form (CRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF (See Section 7.2 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the AE CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF and on the paper SAE report form. The overdose itself should not be reported as an SAE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 56 days (8 weeks) after the last dose of apremilast and all SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study. All adverse events (serious/non-serious) will be recorded on the AE page of the CRF and, on the paper SAE report form (for SAEs) and in the subject's source documents. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by recording on the eCRF and submitting the SAE information using the paper Serious Adverse Event Report Form by facsimile/email directly to Amgen Global Patient Safety.
Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.1.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

Approved

EDMS Doc. Number: 24696321 - 24085605

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to apremilast, action taken regarding apremilast treatment, and outcome.

10.1.2. Severity/Intensity

For each AE, the Investigator must assess the severity/ intensity of the event based on the descriptions listed below.

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Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.1.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

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Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional non-IP that has not been manufactured or provided by Amgen, please provide the name of the manufacturer when reporting the event.

10.1.4. Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.1.5. Action Taken

The Investigator will report the action taken with apremilast as a result of each AE, as applicable (eg, discontinuation or interruption of apremilast, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.1.6. Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.2. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.3. Pregnancy

All pregnancies or suspected pregnancies are immediately reportable events.

Approved

EDMS Doc. Number: 24696321 - 24085605

10.3.1. Females of Childbearing Potential – Collection of Pregnancy Information

Pregnancies and suspected pregnancies (including elevated β-subunit of chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is taking apremilast, or within 28 days of the subject's last dose of apremilast, are considered immediately reportable events. Apremilast is to be discontinued immediately and the subject instructed to return any unused portion of the apremilast to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Global Patient Safety immediately by email, or facsimile, or other appropriate method, using the Pregnancy Notification Form or approved equivalent form (refer to Appendix F). The Pregnancy Notification Form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking IP through 28 days of the subject's last dose of IP. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted 12 months after the birth of the child (if applicable).

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Amgen Global Patient Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Amgen Global Patient Safety by facsimile, email or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the paper SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to apremilast should also be reported as an SAE to Amgen Global Patient Safety by facsimile, email or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the paper SAE Report Form or approved equivalent form.

10.3.2. Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking IP through 28 days post last dose of IP.
- Information will be recorded on the Lactation Notification Form (refer to Appendix G) and submitted by facsimile or email to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study.

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EDMS Doc. Number: 24696321 - 24085605

With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking IP through 28 days after discontinuing IP.

10.3.3. Male Subjects With Partners Who Become Pregnant

In the event a male subject fathers a child during treatment, and for an additional 28 days after discontinuing IP, the information will be recorded on the Pregnancy Notification Form (refer to Appendix F)**.** The form must be submitted to Amgen Global Patient Safety with 24 hours of the investigator's/site's awareness of the pregnancy (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.4. Reporting of Serious Adverse Events

Any AE that meets any seriousness criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to apremilast) that occur during the study (from the time the legal guardian signs informed consent and subject signs assent until 56 days after the last dose of apremilast) and all SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study. Serious adverse events occurring prior to treatment (after signing the ICF/assent) will be collected/recorded/reported.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen Global Patient Safety as soon as these become available. Any follow-up data should be detailed in the AE page/screen of the eCRF and, , the paper SAE Report form or approved equivalent form must be completed as well.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant

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EDMS Doc. Number: 24696321 - 24085605

initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Amgen and the IRB/EC.

Serious Adverse Event Reporting transmitted via paper Serious Adverse Event Report Form:

- Facsimile transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information. If facsimile is unavailable, the email method to transmit this information is acceptable (refer to Appendix E).
- In rare circumstances and in the absence of facsimile equipment, this form may be sent via email, or notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form in English language sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting timeframes.
- Once the study has ended, serious adverse events (regardless of causality) should be reported to Amgen Global Patient Safety if the investigator becomes aware of them and may use the paper Serious Adverse Event Report Form (refer to Appendix E**).**

10.4.1. Safety Queries

Queries pertaining to SAEs will be communicated/generated from Amgen Global Patient Safety to the site via Amgen's global paper safety query process.).. With regards to urgent queries (eg, missing causality assessment) may be handled by telephone, facsimile or email

10.5. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Amgen Global Patient Safety will determine the expectedness of events suspected of being related to apremilast based on the Investigator Brochure.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Amgen or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Amgen or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR)
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

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Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. (See Section 14.3 for record retention information).

