NDA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application (Original 1 and Original 2)
Application Number(s)	210745
Priority or Standard	Standard
Submit Date(s)	10/30/2024
Received Date(s)	10/30/2024
PDUFA Goal Date	8/30/2025
Division/Office	Division of Rheumatology and Transplant Medicine and Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	8/27/2025
Established/Proper Name	Apremilast extended release
(Proposed) Trade Name	OTEZLA XR
Pharmacologic Class	PDE-4 inhibitor
Applicant	Amgen Inc.
Dosage form	Film-coated extended-release tablet
Applicant proposed Dosing Regimen	75 mg once daily
Applicant Proposed Indication(s)/Population(s)	• Treatment of adult patients with active PsA. • Treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with active PsA. • Treatment of adult patients with PsO who candidates for phototherapy or systemic therapy are. • Treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy. • Treatment of adult patients with oral ulcers associated with Behçet's disease.
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of adult patients with active PsA. • Treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with active PsA. • Treatment of adult patients with PsO who candidates for phototherapy or systemic therapy are. • Treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with moderate to severe PsO

	who are candidates for phototherapy or systemic therapy. • Treatment of adult patients with oral ulcers associated with Behçet's disease.
Recommended Dosing Regimen	75 mg once daily

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Apremilast (OTEZLA) is an oral small molecule inhibitor of phosphodiesterase type 4 (PDE4). The inhibition of PDE4 is hypothesized to result in elevation of cyclic adenosine monophosphate (cAMP) levels in immunocompetent cells, which in turn modulates a network of pro-inflammatory and anti-inflammatory mediators.

Apremilast is marketed worldwide as a solid oral dosage form and is commercially available as diamond-shaped, film-coated immediate-release (IR) tablets in the following dosage strengths: 10 mg pink tablets, 20 mg brown tablets, and 30 mg beige tablets. In 2014, apremilast was initially approved in the United States (US) under new drug application (NDA) 205437 for the treatment of adult patients with active psoriatic arthritis (PsA) and subsequently for the treatment of adult patients with plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; and adult patients with oral ulcers associated with Behçet's Disease (BD). The recommended dosage of apremilast for the approved adult indications is 30 mg twice daily (BID) after an initial 5-day titration period. For pediatric patients, the recommended dosage of apremilast is based on body weight: 30 mg BID for pediatric patients who weigh at least 50 kg and 20 mg BID for pediatric patients who weigh from 20 kg to < 50 kg, following an initial titration schedule appropriate for the patient's body weight category.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical pharmacology data submitted to the current submission was reviewed and demonstrated bioequivalence between the apremilast IR 30 mg BID formulation and the apremilast 75 mg extended-release dosing formulation. There were no new safety signals identified in review of the safety data for submitted clinical pharmacology studies. Taken together, these data provide the basis for justification of the extrapolation between the two formulations regarding the efficacy and safety for the currently approved indications.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The clinical pharmacology data submitted to the current submission was reviewed and demonstrated bioequivalence between the apremilast IR 30 mg BID formulation and the apremilast 75 mg extended-release dosing formulation. There were no new safety signals identified in review of the safety data for submitted clinical pharmacology studies. Taken together, these data provide the basis for justification of the extrapolation between the two formulations regarding the efficacy and safety for the currently approved indications.

The Agency recommends approval of OTEZLA XR 75 mg formulation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The reader is referred to the original completed reviews for approval of apremilast for the treatment of adult patients with PsA, adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; and adult patients with oral ulcers associated with BD.	Apremilast is approved for the treatment of patients with PsO, PsA, and Behçet's disease. These conditions are well defined and have been discussed in the individual NDA reviews.
Current Treatment Options	The reader is referred to the original completed reviews for approval of apremilast for the treatment of adult patients with PsA, adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; and adult patients with oral ulcers associated with BD.	Treatment of patients with PsO, PsA, and Behçet's disease have been discussed in the individual NDA reviews.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The OTEZLA XR formulation will provide a potentially more convenient formulation for patients and potentially increase compliance and limiting missed doses of apremilast.	The OTEZLA XR formulation will provide a potentially more convenient formulation for patients and potentially increase compliance and limiting missed doses of apremilast.
Risk and Risk Management	The risks of OTEZLA XR are the same as those that are currently included in the OTEZLA IR US package insert.	The risks of OTEZLA XR are the same as those that are currently included in the OTEZLA IR US package insert.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

The reader is referred to the original completed reviews for approval of apremilast for the treatment of adult patients with active PsA; treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA; and adult patients with oral ulcers associated with BD.

2.2. Analysis of Current Treatment Options

The reader is referred to the original completed reviews for approval of apremilast for the treatment of adult patients with PsA; treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA; and adult patients with oral ulcers associated with BD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Regulatory History

Apremilast (OTEZLA) is an oral small molecule inhibitor of phosphodiesterase type 4 (PDE4). The inhibition of PDE4 is hypothesized to result in elevation of cyclic adenosine monophosphate (cAMP) levels in immunocompetent cells, which in turn modulates a network of pro-inflammatory and anti-inflammatory mediators.

Apremilast is marketed worldwide as a solid oral dosage form and is commercially available as diamond-shaped, film-coated immediate-release (IR) tablets in the following dosage strengths: 10 mg pink tablets, 20 mg brown tablets, and 30 mg beige tablets. In 2014, apremilast was initially approved in the United States (US) under new drug application (NDA) 205437 for the treatment of adult patients with active psoriatic arthritis (PsA) and subsequently for the treatment of adult patients with plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; and adult patients with oral ulcers associated with Behçet's Disease (BD). The recommended dosage of apremilast for the approved adult indications is 30 mg twice daily (BID) after an initial 5-day titration period. For pediatric patients, the recommended dosage of apremilast is based on body weight: 30 mg BID for pediatric patients who weigh at least 50 kg and 20 mg BID for pediatric patients who weigh from 20 kg to < 50 kg, following an initial titration schedule appropriate for the patient's body weight category.

Amgen (Applicant) has developed a 75 mg extended-release (XR) tablet of apremilast for once daily (QD) oral administration after a 5-day titration with the IR tablets for use in the following indications in which the apremilast IR formulation is approved at a dose of 30 mg BID:

- Treatment of adult patients with active PsA.
- Treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy.
- Treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy.
- Treatment of adult patients with oral ulcers associated with BD.

The extended release (XR) formulation of apremilast was originally developed by the prior sponsor, Celgene. Various prototype formulations and strengths were developed and evaluated in previous exploratory bioavailability (BA) studies conducted by Celgene under Investigational New Drug (IND) Application 121919. Based on this development work, a 75 mg XR (b) (4) formulation was selected, which has been previously demonstrated to be equivalent to the 30 mg BID IR formulation in relative bioavailability studies. The apremilast XR formulation was designed using (b) (4). (b) (4)

(b) (4)

As a pediatric XR formulation equivalent to 20 mg BID is not yet available, the current application proposes use of apremilast XR tablets in pediatric patients weighing at least 50 kg, for whom the IR tablet BID dose is 30 mg BID, which corresponds to the 75 mg XR QD dose. The 75 mg XR QD dose would not be equivalent to the 20 mg BID dose of the IR tablet that is recommended for pediatric patients between 20 kg and < 50 kg. The application for registration of the pediatric XR formulation for use in children weighing 20 kg to < 50 kg will be submitted once an appropriate presentation is developed.

The XR formulation of apremilast was previously developed by Celgene under IND 121919. Celgene submitted NDA 210745 for registration of the XR tablets on December 15, 2017, based on the results of relative BA studies CC-10004-CP-034 and CC-10004-CP-035, which demonstrated equivalent pharmacokinetic (PK) exposure (area under the plasma concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) between the 75 mg apremilast XR formulation administered QD and the 30 mg IR formulation administered BID. Celgene subsequently withdrew the NDA on August 17, 2018, prior to an action on the application by the Agency.

In November 2019, the current Applicant acquired worldwide rights for apremilast from Celgene. Ownership of the active NDA for the IR tablets (NDA 205437) was transferred to Amgen on December 11, 2019, and ownership of the INDs for apremilast (IND 070270, IND 101761, IND 119696, and IND 121919) was transferred to Amgen on April 3, 2020. Ownership of the withdrawn NDA for the XR tablets (NDA 210745) was transferred to Amgen on June 21, 2022.

As the current sponsor of apremilast, the Applicant is pursuing further development and registration of the XR tablets. The manufacturing of the (b) (4) is performed at the same facility previously used by Celgene, (b) (4) . However, the commercial drug product (DP) manufacturing site for the XR tablets has changed (b) (4) . The formulation composition, overall manufacturing processes and controls, and container closure system planned for the XR tablets are unchanged. Due to the change in drug product manufacturing site since Celgene's prior PK studies evaluating the relative BA of the IR and XR formulations, the Applicant has conducted a new PK study (Study 20200369), which used apremilast 75 mg XR tablets produced by the intended commercial manufacturing sites (i.e., (b) (4)). Study 20200369 evaluated the relative BA of the 75 mg XR tablets administered QD compared with the 30 mg IR tablets administered BID after single and repeated doses under fasted conditions and assessed the effect of food on the PK of the apremilast 75 mg XR tablet after a single dose.

Multiple interactions with the FDA took place throughout the development program for the apremilast XR formulation as follows:

- November 23, 2015
  - Type C meeting regarding Celgene's seeking advice from the Agency regarding developmental plans for a once-daily apremilast formulation.
- April 24, 2017
  - Type C meeting regarding Celgene seeking of agreement with the Agency for the development program of the 75 mg XR QD formulation regarding appropriate developmental studies, proposed dissolution method, and the proposed stability data package.
- May 17, 2017
  - Type B pre-IND meeting between Celgene and the Agency seeking concurrence that the clinical PK data generated from the BA Study CC-10004-CP-035 were suitable to support the registration of the daily apremilast 75 mg XR tablet in the indications for which the 30 mg IR BID formulation was approved.
- July 10, 2017
  - Type C meeting between Celgene and the Agency to reach agreement that the results of the drug-alcohol interaction studies for the 75 mg XR daily formulation demonstrated that no alcohol-induced dose dumping occurred and that no further studies were required.
- December 15, 2017
  - Celgene submitted NDA 210745 for the registration of the 75 mg XR formulation.
- August 17, 2018
  - Celgene withdrew NDA 210745, which was confirmed by the Agency with an acknowledging letter on August 27, 2018.
- December 11, 2019
  - Transfer from Celgene to the current Applicant regarding ownership of NDA 205437 for the apremilast IR formulation.
- April 3, 2020
  - Transfer from Celgene to the current Applicant of IND 121919 regarding the apremilast QD formulation.
- April 8, 2022
  - Type C meeting regarding the Applicant seeking advice from the Agency regarding resubmission of the NDA for the 75 mg XR formulation.
- Jun 21, 2022
  - Ownership of the previously withdrawn NDA 210745 for the 75 mg XR formulation from Celgene to the Applicant. Confirmation from the Agency was communicated on January 27, 2023.
- August 16, 2022
  - The Applicant submitted the protocol for Study 2200369.