Amgen Global Patient Safety Contact Information (fax/email):

For Amgen Global Patient Safety contact information, please refer to your site's paper Serious Adverse Event Report Form, paper Pregnancy Notification Form and/or paper Lactation Notification Form (Appendix E, Appendix F, Appendix G).

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11. DISCONTINUATIONS

Subjects who have psoriasis disease flare during the Long-term Extension Phase and require systemic conventional therapies, biologics, phototherapy, or prohibited topical therapies (defined in Section 8.1) will be discontinued from the study and properly treated according to local treatment guidelines. In the case of psoriasis disease flare during the Long-term Extension Phase, the reason for discontinuation will be lack of efficacy. Subjects will not be withdrawn from the study if the disease flare and the need for treatment occur during the follow-up periods. Every attempt will be made to collect all or specific final data on a discontinued subject. Any subject whose calculated BMI falls below the 5th percentile on the Centers for Disease Control (CDC) growth chart (CDC, 2000) at any visit will be discontinued from the study.

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse event
- Lack of efficacy
- Withdrawal by parent/guardian or subject
- Death
- Lost to follow-up
- Non-compliance with apremilast
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents. Additional site monitoring may be performed to ensure accurate identification and documentation of the reason behind any early termination due to an adverse event.

When a subject is discontinued from treatment, the Investigator should make every attempt possible to have the subject evaluated at the Early Termination Visit within 4 days of the last intake of apremilast.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

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EDMS Doc. Number: 24696321 - 24085605

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Adverse event
- Withdrawal by parent/guardian or subject
- Death
- Lost to follow-up
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

Approved

EDMS Doc. Number: 24696321 - 24085605

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should use their medical judgement to provide appropriate medical care of clinical trial subjects. The Investigator may also contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached,the Investigator may also contact the Amgen Medical Information number at 1-800-77-AMGEN (1-800-772-6436) . The representatives are responsible for obtaining your call-back information and contacting the on-call Amgen/contract research organization Medical Monitor, who will then contact you promptly.

12.2. Emergency Identification of Investigational Products

Not Applicable

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EDMS Doc. Number: 24696321 - 24085605

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Amgen, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Amgen staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff. The specific study-appropriate qualifications of each investigator are assessed during the site feasibility and selection process.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Amgen information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Amgen on public registry websites) is considered Amgen confidential information. Only information that is previously disclosed by Amgen on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Amgen protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Amgen. Information proposed for posting on the Investigator's or their institution's website must be submitted to Amgen for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Amgen will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their legal guardian as agreed by the subject.

13.3. Subject Information and Informed Consent

Both an age-specific assent (by the study subject) and an informed consent form (ICF; by subject's legal guardian) must be signed before any study-related assessments are performed.

Approved

EDMS Doc. Number: 24696321 - 24085605

Documentation that the subject assent and legal guardian informed consent occurred prior to the study subject's entry into the study and of the assent/informed consent process should be recorded in the study subject's source documents including the date. The original assent and informed consent documents signed and dated by the study subject (assent), subject's legal guardian (ICF), and by the person facilitating the process (assent and ICF), prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject's legal guardian. In addition, if a protocol is amended and it has an impact on the content of the assent and informed consent, the two documents must be revised. Study subjects participating in the study, and their legal guardians, must repeat the assenting/consenting process with the revised assent/consent documents when the amended protocol is implemented. The revised documents signed and dated by the study subject, subject's legal guardian, and by the person facilitating the process, must be maintained in the Investigator's study files and a copy given to the study subject's legal guardian.

13.4. Confidentiality

Amgen affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Amgen requires the Investigator to permit Amgen's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Amgen Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, legal guardian ICF, subject assents, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Apremilast can only be supplied to an Investigator by Amgen or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Amgen or its authorized representative. This documentation must also include a list of the

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members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Amgen and the IRB/EC prior to use.

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13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Amgen reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Amgen has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or compact disc, read only memory device (CD-ROMs).

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Amgen standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed legal guardian ICFs and assents for all subjects;
- Subject identification code list and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Amgen, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

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- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Amgen if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Amgen prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Amgen for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

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EDMS Doc. Number: 24696321 - 24085605

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Amgen or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Amgen ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Amgen representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Amgen representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Quality, Compliance & Audit. Learning & Performance unit exists within Amgen. Representatives of this unit will conduct audits of clinical research activities in accordance with Amgen SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Amgen immediately.