- August 19, 2022
    - Type C meeting request was received regarding the Applicant seeking agreement with the Agency that the proposed stability data package would support the proposed expiatory periods for the bottle and blister presentations of the apremilast XR tablets and the proposed submission strategy for the stability data package was acceptable.
- December 19, 2022
    - The Applicant sought advice from the Agency's User Fee Office to determine if a user fee would be required for the NDA for the 75 mg XR tablet formulation.
- February 13, 2023
    - The Applicant sought advice from the Agency regarding whether NDA 210745 would require a bioresearch monitoring package for the pivotal relative BA Study 20200369 in the application for the resubmitted NDA.
- June 2, 2023
    - Type B meeting with the Agency to reach agreement on the proposed plans for filing NDA 210745.
- March 1, 2024
    - The Applicant sought further advice from the Agency's User Fee Office due to issuance of the Agency's July 2023 *Guidance for Industry, Assessing User Fees Under the Prescription Drug User Fee Amendments of 2022*.
- November 6, 2024
    - The Applicant resubmitted NDA 210745 for OTEZLA XR tablets (current submission).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for Study 20200369 (NDA 210745, OTEZLA XR™ Extended-Release Tablets) at one analytical site and three clinical sites.

The OSIS conducted the inspection at one of the three clinical sites i.e., QPS Bio-Kinetic Clinical Applications, LLC, Springfield, MO. Form FDA 483 was not issued to QPS Bio-Kinetic Clinical Applications, LLC, Springfield, MO, at the inspection close-out. There was one discussion item regarding documentation. Based on the inspection finding, the discussion item has no impact on the reliability of the data and human subject protection for study 20200369 conducted at QPS Bio-Kinetic Clinical Applications, LLC, Springfield, MO. See Bioequivalence Establishment Inspection Report Review by Dr. Xikui Chen in DARRTS dated 04/24/2025.[1]

For the other two clinical sites (QPS-Miami Research Associates and Altasciences Clinical Research, Inc.) and one analytical site (b) (4), OSIS determined that inspections are not needed, as the Office of Inspections and Investigations conducted inspections for these sites in 2023-2024 and concluded that the data from the reviewed studies were reliable. See Bioequivalence Establishment Inspection Report Review by Dr. Folaremi Adeyemo, in DARRTS dated 02/04/2025.[2]

4.2. Product Quality

The Office of Product Quality has reviewed the data submitted under NDA 210745 and recommend for approval. See Integrated Quality Review submitted by Dr. Craig Bertha in DARRTS dated 07/22/2025.[3]

Drug Product

There are no novel excipients, (b) (4) in the tablet formulation. There are no human or animal derived excipients in the drug product formulation. The proposed drug product specification is adequate to assure the identity, strength, purity and quality of Otezla Extended-release tablets, 75 mg.

Based on the results of the long-term and accelerated stability study on multiple primary stability batches of Otezla Extended-release tablet, 75 mg up to 24 months of shelf-life is

[1] Reference ID: 5578711
[2] Reference ID: 5523997
[3] Reference ID: 5628664

granted, when packaged in blisters and up to 36 months of shelf-life is granted when packaged in bottles and stored at 20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F).

Manufacturing/Facilities
All the associated facilities, i.e., DS manufacturing/testing, (b) (4) sites for DS manufacturing/testing and DP manufacturing/testing facilities are acceptable in this review cycle.

Biopharmaceutics
The Applicant's proposed dissolution method [USP apparatus II (paddle) with sinkers at 75 rpm; 900 mL of 0.5% Tween 80 in sodium acetate buffer pH 5.5 at 37 °C] is acceptable. The proposed dissolution method was demonstrated to be discriminatory towards changes in the amount of (b) (4)

There is no alcohol-induced dose-dumping observed in 0.1 N HCl with alcohol up to 2 hours, indicating that the presence of alcohol would have insignificant impact on drug release from the proposed ER drug product in the relevant physiologic condition with consumption of alcohol or alcohol beverages. The effect of 40% alcohol or noticeable separation in drug release profile, as seen in cumulative amount overtime, did not become apparent until after 10-12 hours encompassing the small intestine transit time, and reached approximately 31% higher vs. control.

4.3. Office of Prescription Drug Promotion

OPDP has reviewed the proposed Prescribing Information (PI) for the original NDA submission for OTEZLA XR™ (apremilast) based on the draft labeling emailed to OPDP on June26, 2025 and did not have any comments. See Labeling Consult Review in DARRTS by Montherson Saint Juste dated 7/15/2025 and 07/30/2025. [4,5]

[4] Reference ID: 5625154
[5] Reference ID: 5631920

5 Clinical Pharmacology

5.1. Executive Summary

On 30 October 2024, the Applicant, Amgen Inc., submitted NDA 210745 (Sequence No. [SN] 0017) seeking approval of apremilast 75 mg extended-release (XR) tablets for the treatment of adult patients with plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy, psoriatic arthritis (PsA), oral ulcers associated with Behçet's disease (BD), and pediatric patients 6 years of age and older and weighing at least 50 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy. NDA 210745 was originally submitted on 15 December 2017 (SN 0001) and subsequently withdrew on 17 August 2018 (SN 0014), prior to an action on the application by the FDA. On 23 July 2025, apremilast immediate release (IR) tablets indications were expanded to include pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA under NDA 205437 supplement 14, and the Applicant, thereafter, proposed to include pediatric patients 6 years of age and older and weighing at least 50 kg with active PsA for apremilast 75 mg XR tablets in the current NDA submission.

The current NDA is based on data from a relative bioavailability study demonstrating that the 75 mg XR formulation administered once daily is bioequivalent to the approved 30 mg IR formulation (OTEZLA®) administrated twice daily. In the previous NDA submission in 2017, the Applicant conducted two pharmacokinetic (PK) studies evaluating the relative bioavailability of the IR and XR formulations (Studies CC-10004-CP-034 and CC-10004-CP-035). However, due to the change in drug product manufacturing site, the Applicant conducted a new relative bioavailability study, Study 20200369, which evaluated the to-be-marketed apremilast 75 mg XR tablets manufactured by the new commercial manufacturing sites (i.e., (b) (4)). Study 20200369 is the pivotal relative bioavailability study that supports the current NDA.

In Study 20200369, the Applicant demonstrated comparable PK between the 75 mg XR once-daily and 30 mg IR twice-daily formulations, with geometric mean ratios (GMRs) of AUC_{0-24} and C_{max} meeting bioequivalence criteria after repeated once daily administration. Although the XR formulation showed lower trough concentrations (C_{trough}) with GMR of 0.808 compared to IR formulation, exposure response (E-R) analysis (Study 157815) supported that $AUC_{0-24,ss}$ has a stronger correlation with ACR20 in PsA patients than C_{trough}, and similar correlation with sPGA and PASI-75 in PsO patients.

The Applicant supported the use of apremilast XR in oral ulcers associated with BD with PK bridging and mechanistic justification including, similar TNF-α-mediated pathophysiology across conditions, and comparable TNF-α inhibition demonstrated in ex vivo studies.

Recommendation: The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical

pharmacology data submitted under NDA 210745. This NDA is recommended for approval from a clinical pharmacology perspective for the treatment of adult patients with PsO, PsA, oral ulcers associated with BD, and pediatric patients 6 years of age and older and weighing at least 50 kg or more with moderate to severe PsO and active PsA.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings from the current review:

1) Bioavailability and Pharmacokinetics: Study 20200369 demonstrated that 75 mg XR once daily is bioequivalent to 30 mg IR twice daily based on repeat-dose assessment i.e., $AUC_{0-24,ss}$ GMR of 0.941 (90% Confidence Interval [CI]: 0.896-0.987) and C_{max} GMR of 0.851 (90% CI: 0.820-0.883). However, the GMR for C_{trough} was 0.808 (90% CI: 0.738, 0.884).

2) Plaque psoriasis and psoriatic arthritis: $AUC_{0-24,ss}$ was identified as the primary predictor of clinical efficacy across PASI-75, sPGA, and ACR20 endpoints. Predicted clinical response rates showed minimal differences between apremilast XR and IR formulations for active PsA and PsO.

3) Oral ulcers associated with Behçet's Disease: PK bridging and mechanistic justification was provided for Behçet's disease indication. Justification included equivalent systemic exposure between XR and approved IR formulations, similar pathophysiology involving TNF-α dysregulation across Behçet's disease, psoriatic arthritis, and psoriasis, comparable TNF-α inhibition demonstrated in ex vivo studies with both formulations maintaining plasma concentrations above the effective IC_{50} threshold.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

The apremilast 75 mg XR tablet is intended for once-daily oral administration after a 5-day titration with the apremilast IR tablets (OTEZLA®). It is proposed for use in the indications for which the IR formulation is approved at a dose of 30 mg BID.

Therapeutic Individualization

Not applicable.

Outstanding Issues

None.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

Apremilast is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. The specific mechanism(s) by which apremilast exerts its therapeutic action is not well defined.

OTEZLA IR when taken orally is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of ~2.5 hours. Coadministration with food does not alter the extent of absorption of OTEZLA IR. OTEZLA XR when taken orally is absorbed with C_{max} occurring at a median t_{max} of ~6 hours. OTEZLA XR 75 mg administered once daily demonstrates comparable PK exposure (steady state AUC and C_{max}) to OTEZLA 30 mg twice daily. OTEZLA XR t_{max} was delayed by 3 hours, C_{max} and AUC were increased by ~28%, with a high-fat meal compared to fasted conditions. Therefore, OTEZLA XR may be taken without regard to meals.

Following oral administration in humans, apremilast is a major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O- demethylated apremilast. The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half- life of approximately 6 - 9 hours. Following oral administration of radiolabeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and feces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and feces, respectively.

The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment. The pharmacokinetics of apremilast is not affected by mild or moderate renal impairment. In 8 adult subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and C_{max} of apremilast increased by approximately 88% and 42%, respectively.

5.3.2. Clinical Pharmacology Questions

What are the major findings in the relative bioavailability study?

The Applicant conducted a bioavailability study (Study 20200369) to determine the relative bioavailability of apremilast XR tablet after single and repeated doses (Part 1) to that after dosing with the apremilast IR tablet, and to assess the effect of food (Part 2) on the PK of an apremilast XR tablet after a single dose. During the study, each subject received 2 treatments (Part 1: apremilast XR 75 mg and apremilast IR 30 mg; Part 2: apremilast XR 75 mg administered under fed and fasted conditions). Healthy male or female subjects, aged between 18 and 65 years, inclusive, and with a body mass index (BMI) between 18 and 32 kg/m^2, inclusive, were selected.

Study 20200369Part 1 was a 2-period, 2-sequence, randomized crossover study designed to assess the relative bioavailability of apremilast XR versus IR formulations in healthy subjects. The study enrolled 211 healthy male and female subjects (Table 1) who were randomized into two treatment sequences: Sequence 1 (BA) received apremilast IR 30 mg twice daily in Period 1 followed by apremilast XR 75 mg once daily in Period 2, while Sequence 2 (AB) received the treatments in reverse order. Each treatment period included a single drug administration on Day 1 and repeated once daily dosing on Days 4-8 for apremilast XR, and twice daily drug administration on Day 1 and repeated twice daily dosing on Days 4-8 for apremilast IR, with all doses administered in the fasted state. The primary endpoints are:

Following apremilast dose administration on Day 1 of each period:

- C_{max}
- area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last})
- area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}).

Following apremilast dose administration on Day 8 of each period:

- C_{max}
- area under the plasma concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}).

A total of 197 subjects (93.4%) completed the study (Table 1), providing reasonable sample size for the primary objective of evaluating the relative bioavailability of the XR formulation compared to the reference IR formulation.

Table 1: Subject disposition for Part 1 of the study.

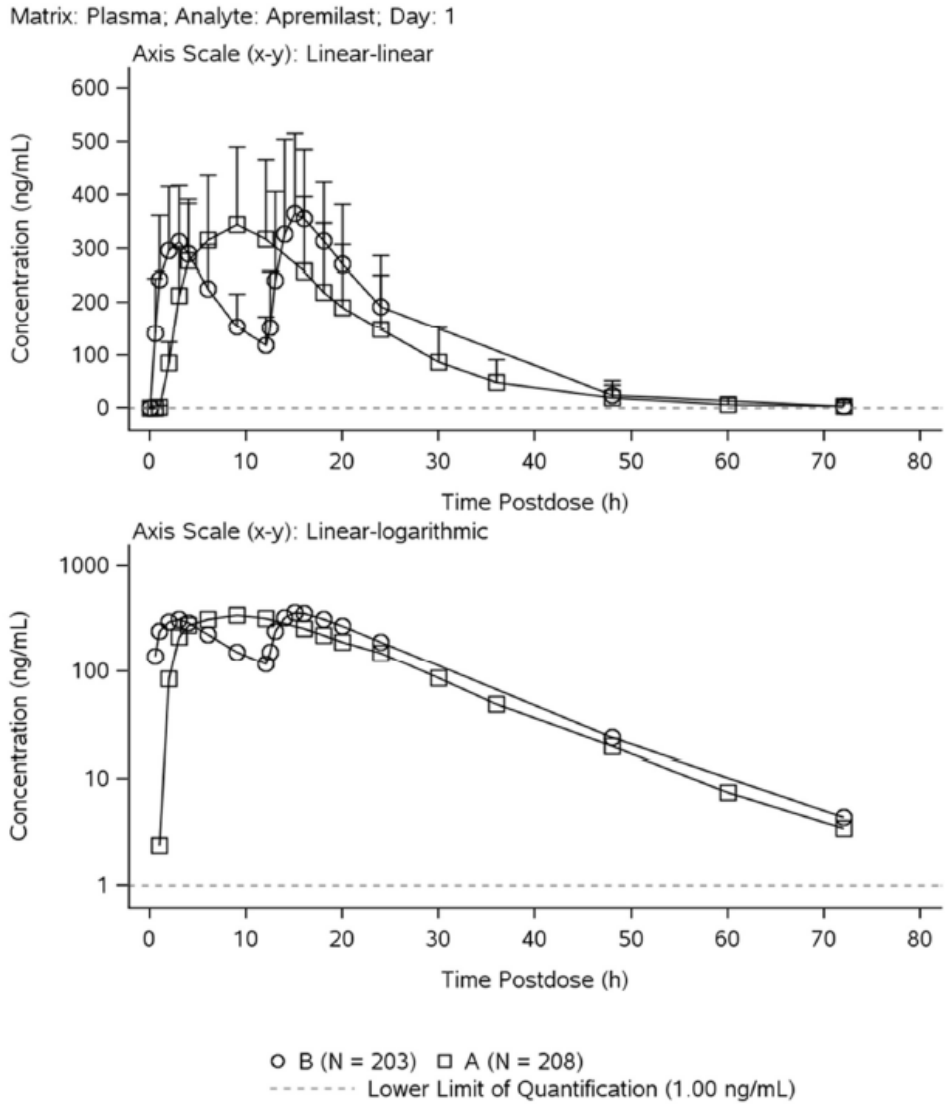
Demographic	BA (N = 104) n(%)	AB (N = 107) n(%)	Overall (N = 211) n(%)
Population			
Safety	104 (100%)	107 (100%)	211 (100%)
Pharmacokinetic	104 (100%)	107 (100%)	211 (100%)
Completed the Study	101 (97.1%)	96 (89.7%)	197 (93.4%)
Discontinued the Study	3 (2.9%)	11 (10.3%)	14 (6.6%)
Noncompliance	1 (1.0%)	4 (3.7%)	5 (2.4%)
Adverse Event	2 (1.9%)	5 (4.7%)	7 (3.3%)
Other	---	2 (1.9%)	2 (0.9%)

Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart). n = number of subjects with valid observations; N = number of subjects; QD = once daily; BID = twice daily; % = percentage of subjects with valid observations (n/N×100) The safety population will include all subjects who received at least 1 dose of apremilast. The pharmacokinetic population will include all subjects who received at least 1 dose of apremilast and have evaluable PK data.

Source: Table 7, CSR-20200369, Page no. 42

The comparison of plasma concentration time profiles of apremilast after administration of apremilast XR 75 mg once daily and apremilast IR 30 mg twice daily on Day 1 is shown in Figure 1.

Figure 1: Arithmetic Mean (+SD) Pharmacokinetic Concentration-time Profiles (PK Population) on Day 1 for Part 1



N=number of subjects, QD=once daily, BID=twice daily
Treatment A: apremilast XR 75 mg oral tablet, administered QD, Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart).
Source: Figure 3, CSR-20200369, Page no. 52

The XR formulation demonstrated a median t_{max} of 9.00 hours and mean half-life of 7.77 hours, compared to the IR formulation's median t_{max} of 14.0 hours (following the second dose) and mean half-life of 7.68 hours (Table 2).

Table 2: Summary of Part 1 Day 1 Pharmacokinetic Parameters (Pharmacokinetic Population)

Matrix	Parameter	B (N = 203)	A (N = 208)
Plasma	AUC_{last} (h*ng/mL)	8150 (38.8) [187]	6520 (60.9) [200]
	AUC_{inf} (h*ng/mL)	8270 (38.2) [185]	6620 (59.4) [199]
	C_{max} (ng/mL)	440 (30.2) [187]	380 (36.3) [200]
	t_{max} (h)	14.0 (0.500-24.0) [187]	9.00 (3.00-18.0) [200]
	t_{lag} (h)	0 (0-0) [187]	0.500 (0-1.05) [200]
	$t_{1/2}$ (h)	7.68 (2.19) [185]	7.77 (2.43) [199]
	λ_z (1/h)	0.0935 (27.0) [185]	0.0930 (29.5) [199]
	CL/F (L/h)	7.25 (38.2) [185]	11.3 (59.4) [199]
	V_z/F (L)	77.5 (32.5) [185]	122 (56.3) [199]

Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart) QD = once daily; BID = twice daily. AUCinf = area under the concentration-time curve from time 0 extrapolated to infinity; AUClast = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; Cmax = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; tmax = time of the maximum observed concentration; Vz/F = apparent volume of distribution during the terminal phase; Geometric mean (Geometric CV) [n] statistics presented; for tmax, tlag, median (minimum-maximum) [n] statistics presented; for t1/2, arithmetic mean (standard deviation) [n] statistics

Source: Table 11, CSR-20200369, Page no. 53

The statistical analysis results from study Part 1, Day 1, showed that apremilast XR 75 mg once daily compared to apremilast IR 30 mg twice daily had GMRs of 0.789 (90% CI: 0.746, 0.835) for AUC_{last}, 0.794 (90% CI: 0.751, 0.839) for AUC_{inf}, and 0.855 (90% CI: 0.821, 0.890) for C_{max}, with within-subject variabilities of 34.0%, 33.2%, and 24.1%, respectively (Table 3). While C_{max} met bioequivalence criteria (90% CI within 0.80-1.25), AUC_{last} and AUC_{inf} did not meet bioequivalence criteria in the primary analysis, showing lower exposures for the XR formulation.

Table 3: Statistical Analysis of Pharmacokinetic Parameters (Relative Bioavailability Assessment) on Day 1

Parameter	Treatment	n	GLSM	Test versus Reference: Ratio of GLSMs (90% CI)	Test versus Reference: Within-subject CV (%)
AUC_{last} (h*ng/mL)	Treatment B (reference)	187	8250		
	Treatment A (test)	200	6510	0.789 (0.746, 0.835)	34.0
AUC_{inf} (h*ng/mL)	Treatment B (reference)	185	8340		
	Treatment A (test)	199	6620	0.794 (0.751, 0.839)	33.2
C_{max} (ng/mL)	Treatment B (reference)	187	444		
	Treatment A (test)	200	379	0.855 (0.821, 0.890)	24.1

Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart) CI = confidence interval, CV = coefficient of variation (%), GLSM = geometric least squares mean, n = number of subjects with valid observations; QD = once daily; BID = twice daily Model: a linear mixed-effects model is used to analyze the natural log-transformed PK parameters, with planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect. Primary analysis performed using AUCs calculated by linear-linear calculation method. Within-subject CV: CVW(%) = [exp(mse)-1]½ x 100 The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the least square means (LSMs), differences in LSMs, and corresponding CIs on the natural log (ln) scale.

Source: Table 12, CSR-20200369, Page no. 55

An alternate PK analysis (Sensitivity Analysis A) was performed by the Applicant where AUC values were re-calculated using the linear trapezoidal (linear interpolation) rule for increasing concentrations and logarithmic trapezoidal rule for decreasing concentrations (linear up/log down).

When Sensitivity Analysis A was performed using the linear-up-log-down AUC calculation method, all parameters met bioequivalence criteria with GMRs (90% CI) of 0.857 (0.810, 0.907) for AUC_{last}, 0.861 (0.815, 0.911) for AUC_{inf}, and 0.855 (0.821, 0.890) for C_{max}.