15.3. Product Complaint

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product or device after they are released for distribution to market or clinic by either Amgen or by distributors, and partners with whom Amgen manufactures the material. This includes any drugs, devices, or combination products

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EDMS Doc. Number: 24696321 - 24085605

provisioned and/or repackaged/modified by Amgen. Drugs or devices include investigational product. Any product complaints associated with an investigational products, or non-investigational products or devices supplied by Amgen are to be reported according to the instructions provided in the Investigational Product Instruction Manual or equivalent.

If you become aware of a suspected PC, you are obligated to report the issue within 24 hours of discovery or notification of the concern or irregularity. Amgen requires notification of any concern or irregularity at any stage of the study.

How to Report a Product Complaint to Amgen

- Complete Amgen's paper Clinical Product Complaint Intake Form and email the form to the following Amgen email address: Clinical-Complaint-Intake@amgen.com

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16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Amgen on public registry websites, is considered Amgen confidential information and is not to be used in any publications. Amgen protocol-related information proposed for use in a publication must be submitted to Amgen for review and approval and should not be utilized in a publication without express written approval from Amgen, or as described in the Clinical Trial Agreement.

Amgen will ensure Amgen-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 2 and Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for authorship will be in alignment with ICMJE authorship criteria and be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, and contribution to abstract, presentation and/or publication development.

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EDMS Doc. Number: 24696321 - 24085605

17. REFERENCES

Benoit S, Hamm H. Childhood psoriasis. Clin Dermatol. 2007;25(6):555-62.

Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in children and adolescents: diagnosis, management and comorbidities. Paediatr Drugs. 2015 Oct;17(5):373-84.

Carey W, Glazer S, Gottlieb AB, Lebwohl M, Leonardi C, Menter A, et al. Relapse, rebound, and psoriasis adverse events: an advisory group report. J Am Acad Dermatol. 2006 Apr:54(4 Suppl 1):S171-81.

Centers for Disease Control (CDC) National Center for Health Statistics Clinical Growth Charts [Internet]; Modified 2000 [cited 2018 Aug 15]. Available from: https://www.cdc.gov/growthcharts/clinical_charts.htm.

Chan CS, Van Voorhees AS, Lebwohl MG, Korman NJ, Young M, Bebo BF, et al. Treatment of severe scalp psoriasis: From the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009 Jun;60(6):962-71.

Christophers E. Psoriasis - epidemiology and clinical spectrum. Clin Exp Dermatol. 2001 Jun;26(4):314-20.

Fan X, Xiao FL, Yang S, Liu JB, Yan KL, Liang YH, et al. Childhood psoriasis: a study of 277 patients from China. J Eur Acad Dermatol Venereol. 2007 Jul;21(6):762–5.

Gordon KB, Feldman SR, Koo JY, Menter A, Rolstad T, Krueger G. Definitions of measures of effect duration for psoriasis treatments. Arch Dermatol. 2005 Jan;141(1):82-4.

Howie, SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011 Jan;89(1):46-53.

Kimball AB, Wu EQ, Guérin A, Yu AP, Tsaneva M, Gupta SR, et al. Risks of developing psychiatric disorders in pediatric patients with psoriasis. J Am Acad Dermatol. 2012 Oct;67(4):651-7.

Kragballe K, Menter A, Lebwohl M, Tebbey PW, van der Kerkhof PC, International Psoriasis Council. Long-term management of scalp psoriasis: perspectives from the International Psoriasis Council. J Dermatolog Treat. 2013 Jun;24(3):188-92.

Lebwohl M. Psoriasis. Lancet. 2003 Apr 5;361(9364):1197-204.

Mallbris L, Larsson P, Bergqvist S, Vingård E, Granath F, Ståhle M. Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. J Invest Dermatol. 2005 Mar;124(3):499–504.

Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. Dermatol Clin. 2013 Apr;31(2):267-88.

McMurtry CM, Taddio A, Noel M, Antony MM, Chambers CT, Asmundson GJ, et al. Exposure-based interventions for the management of individuals with high levels of needle fear across the lifespan: a clinical practice guideline and call for further research. Cogn Behav Ther. 2016 May;45(3):217-35.

Michalek IM, Loring B, John SM A systemic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-12.

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Morris A, Rogers M, Fischer G, Williams K. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol. 2001 May-Jun;18(3):188–98.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

Raychaudhuri SP, Farber EM. The prevalence of psoriasis in the world. J Eur Acad Dermatol Venereol. 2001 Jan;15(1):16-7.