The clinical pharmacology reviewer conducted independent analysis of the PK data (using AUC calculation method in the primary analysis i.e., linear trapezoidal-linear interpolation rule) and observed the difference in PK sampling timepoints between reference and test arms (Table 4). The reference arm (30 mg IR tablets) had more PK sampling timepoints between 12 to 16 hours and less PK sampling timepoints between 24 to 72 hours. The reviewer reanalyzed the PK data with additional analyses for partial AUC from 0 to 24 hours ($pAUC_{0-24}$) i.e., dosing interval for XR formulation and observed that $pAUC_{0-24}$ met the equivalence criteria with GMR (90% CI) of 0.955 (0.896, 1.017), indicating that differences in sampling timepoints between the formulations in the exponentially declining terminal elimination phase may have contributed towards less precise calculation of AUC_{inf}. The observation was further supported by the sensitivity analysis A where when linear-up-log-down-AUC calculation method was used similar to $pAUC_{0-24}$, all parameters met bioequivalence criteria with GMRs (90% CI) of 0.857 (0.810, 0.907) for AUC_{last}, 0.861 (0.815, 0.911) for AUC_{inf}, and 0.855 (0.821, 0.890) for C_{max} indicating that linear-up-log-down-AUC calculation method is better in accounting for the differences in sampling timepoints between formulations in the exponentially declining terminal elimination phase and bioequivalence can be concluded after single dose administration.

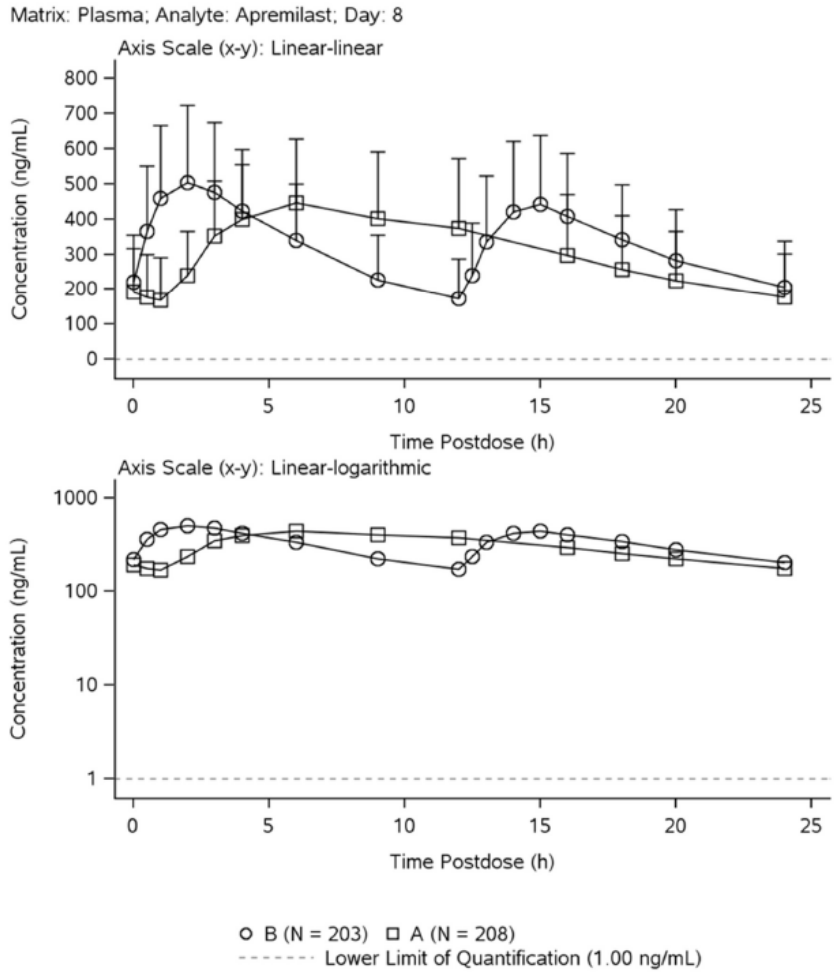
Table 4: Pharmacokinetic Sampling Time Points for Part 1 of the Study

Formulation	Dose on Day 1 of Each Period	Dose on Day 8 of Each Period
Apremilast XR QD (Test) 75 mg tablets	Predose (0 hours), 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 18, 20, 24, 30, 36, 48, 60, and 72[a] hours postdose	Predose (0 hours), 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 18, 20, and 24 hours postdose
Apremilast IR BID (Reference) 30 mg tablets	Predose (0 hours), 0.5, 1, 2, 3, 4, 6, 9, 12 (prior to evening dose), 12.5, 13, 14, 15, 16, 18, 20, 24, 48, and 72[a] hours postdose	Predose (0 hours), 0.5, 1, 2, 3, 4, 6, 9, 12 (prior to evening dose), 12.5, 13, 14, 15, 16, 18, 20, and 24 hours postdose
Sampling Time Windows for all PK samples	Predose (0 hour): 60 minutes prior to dosing Postdose Timepoints: 0.5 up to 3 hours postdose (±5 minutes); from 3 to 24 hours postdose (±10 minutes); after 24 hours postdose (±60 minutes)	

Abbreviations: BID = twice daily; IR = immediate-release; PK = pharmacokinetic; QD = once daily; XR = extended-release.
[a] The 72 hour postdose sample on Day 1 of each period was taken prior to the dose administered on Day 4 of each period.

The comparison of plasma concentration time profile of apremilast after repeated administration of apremilast XR 75 mg once daily and apremilast IR 30 mg twice daily on Day 8 is shown in Figure 2.

Figure 2: Arithmetic Mean (+SD) Pharmacokinetic Concentration-time Profiles on Day 8 (Pharmacokinetic Population) for Part 1



N=number of subjects, QD=once daily, BID=twice daily
Treatment A: apremilast XR 75 mg oral tablet, administered QD, Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart).
Source: Figure 4, CSR-20200369, Page no. 57

The XR formulation showed a delayed median t_{max} of 6.00 hours compared to 3.00 hours for the IR formulation, and slightly lower average concentrations (282 ng/mL vs 302 ng/mL) and trough concentration (152 ng/mL vs 186 ng/mL) (Table 5).

Table 5: Summary of Part 1 Day 8 Pharmacokinetic Parameters (Pharmacokinetic Population)

Matrix	Parameter	B (N = 203)	A (N = 208)
Plasma	AUC_{0-24} (h*ng/mL)	7150 (44.6) [189]	6770 (49.1) [196]
	C_{max} (ng/mL)	550 (36.6) [189]	469 (34.4) [196]
	t_{max} (h)	3.00 (0-20.0) [189]	6.00 (0-18.0) [196]
	C_{min} (ng/mL)	138 (77.3) [189]	NC (NC) [196]
	C_{trough} (ng/mL)	186 (72.6) [189]	152 (91.6) [195]
	C_{avg} (ng/mL)	302 (46.5) [189]	282 (49.1) [196]

Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart) QD = once daily; BID = twice daily. Cmax = maximum observed concentration; Cmin = lowest

concentration in the dosing interval; Ctrough = concentration at the end of the dosing interval; Cavg = average concentration during the dosing interval; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; NC = not calculated; AUC0-24 = area under the concentration-time curve from Hour 0 to 24 hours postdose; tmax = time of the maximum observed concentration; Geometric mean (Geometric CV) [n] statistics presented; for tmax, median (minimum-maximum) [n] statistics presented; for t1/2, arithmetic mean (standard deviation) [n] statistics

Source: Table 13, CSR-20200369, Page no. 58

The repeat-dose PK assessment on Day 8 of Study 20200369 Part 1 demonstrated that the 75 mg apremilast XR formulation administered once daily met bioequivalence criteria compared to the 30 mg apremilast IR formulation administered twice daily. The GMRs for AUC_{0-24} was 0.941 (90% CI: 0.896, 0.987) with 29.0% within-subject variability, and for C_{max} was 0.851 (90% CI: 0.820, 0.883) with 21.8% within-subject variability, both meeting bioequivalence criteria with 90% CIs within the 0.80-1.25 range (Table 6). This repeat-dose assessment is considered more clinically relevant data from the study since apremilast is used for chronic conditions requiring long-term treatment rather than single-dose applications.

Table 6: Statistical Analysis of Pharmacokinetic Parameters (Relative Bioavailability Assessment) on Day 8

				Test versus Reference	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV (%)
AUC_{0-24} (h*ng/mL)	Treatment B (reference)	189	7160		
	Treatment A (test)	196	6730	0.941 (0.896, 0.987)	29.0
C_{max} (ng/mL)	Treatment B (reference)	189	549		
	Treatment A (test)	196	467	0.851 (0.820, 0.883)	21.8

Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart) CI = confidence interval, CV = coefficient of variation (%), GLSM = geometric least squares mean, n = number of subjects with valid observations; QD = once daily; BID = twice daily Model: a linear mixed-effects model is used to analyze the natural log-transformed PK parameters, with planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect. Primary analysis performed using AUCs calculated by linear-linear calculation method. Within-subject CV: CVW(%) = [exp(mse)-1]½ x 100 The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the least square means (LSMs), differences in LSMs, and corresponding CIs on the natural log (ln) scale.

Source: Table 14, CSR-20200369, Page no. 59

The GMR for C_{trough} was 0.808 (90% CI: 0.738, 0.884) with 56.8% within-subject variability (Table 7).

Table 7: Statistical Analysis of Pharmacokinetic Parameters for C_{trough} (Relative Bioavailability Assessment) (Pharmacokinetic Population)-Part 1, Day 8

Matrix: Plasma; Analyte: Apremilast; Day: 8

				Test versus Reference	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV (%)
C_{trough} (ng/mL)	Treatment B (reference)	189	186		
	Treatment A (test)	195	150	0.808 (0.738, 0.884)	56.8

AUC = area under the plasma concentration-time curve; BID = twice daily; Cmax = maximum observed plasma concentration; Ctrough = concentration at the end of the dosing interval; CV = coefficient of variation (%); GLSM = geometric least squares mean; n = number of subjects with valid observations; PK = pharmacokinetics; QD = once daily Treatment A: apremilast XR 75 mg oral tablet, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart). Model: a linear mixed-effects model is used to analyze the natural log-transformed PK parameters, with planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect. Same data exclusion rules were applied as in primary analysis for AUCs and Cmax. Within-subject CV: CVW(%) = [exp(mse)-1]½ x 100

The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the least square means (LSMs), differences in LSMs, and corresponding CIs on the natural log (ln) scale.
Source: Table 14.2.1.4, CSR-20200369, Page no. 187

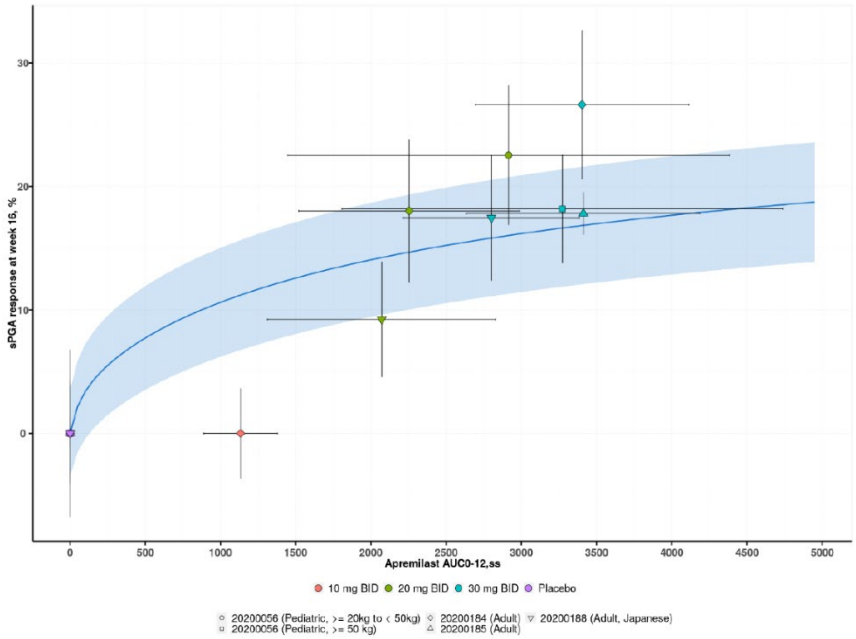
Justification to support the use of apremilast XR tablets in adult patients with PsO who are candidates for phototherapy or systemic therapy and active PsA

The Applicant justified the differences in PK between apremilast XR and IR by emphasizing that area under the curve (AUC) is the primary PK driver of efficacy rather than C_{trough}, supported by exposure-response (E-R) analyses (Refer to section .1 for details). The E-R analysis conducted by the Applicant (Study 157815) identified that $AUC_{0\text{-}24,ss}$ (steady-state area under the curve from 0-24 hours) has a stronger correlation with ACR20 in PsA patients than C_{trough}, and similar correlation with sPGA and PASI-75 in PsO patients. Based on the observed apremilast XR tablet exposures in Study 20200369, the E-R analysis predicted similar response rates for PASI-75, sPGA, and ACR20 compared to the approved IR tablet formulation, supporting that the XR formulation will provide similar efficacy to the IR formulation. Safety data from Study 20200369 demonstrate that differences in plasma concentration profiles, including lower trough levels, do not result in meaningful changes in safety and tolerability between formulations (refer to section 8.2). Overall, based on E-R analyses AUC appears to be the primary PK driver of efficacy rather than C_{trough}, and lower C_{trough} and similar C_{max} do not raise any concern in safety and tolerability, hence the PK results along with E-R analysis support the use of apremilast XR tablets in adult patients with active PsA and PsO who are candidate for phototherapy or systemic therapy.

Justification to support the use of apremilast XR tablets in pediatric patients with moderate to severe PsO who are candidates for phototherapy or systemic therapy

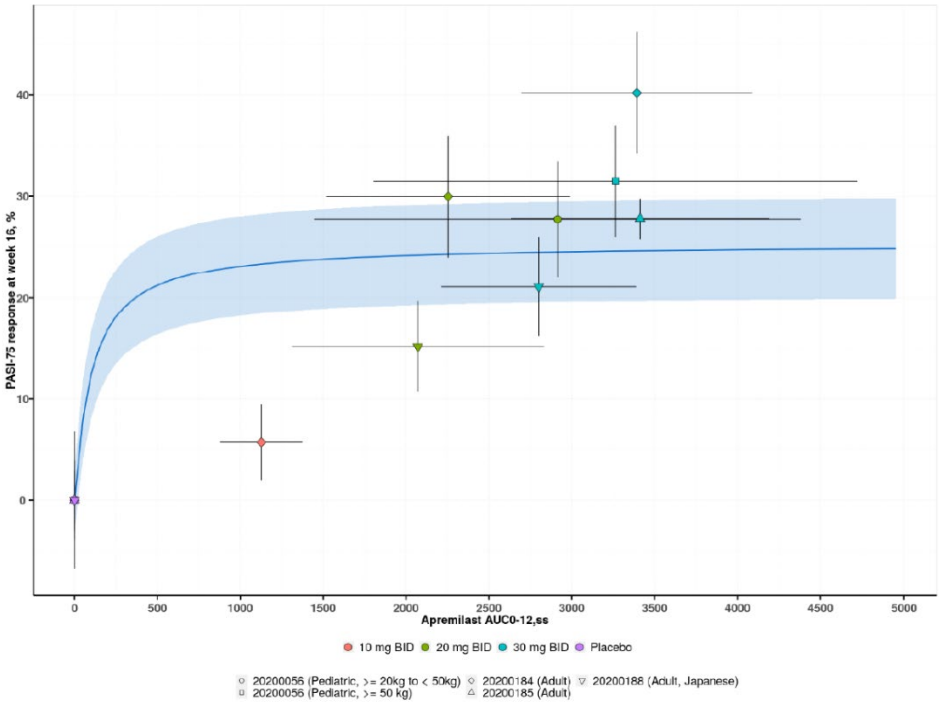
The above E-R conclusions are applicable for both adult patients and pediatric patients weighing < 50 kg whose approved dosage for the IR formulation is 30 mg BID. It has previously been demonstrated that the E-R relationship for apremilast IR tablets is similar between adults and pediatric patients with moderate to severe plaque psoriasis. Model-based simulations confirmed that the recommended dosage regimen of 30 mg BID for pediatric patients weighing ≥ 50 kg is appropriate to achieve exposure levels associated with clinical response (sPGA and PASI-75 response) consistent with response rates observed in adults with moderate to severe plaque psoriasis.(Figure 3 and Figure 4)

Figure 3: Placebo-Corrected Exposure-sPGA Response After 16 Weeks of Apremilast Treatment by Study and Dosing Regimen



Source: Figure 11-20, Page no. 80, Pharmacometrics Report: 157167; Adapted from Figure 5 in sNDA 205437/013 Multi-Disciplinary Review and Evaluation
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; sPGA, static Physician's Global Assessment

Figure 4: Placebo-Corrected Exposure-PASI-75 Response After 16 Weeks of Apremilast Treatment by Study and Dosing Regimen



Source: Figure 11-20, Page no. 80, Pharmacometrics Report: 157167; Adapted from Figure 6 in sNDA 205437/013 Multi-Disciplinary Review and Evaluation

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; PASI, Psoriasis Area and Severity Index

Based on the evidence supporting an expectation of similar efficacy between the 75 mg XR QD formulation and the 30 mg IR BID formulation in adults and the similar E-R relationship established for apremilast 30 mg IR BID in adults and children weighing ≥ 50 kg, the 75 mg XR QD formulation is expected to achieve similar efficacy in pediatric PsO patients weighing ≥ 50 kg compared to the 30 mg IR BID formulation.

Justification to support the use of apremilast XR tablets in pediatric patients with active PsA

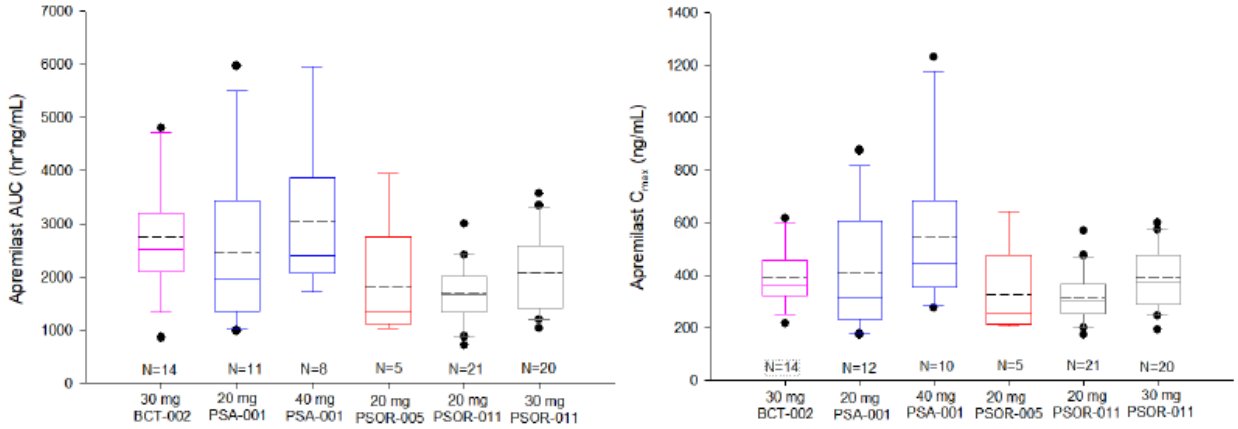
Apremilast 30 mg BID has been approved as the safe and efficacious dose of the apremilast IR formulation for pediatric patients with active PsA 6 years of age and older and weighing at least 50 kg. Based on the evidence supporting an expectation of similar clinical outcomes between the 75 mg XR QD formulation and the 30 mg IR BID formulation in adults and the similar PK for apremilast 75 mg XR QD in adults and pediatrics weighing at least 50 kg, it is expected that the efficacy and safety of the 75 mg XR QD formulation will be consistent with that of the apremilast 75 mg XR QD formulation in adult patients with PsA. This supports that the 75 mg XR QD formulation has a favorable benefit-risk profile in pediatric patients with PsA 6 years of age and older and weighing at least 50 kg and offers a meaningful therapeutic option in this patient population.

Justification to support the use of apremilast XR tablets in patients with oral ulcers associated with Behçet's disease

No scientific justification was originally provided to support the indication for "the treatment of adults patients with oral ulcers associated with Behçet's disease" in the current NDA submission. The Applicant was asked to provide additional justification to support that Otezla XR is safe and efficacious in adult patients with oral ulcers associated with Behçet's disease in two information requests on 7th April and 6th June 2025. The Applicant responded to the information requests on 18th April (SN 0025) and 16th June 2025 (SN 0027).

Exposure response relationship in adults with oral ulcers associated with BD was not developed due to lack of PK samples in the pivotal efficacy and safety study supported the approval of apremilast IR in this patient population. Therefore, the Applicant's justification for using apremilast XR tablets in patients with oral ulcers associated with Behçet's disease relies primarily on PK bridging and mechanistic evidence. The 75 mg apremilast XR once daily formulation demonstrates bioequivalent steady-state systemic exposure (AUC and C_{max}) to the approved 30 mg IR twice daily formulation, with PK parameters showing overlap across patients with Behçet's disease, PsA, and PsO (Figure , Table 8). The E-R analysis indicated that apremilast XR 75 mg QD will translate to efficacy responses similar to apremilast IR 30 mg BID in patients with PsA and PsO, and the efficacious dosage of the apremilast IR formulation in patients with BD is also 30 mg BID, it appears reasonable to expect that patients with BD will also achieve similar efficacy responses with apremilast XR 75 mg QD.