Shah KN. Diagnosis and treatment of pediatric psoriasis: Current and future. Am J Clin Dermatol. 2013 Jun;14(3):195-213.

Silverberg NB. Update on pediatric psoriasis, part 1: clinical features and demographics. Cutis. 2010 Sep;86(3):118-24.

Ståhle M, Atakan N, Boehncke WH, Chimenti S, Daudén E, Giannetti A, et al. Juvenile psoriasis and its clinical management: a European expert group consensus. J Dtsch Dermatol Ges. 2010 Oct;8(10):812-18.

Tollefson MM, Crowson CS, McEvoy MT, Maradit Kremers H. Incidence of psoriasis in children: a population-based study. J Am Acad Dermatol. 2010;62(6):979-87.

Vogel SA, Yentzer B, Davis SA, Feldman SR, Cordoro KM. Trends in pediatric psoriasis outpatient health care delivery in the United States. Arch Dermatol. 2012;148(1):66-71.

Weinstein GD, Menter MA. An overview of psoriasis. In: Weinstein GD, Gottlieb AB, editors. Therapy of moderate to severe psoriasis. New York, NY: National Psoriasis Foundation; 2003. p. 1-28.

World Health Organization (WHO). Antiretroviral therapy for HIV infection in infants and children: towards universal access: recommendations for a public health approach: 2010 Revision [Internet]; 2010 [cited 2018 Jun 26]. Available from: http://apps.who.int/iris/bitstream/10665/164255/1/9789241599801_eng.pdf?ua=1.

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BID	Twice per day
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CDC	Centers for Disease Control
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic case report form
EEA	European Economic Area
EU	European Union
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology

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Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
PDE4	Phosphodiesterase type 4
PI	Principal Investigator
PK	Pharmacokinetics
PC	Product Complaint
PUVA	Psoralens with long-wave ultraviolet radiation
RBC	Red blood cell
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
sPGA	Static Physician Global Assessment
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
US	United States
UV	Ultraviolet
WBC	White blood cell
WHO	World Health Organization

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APPENDIX B. STATIC PHYSICIAN GLOBAL ASSESSMENT (sPGA)

Score	Category	Description
0	Clear	**Plaque elevation** = 0 (no elevation over normal skin) **Scaling** = 0 (no evidence of scaling) **Erythema** = 0 (except for residual hyperpigmentation/ hypopigmentation)
1	Almost Clear	**Plaque elevation** = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) **Scaling** = ± (surface dryness with some desquamation) **Erythema** = ± (faint, diffuse pink or slight red coloration)
2	Mild	**Plaque elevation** = slight (slight but definite elevation, typically edges are indistinct or sloped) **Scaling** = fine (fine scale partially or mostly covering lesions) **Erythema** = mild (light red coloration)
3	Moderate	**Plaque elevation** = marked (marked definite elevation with rough or sloped edges) **Scaling** = coarser (coarser scale covering most or all of the lesions) **Erythema** = moderate (definite red coloration)
4	Severe	**Plaque elevation** = marked (marked elevation typically with hard or sharp edges) **Scaling** = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) **Erythema** = severe (very bright red coloration)

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APPENDIX C. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) CHILDREN'S SINCE LAST VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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EDMS Doc. Number: 24696321 - 24085605

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 1 of 2

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX D. TANNER STAGING

Female

Stage	Breast Growth	Pubic Hair Growth	Other Changes
I	Pre-adolescent	None	Pre-adolescent
II	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II
III	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III
IV	Separation of contours; areola and nipple form secondary mound above breasts tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche
V	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.

Male

Stage	Testes Growth	Penis Growth	Pubic Hair Growth	Other Changes
I	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
IV	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
V	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

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APPENDIX E. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

AMGEN CC-10004-PPS0-004 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	☐New ☐Follow-up

Please refer to your site's Serious Adverse Event Report Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex ☐F ☐M	Race	If applicable, provide End of Study date

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the AE/Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event co-occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 Apremilast No Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg. biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event				Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
		Date of Dose Day Month Year	Dose	Route	Frequency		
Apremilast ☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*

Page 1 of 3

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AMGEN CC-10004-PPSO-004 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	☐New ☐Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

Approved

AMGEN CC-10004-PPSO-004 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	☐New ☐Follow-up