Figure 5: Comparison of Observed Apremilast AUC and Cmax at Steady State in Adults With BD, Adults with PsA, and Adults with PsO Following Oral Administration of Apremilast



AUC = area under the drug concentration time curve; BD = Behçet's disease; BID = twice daily; PsA = psoriatic arthritis; PsO = plaque psoriasis; QD = once daily; AUC is from time 0 to 8 hours postdose for Studies PSA-001, PSOR-005, and PSOR-011. AUC is from time 0 to 12 hours postdose for Study BCT-002. Dose is BID except for 40 mg dose in PSA-001 which was QD. Boxes display mean (dashed lines), median (solid lines), 25th (bottom) percentile, and 75th (top) percentile. Whiskers represent the 10th (bottom) and 90th (top) percentiles. Closed circles represent minimum and maximum outliers.
Source: Response to information request 7th April 2025, Figure 1, Page no. 7.

Table 8: Comparison of PK in Adults With BD, Adults with PsA and Adults with PsO Based on Observed Data

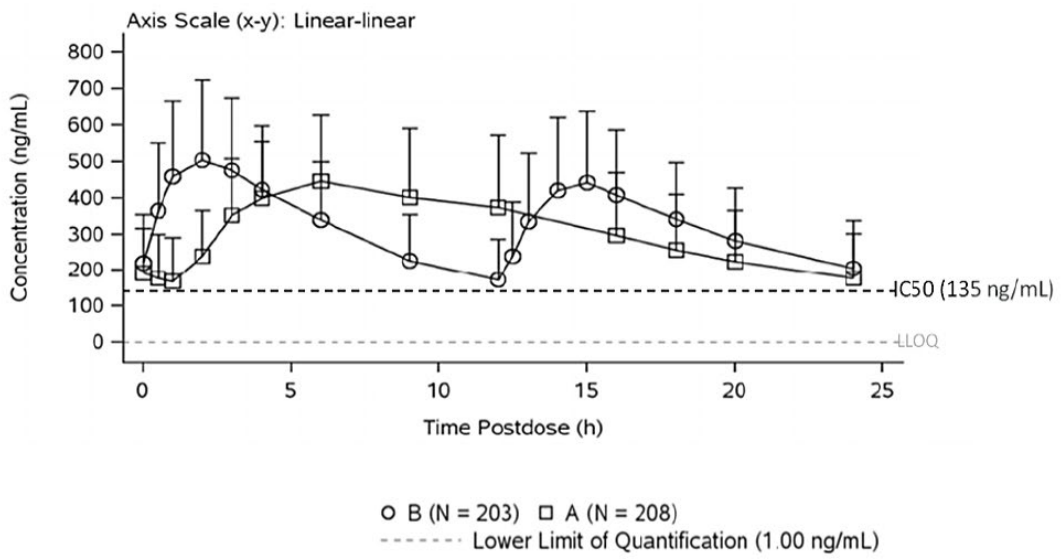
	BD (Week 16)	PsA (combined Week 10 and Week 12)		PsO (Week 14 [W14] or Week 20 [W20])			
Pharmacokinetic Parameter (unit)	BCT-002 30 mg BID (N=14)	PSA-001 20 mg BID (N=12)	PSA-001 40 mg QD (N=10)	PSOR-005-E-LTE 20 mg BID (N=5) W14	PSOR-005-E-LTE 30 mg BID (N=3) W14	PSOR-011 20 mg BID (n=21) W20	PSOR-011 30 mg BID (n=20) W20
$AUC_{0\text{-}8h}$ (ng•h/mL)	NA	2137 (59.9)[a]	2816 (43.4)[b]	1591 (56.9)	3467 (20.8)	1599 (36.9)	1967 (36.3)
$AUC_{0\text{-}12h}$ (ng•h/mL)	2545 (45.2)	NA	NA	2409(61.8)[c]	4421 (24.1)	1957 (38.7)	2397 (39.5)
C_{max} (ng/mL)	377.6 (28.4)	355 (58.5)	493 (46.3)	298 (48.3)	637 (18.7)	304 (30.8)	374 (32.0)
C_{min} (ng/mL)	92.7 (91.7)	148.4 (86.4)	76.8 (73.9)	111 (127.6)	259 (36.5)	90.8 (50.1)	104 (66.6)
t_{max} (h)	1.88 (1.00- 3.00)	2.08 (1.00-4.00)	2.54 (1.08-4.00)	2.00 (1.00-4.00)	1.00 (1.00-2.00)	2.03 (1.00- 4.00)	2.00 (0.98 – 4.00)

AUC = area under the plasma concentration-time curve; AUC0-8h = AUC from time 0 to 8 hours postdose; AUC0-12h = AUC from time 0 to 12 hours postdose; BD = Behçet's disease; BID = twice daily; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; PsA = psoriatic arthritis; PsO = plaque psoriasis; N = number of subjects; NA = not available, tmax = time to maximum observed plasma concentration. Descriptive statistics are presented as geometric mean (Geo CV%) except for tmax shown as median (range). Calculated parameters are for doses as listed; no additional dose normalization was included.
a N = 11
b N = 8
c N = 3
Source: Response to information request 7th April 2025, Table 1, Page no. 6.

The PK bridging was further supported by pharmacodynamic justification provided by the Applicant. The Applicant noted that the pathophysiology of oral ulcers associated with BD is driven by dysregulation of Th1/Th17 cells, resulting in increased inflammatory cytokines, which

shares similarities with PsA and PsO, particularly regarding the established role of TNF-α across all three conditions. Apremilast treatment reduces TNF-α production in patients with oral ulcers associated with BD, PsA, and PsO. The apremilast XR formulation has demonstrated TNF-α inhibition comparable to the immediate-release formulation (Study CC-10004-CP-035). Study CC-10004-CP-035 (this study included an exploratory PD sub study to assess the effect of both formulations on the production of TNF-α and other cytokines in an ex vivo whole blood assay) showed that 75 mg apremilast XR once daily achieved comparable PK exposure (AUC and C_{max}) to 30 mg IR twice daily in healthy volunteers. In exploratory PD assessments, both formulations produced similar TNF-α inhibition in ex vivo whole blood assays, with maximum mean inhibition values of 42.6% for IR and 37.7% for XR. Nonclinical in vitro data established that apremilast effectively inhibits LPS-induced TNF-α production with an IC_{50} of 294 nM (135 ng/mL). Importantly, plasma concentrations from both formulations remain above this IC_{50} throughout the dosing interval (Figure), with the IR formulation maintaining trough levels 1.4-fold above IC_{50} and peak levels 4-fold above IC_{50}, while the XR formulation maintains trough levels 1.1-fold above IC_{50} and peak levels 3.5-fold above IC_{50}.

Figure 6: Arithmetic Mean (+SD) Pharmacokinetic Concentration-time Profiles on Day 8 in Study 20200369 (Pharmacokinetic Population) With IC_{50} for LPS-induced TNF-α Production in Whole Blood In Vitro



BID = twice daily; IC50 = half maximal inhibitory concentration; LPS = lipopolysaccharide; N = number of subjects; QD = once daily; TNF-α= tumor necrosis factor alpha Treatment A: apremilast XR 75 mg oral table, administered QD; Treatment B: apremilast IR 30 mg oral tablet, administered BID (with each dose administered approximately 12 hours apart).
Source: Response to information request 6th June 2025, Figure 2, Page no. 8, NDA 210745/eCTD 1.11.3

While exposure-response analysis was not performed for Behçet's disease due to limited PK data (only 14 subjects), the Applicant stated that given the similar TNF-α inhibition profiles between formulations, combined with previously established PK bridging justification, the apremilast XR 75 mg once-daily formulation is expected to provide clinical efficacy consistent with the established IR 30 mg twice-daily formulation in adults with BD.

The review team agrees with Applicant's PK bridging and mechanistic justification to support the indication for "treatment of adults patients with oral ulcers associated with Behçet's disease" in this NDA submission.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimens of apremilast XR formulation in adult subjects (Table 9) and pediatric subjects 6 years of age and older weighing at least 50 kg with moderate to severe PsO (Table 10) are reasonable from a clinical pharmacology perspective.

Table 9: Dosage Titration Schedule for Adult Patients with Psoriatic Arthritis, Plaque Psoriasis, or Behçet's Disease

OTEZLA Dosage Titration[a]									OTEZLA/OTEZLA XR Maintenance Dosage
Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter
AM	AM	PM	AM	PM	AM	PM	AM	PM	
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	OTEZLA 30 mg BID **OR** OTEZLA XR 75 mg QD

BID = twice daily; QD = once daily
[a] OTEZLA tablets should be used for the initial titration regardless of whether OTEZLA or OTEZLA XR will be used for the maintenance dosage.

Table 10: Dosage Titration Schedule for Pediatric Patients 6 Years of Age and Older and Weighing at Least 50 kg with Moderate to Severe Plaque Psoriasis

	OTEZLA Dosage Titration[a]									OTEZLA/OTEZLA XR Maintenance Dosage
Body Weight	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter
	AM	AM	PM	AM	PM	AM	PM	AM	PM	
50 kg or more	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	OTEZLA 30 mg BID **OR** OTEZLA XR 75 mg QD

BID = twice daily; QD = once daily
[a] OTEZLA tablets should be used for the initial titration regardless of whether OTEZLA or OTEZLA XR will be used for the maintenance dosage.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

In adult subjects with severe renal impairment, single-dose oral administration of 30 mg apremilast resulted in approximately 88% increased exposure (AUC_{inf}) based on Study CC-10004-CP-019, resulting in dose reduction to 30 mg once daily for adults and pediatric patients weighing at least 50 kg with severe renal impairment. Since the XR tablet is only available as a 75 mg strength, dose reduction is not feasible with the XR formulation, making it unsuitable for patients with severe renal impairment. Therefore, the 75 mg XR tablet is not recommended for subjects with severe renal impairment.

Are there clinically relevant food-drug interactions, and what is the appropriate management strategy?

There is no clinically relevant effect of food on the bioavailability of apremilast XR tablets. Results from the food effect study (Study 20200369 Part 2) showed that food increases the extent of absorption of apremilast (~28% higher C_{max} and AUC) and delayed absorption (t_{max}, 12.0 hours compared to 9.0 hours) when compared to fasted conditions. These food-effect results were confirmed by the clinical pharmacology reviewer, and the observed food effect is not considered clinically meaningful.

Study 20200369 Part 2 is as an open-label, randomized, 2-period, 2-sequence crossover study to assess the effect of food on the PK of the apremilast XR tablet after a single dose. The study enrolled 20 healthy adult male and female subjects (10 subjects per sequence) who were randomized on Period 1 Day 1 to either Sequence 3 (CD) or Sequence 4 (DC) (Table 11). In Sequence 3, subjects received apremilast XR 75 mg under fed conditions on Period 1 Day 1 followed by apremilast XR 75 mg under fasted conditions on Period 2 Day 1, while Sequence 4 (DC) followed the reverse order. There were at least 7 days between the doses administered in Period 1 and Period 2. For the fed condition, subjects underwent an overnight fast of at least 10 hours, then consumed the entirety of a standard high-fat breakfast within 20 minutes, followed by dose administration 30 minutes after the start of the meal. For the fasted condition, subjects underwent an overnight fast of at least 10 hours before dose administration. The primary objective of Part 2 was to evaluate the effect of food on apremilast XR, with primary endpoints being C_{max}, AUC_{last}, and AUC_{inf} following single-dose administration on Day 1.

All 20 subjects completed the study.

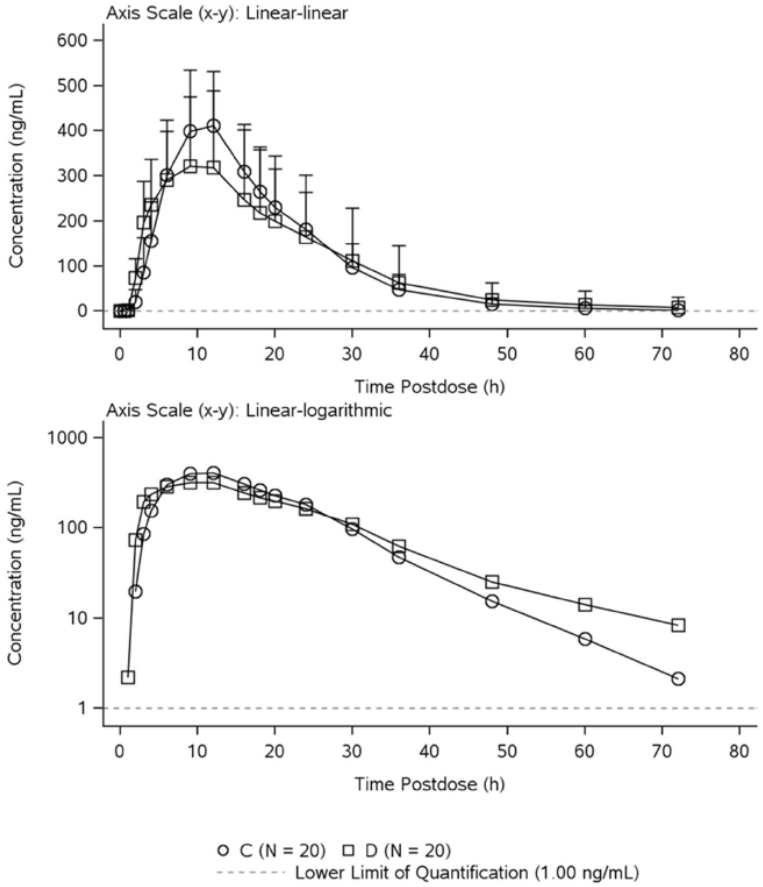
Table 11: Subject disposition for Part 2 of the Study

Demographic	CD (N = 10) n(%)	DC (N = 10) n(%)	Overall (N = 20) n(%)
Population			
Safety	10 (100%)	10 (100%)	20 (100%)
Pharmacokinetic	10 (100%)	10 (100%)	20 (100%)
Completed the Study	10 (100%)	10 (100%)	20 (100%)

Treatment C: XR 75 mg oral tablet, single dose administered under fed conditions; Treatment D: XR 75 mg oral tablet, single dose administered under fasted conditions. n = number of subjects with valid observations; N = number of subjects; % = percentage of subjects with valid observations (n/N×100) The safety population will include all subjects who received at least 1 dose of apremilast. The pharmacokinetic population will include all subjects who received at least 1 dose of apremilast and have evaluable PK data.
Source: Table 8, CSR-20200369, Page no. 43

The comparison of plasma concentration time profiles of apremilast after administration of apremilast XR 75 mg single dose under fasted and fed condition is shown in Figure Figure 7.

Figure 7: Arithmetic Mean (+SD) Pharmacokinetic Concentration-time Profiles (PK Population) for Part 2



N=number of subjects, Treatment C: apremilast XR 75 mg oral tablet, administered single dose under fed conditions, Treatment D: XR 75 mg oral tablet, single dose administered under fasted conditions.
Source: Figure 5, CSR-20200369, Page no. 70

Food delayed drug absorption, with the median t_{max} increasing from 9.00 hours under fasted condition to 12.0 hours under fed condition (a 3-hour delay) (Table 12).

Table 12: Summary of Pharmacokinetic Parameters of Apremilast Following Oral Dose Administration in the Fasted and Fed States for Part 2

Matrix	Parameter	C (N = 20)	D (N = 20)
Plasma	AUC_{last} (h*ng/mL)	7570 (38.3) [19]	6280 (78.0) [19]
	AUC_{0-24} (h*ng/mL)	5980 (31.6) [19]	4840 (59.7) [19]
	AUC_{inf} (h*ng/mL)	7610 (38.4) [19]	6360 (79.9) [19]
	C_{max} (ng/mL)	422 (32.2) [19]	342 (40.1) [19]
	t_{max} (h)	12.0 (4.00-12.0) [19]	9.00 (3.00-12.0) [19]
	t_{lag} (h)	1.00 (0.500-2.00) [19]	0.500 (0-1.00) [19]
	$t_{1/2}$ (h)	7.16 (2.09) [19]	8.12 (3.74) [19]
	λ_z (1/h)	0.101 (28.7) [19]	0.0923 (39.9) [19]
	CL/F (L/h)	9.86 (38.4) [19]	11.8 (79.9) [19]
	V_z/F (L)	98.0 (27.6) [19]	128 (58.0) [19]

Treatment C: XR 75 mg oral tablet, single dose administered under fed conditions; Treatment D: XR 75 mg oral tablet, single dose administered under fasted conditions AUCinf = area under the concentration-time curve from time 0 extrapolated to infinity; AUClast = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = apparent total clearance; Cmax = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; AUC0-24 = area under the concentration-time curve from Hour 0 to 24 hours postdose; tmax = time of the maximum observed concentration; Vz/F = apparent volume of distribution during the terminal phase; Geometric mean (Geometric CV) [n] statistics presented; for tmax, tlag, median (minimum-maximum) [n] statistics presented; for t1/2, arithmetic mean (standard deviation) [n] statistics
Source: Table 21, CSR-20200369, Page no. 71

The statistical analysis results from Study 20200369 Part 2 (Table 13) demonstrated approximately 27-28% increases in AUC and C_{max} under fed conditions, suggesting a modest food effect on the apremilast XR formulation when administered under fed condition compared to fasted condition.

Table 13: Statistical Analysis of Pharmacokinetic Parameters (Food Effect Assessment) for Part 2

				Fed versus Fasted	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV (%)
AUC_{last} (h*ng/mL)	Treatment D (Fasted)	19	6150		
	Treatment C (Fed)	19	7870	1.28 (1.036, 1.582)	37.4
AUC_{inf} (h*ng/mL)	Treatment D (Fasted)	19	6230		
	Treatment C (Fed)	19	7950	1.276 (1.032, 1.578)	37.6
C_{max} (ng/mL)	Treatment D (Fasted)	19	336		
	Treatment C (Fed)	19	430	1.281 (1.116, 1.471)	24.1

Treatment C: XR 75 mg oral tablet, single dose administered under fed conditions; Treatment D: XR 75 mg oral tablet, single dose administered under fasted conditions. CI = confidence interval, CV = coefficient of variation (%), GLSM = geometric least squares mean, n = number of subjects with valid observations; QD = once daily; BID = twice daily Model: a linear mixed-effects model is used to analyze the natural log-transformed PK parameters, with planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect. Within-subject CV: CVW(%) = [exp(mse)-1]½ x 100 The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the least square means (LSMs), differences in LSMs, and corresponding CIs on the natural log (ln) scale.
Source: Table 22, CSR-20200369, Page no. 72

These modest increases in apremilast systemic exposure were considered not clinically meaningful, supporting that apremilast XR can be administered without regard to meals.

What are the characteristics of bioanalytical method?
The bioanalytical method CC-10004-DMPK-024 (previously reviewed under NDA 205437) for apremilast quantification underwent partial validation to accommodate methodological changes, including increased citric acid concentration from 0.04 M to 0.2 M and reduction of plasma sample volume from 100 µL to 25 µL. The validation was conducted at (b) (4) . Given apremilast's susceptibility to hydrolysis at physiological pH and stability under acidic conditions, the use of citric acid-containing collection tubes was appropriately implemented to maintain analyte integrity. The method employed liquid-liquid extraction for sample preparation with stable isotope-labeled apremilast serving as internal standard, followed by reversed-phase LC-MS/MS detection. The calibration range of 1-1000 ng/mL was maintained throughout the validation process.

The method demonstrated acceptable performance. Incurred sample re-analysis was performed in 5.4% of study samples, and 97.9% of the samples met the pre-specified criteria. Analysis of samples began on 30 Aug 2022 (date of first extraction) and concluded on 30 Nov2022 (date of last injection). A total of 113 days transpired between the first sample collection date and the last extraction date. All study samples were analyzed within the established long-term stability of 677 days at -20°C.

Overall, method validation, and sample analysis supporting relative bioavailability study 20200369 were in-line with the Agency’s recommendations outlined in the Guidance for Industry:M10 Bioanalytical Method Validation and Study Sample Analysis (Nov 2022), and all criteria as specified in the guidance were met and are acceptable.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 14: Listing of Clinical Trials Included in this NDA

Study Identification (Sponsor)	Trial Design	Dosing Regimen	Study Endpoint	Number of Subjects Enrolled N	Study Population
Study CC-10004-CP-034 (Celgene)	single-center, phase 1, open-label, randomized, three-period, six-sequence, crossover study.	Treatment A: one 30-mg IR oral tablet twice daily for five days. Treatment B: Apremilast XR (APRE XR) 75-mg QD formulation once daily for five days. Treatment C: Apremilast prototype 12 (PT12) 75-mg QD formulation once daily for five days.	Comparison of the pharmacokinetics of APRE XR QD formulation (test) with IR BID formulation (reference).	18	Healthy Volunteers
Study CC-10004-CP-035 (Celgene)	Two Part Study. Part 1: multicenter, phase 1, open-label, randomized, multiple-dose two-period, two-sequence, crossover study in healthy subjects.	Part 1: Treatment A: one 30-mg IR oral tablet twice daily for eight days. Treatment B: Apremilast XR (APRE XR) 75-mg QD formulation once daily for eight days.	Comparison of the pharmacokinetics of APRE XR QD formulation (test) with IR BID formulation (reference).	Part 1: 100 subjects Part 2: 20 subjects	Healthy Volunteers

Study Identification (Sponsor)	Trial Design	Dosing Regimen	Study Endpoint	Number of Subjects Enrolled N	Study Population
	Part 2: single center, open-label, randomized, four-period, four-sequence crossover study assessing fed, fasted, and high-fat meal conditions.	Part 2: Treatment C: one 30-mg IR oral tablet twice daily for two days in fasting subjects for two days. Treatment D: APRE XR 75-mg QD formulation once daily in fasting subjects for two days. Treatment E: one 30-mg IR oral tablet twice daily for two days in subjects fed a standard meal for two days. Treatment F: APRE XR 75-mg QD formulation once daily in subjects fed a high fat meal for two days			
Study 20200369 (Amgen)	Two part study. Part 1: two-period, two-sequence study.	Part 1: Treatment A: one 30-mg IR oral tablet twice daily for eight days.	Comparison of the pharmacokinetics of APRE XR QD formulation (test) with IR BID formulation (reference).	Part 1: 211 subjects Part 2: 20 subjects	Healthy Volunteers

Study Identification (Sponsor)	Trial Design	Dosing Regimen	Study Endpoint	Number of Subjects Enrolled N	Study Population
	Part 2: two-period, two-sequence study assessing fed and fasted conditions.	Treatment B: Apremilast XR (APRE XR) 75-mg QD formulation once daily for eight days. Part 2: Treatment A: APRE XR 75-mg QD formulation once daily in fed subjects for two days. Treatment B: APRE XR 75-mg QD formulation once daily in fasting subjects for two days.			