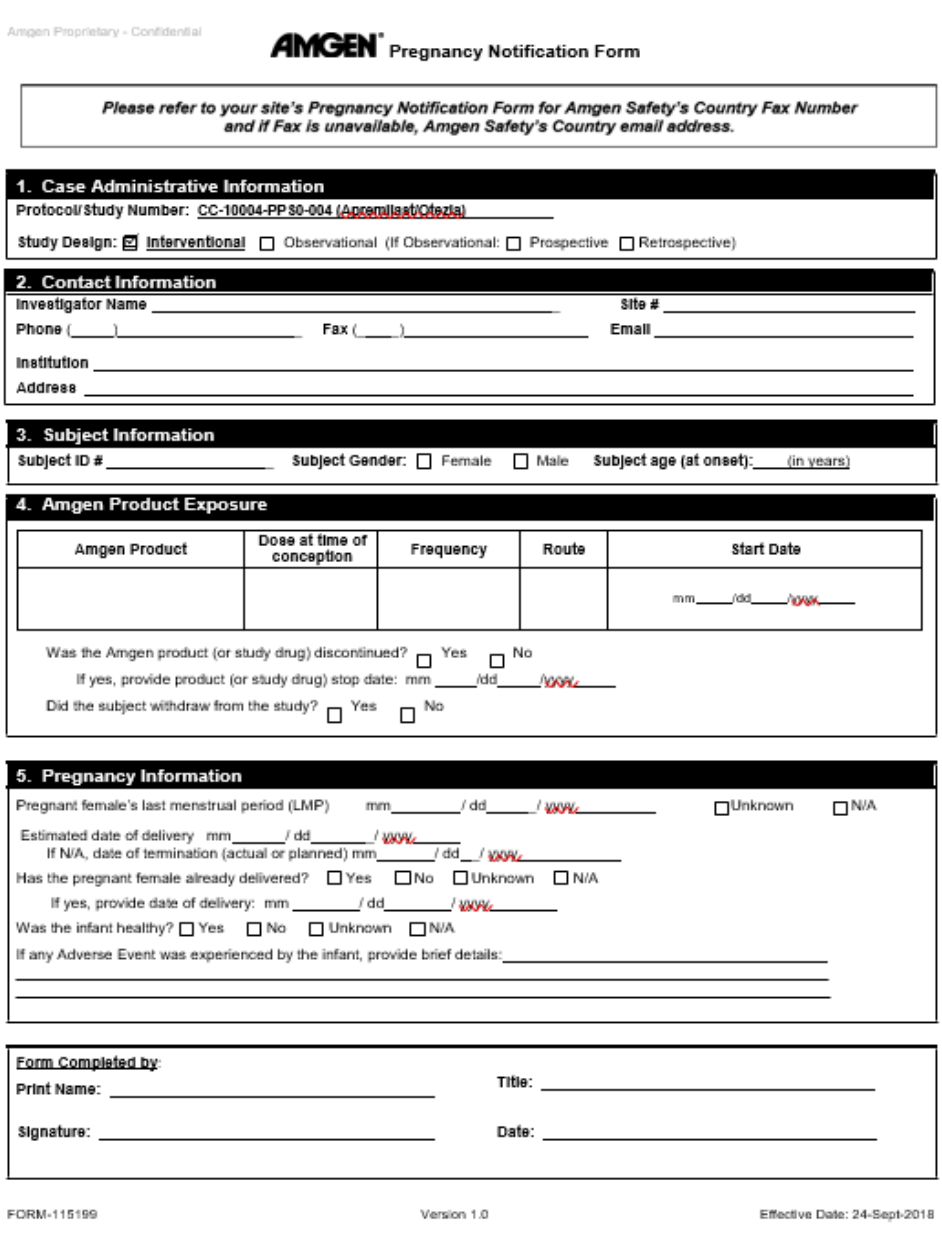
	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

Approved

APPENDIX F. PREGNANCY NOTIFICATION FORM



Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Please refer to your site's Pregnancy Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPSO-004 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject age (at onset):____(in years)

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Approved

APPENDIX G. LACTATION NOTIFICATION FORM

Amgen Proprietary - Confidential

AMGEN Lactation Notification Form

Please refer to your site's Lactation Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPSO-004 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject age (at onset):____(in years)

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Approved

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: Vice President and Head of Immunology & Fibrosis Clinical Develo
Date: Friday, 08 May 2020, 08:43 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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Approved