6.2. Review Strategy

The current submission consists of three clinical pharmacology studies enrolling healthy volunteers receiving up to eight days of apremilast 30 mg IR tablets BID or apremilast XR (APRE XR) 75 mg tablets QD. The purpose of these studies was to demonstrate that the once daily APRE XR tablet QD formulation was bioequivalent to the IR BID formulation. The primary objectives of the submitted studies were for pharmacokinetic data. No efficacy data was planned or collected. Safety data is reviewed by individual study in Section 7.2.

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

The current submission consists of three clinical pharmacology studies enrolling healthy volunteers receiving up to eight days of apremilast 30 mg IR tablets BID or apremilast XR (APRE XR) 75 mg tablets QD. The purpose of these studies was to demonstrate that the once daily APRE XR tablet QD formulation was bioequivalent to the IR BID formulation. No efficacy data was planned or collected. Consequently, there is no review of efficacy data.

The reader is referred to the original completed reviews for approval of apremilast for the treatment of adult patients with active PsA; the treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA; and adult patients with oral ulcers associated with BD.

7.2. Review of Safety

7.2.1. Safety Review Approach

The safety profile of apremilast is derived from pivotal studies conducted in adults and children with PsO, PsA or Behçet's disease. The OTEZLA package insert lists Warnings and Precautions of hypersensitivity, diarrhea, nausea, vomiting, depression, and weight decrease. The most common adverse reactions observed in the clinical trials include diarrhea, nausea, headache, upper respiratory tract infection, and headaches.

The current submission consists of three clinical pharmacology studies enrolling healthy volunteers receiving up to eight days of apremilast 30 mg IR tablets BID or APRE XR 75 mg tablets QD. The purpose of these studies was to demonstrate that the once daily APRE XR tablet QD formulation was bioequivalent to the IR BID formulation. The safety data from these studies is limited due to the design of the studies including small number of enrolled subjects, study population, and limited dosing duration. As a result, this review will include a description of the individual study designs and description of the safety data.

Study CC-10004-CP-034 (Celgene)
Study CC-10004-CP-034 (hereafter referred to as 034) was a single-center, phase 1, open-label, randomized, three-period, six-sequence, crossover study in healthy male subjects. The study comprised a screening period, baseline, three treatment periods, and a follow-up phone call. The eligibility of the subjects was assessed during the screening phase. Eligible subjects were admitted to the study center on Day -1 of Treatment Period 1 for baseline assessments. On Day 1 of Treatment Period 1, subjects received an oral dose of apremilast according to the assigned treatment sequence. The apremilast treatments administered in this study were as follows:

- Treatment A: 60-mg reference formulation (one 30-mg IR oral tablet in the morning and one 30-mg IR oral tablet in the evening of the dosing days) for 5 days. The evening dose was administered approximately 12 hours after the morning dose.
- Treatment B: Apremilast XR (APRE XR) 75-mg QD formulation once daily for 5 days.
- Treatment C: Apremilast prototype 12 (PT12) 75-mg QD formulation once daily for 5 days.

Subjects were randomly assigned to one of the six treatment sequences as shown in Table 15.

Table 15: Treatment Periods: Study CC-10004-CP-034

	Period 1 (5 days)	Period 2 (5 days)	Period 3 (5 days)
Sequence 1 (n=3)	Treatment A: IR BID	Treatment C: PT12	Treatment B: APRE XR
Sequence 2 (n=3)	Treatment C: PT12	Treatment B: APRE XR	Treatment A: IR BID
Sequence 3 (n=3)	Treatment B: APRE XR	Treatment A: IR BID	Treatment C: PT12
Sequence 4 (n=3)	Treatment A: IR BID	Treatment B: APRE XR	Treatment C: PT12
Sequence 5 (n=3)	Treatment C: PT12	Treatment A: IR BID	Treatment B: APRE XR
Sequence 6 (n=3)	Treatment B: APRE XR	Treatment C: PT12	Treatment A: IR BID

Source: CC-10004-CP-034 Study Report, page 13, Table 3. APRE XR=apremilast XR; IR=immediate release; PT12=prototype 12; BID=twice daily

Subjects were confined to the study center on Day -1 (Baseline) of Treatment Period 1 through Day 8 of Treatment Period 3, including a five-day washout between dosing periods. Except for the subjects who discontinued, all subjects were discharged from the study center on Day 8 of Treatment Period 3 following completion of required study procedures. A follow-up phone call was made approximately four days (± two days) after the discharge from the study center.

Subject Disposition and Baseline Demographics:
A total of 23 subjects were enrolled and 18 subjects completed the study with four subjects who discontinued treatment due to a TEAE (discussed below). In general, the healthy male volunteers we White (52%) or Black (44%) with a mean age of 36 years and mean BMI of 26.7.

Extent of Exposure:
As noted above, several subjects did not complete the study and therefore did not receive all prespecified doses. Specifically, Subject (b) (6) received 120 mg of the IR and 375 mg of APRE XR apremilast formulations but did not receive PT12 apremilast. Subject (b) (6) received 300 mg of the IR and 225 mg of PT12 apremilast formulations but did not receive APRE XR apremilast. Subject (b) (6) received 375 mg of the APRE XR and 375 mg of PT12 apremilast formulations but did not receive IR apremilast. Subject (b) (6) received 300 mg of the IR, 150 mg of APRE XR, and 375 mg of PT12 apremilast formulations. Subject (b) (6) received 300 mg of the IR and 300 mg of APRE XR formulations but did not receive PT12 apremilast. All other subjects in the study received 300 mg of the IR, 375 mg of APRE XR, and 375 mg of PT12 apremilast formulations.

Adverse Events:
In general, apremilast was well tolerated when given to healthy subjects in the fed state as multiple oral doses of the IR, APRE XR, or PT12 formulations. The incidence of TEAEs was similar following administration of the three apremilast formulations (Table 16).

Table 16: Summary of Treatment-emergent Adverse Events: Number (%) of Subjects by Treatment.

	Treatment A (N=22)	Treatment B (N=22)	Treatment C (N=21)
	n (%) E	n (%) E	n (%) E
Subjects with ≥1 TEAE	8 (36%) 22	4 (18%) 18	6 (29) 10
Subjects with ≥1 SAE	0	0	0
Subjects discontinued due to TEAE	2 (9)	1 (5)	1 (5)
Deaths	0	0	0

Source: CC-10004-CP-034 Study Report, page 39, Table 11. TEAE=treatment-emergent adverse event; BID=twice daily; E= number of TEAE; PT=prototype; QD=once daily; SAE=serious adverse event; Treatment A=apremilast 30 mg IR BID; Treatment B=APRE XR 75 mg QD; Treatment C= PT12 apremilast 75 mg QD.

Overall, 14 of 23 subjects (61%) reported 50 TEAEs during this study, the majority of which were mild in severity. There were no SAEs or deaths reported in this study. Four subjects were withdrawn due to upper respiratory tract infections (n=3) and one of vomiting (n=1).

- **Subject** (b) (6): 50-year-old, male who received APRE XL on Treatment Period 1 and apremilast IR on Treatment Period 2. On Day 2 of Treatment Period 2, the subject reported malaise, body aches, rhinorrhea, and coughing. Study drug was discontinued and on Day 3 subject developed a fever and he was given acetaminophen. On Day 4 of Treatment period 2 he reported worsening headache and was given ibuprofen and discontinued from the study. All symptoms subsequently resolved.

- **Subject** (b) (6): 32-year-old male who received IR apremilast on Treatment Period 1 and PT12 on Treatment Period 2. On Day -1 of Treatment Period 2, the subject reported sinus congestion and sore throat, which resolved by Day 2 of Treatment Period 2. Later that same day the subject reported a headache and given acetaminophen. On Treatment Period 2, Day 3 the subject reported headache, sore throat, coughing, and low-grade fever. Subject was administered additional acetaminophen and discontinued from the study. All symptoms subsequently resolved.

- **Subject** (b) (6)**:** 33-year-old male who received APRE XR on Treatment Period 1, and PT12 on Treatment Period 2. On Day 5 of Treatment Period 2, subject reported body aches, left ear congestion, cough, chills, and feeling of warmth. Subject was diagnosed with an upper respiratory tract infection and was discontinued from the study. All symptoms subsequently resolved.

- **Subject** (b) (6): 32-year-old male who received PT12 on Treatment Period 1, and apremilast IR on Treatment Period 2, and APRE XR on Treatment Period 3. On Day 1 of Treatment Period 3 the subject developed mild dyspepsia, diarrhea, headache, and abdominal pain. Subject was provided acetaminophen. Symptoms of abdominal pain, nausea, and vomiting worsened and subject was discontinued from the study. Laboratory results demonstrated normal alanine aminotransferase, aspartate aminotransferase, and urinalysis. All symptoms subsequently resolved.

Adverse events from the System Organ Class (SOC) Nervous System Disorders and Gastrointestinal Disorders were the most frequently reported TEAEs, with 6 of 23 subjects (26%) in each category reporting AEs. The most frequently reported TEAEs by Preferred Term (PT) were headache and diarrhea with 5 of 23 subjects (22%). The next most prevalent TEAEs were upper respiratory tract infections (17%), back pain (13%), decreased appetite (13%), and nausea (13%). All other preferred terms occurred in less than 10% of subjects overall. All TEAEs resolved by the end of the study.

During the study, six subjects received concomitant medications for the treatment of TEAEs. Acetaminophen was administered for headache and/or upper respiratory tract infection, and ibuprofen was given for upper respiratory tract infection. Two subjects received heat therapy during the study. Heat therapy was used for the treatment of headache, back pain, and dyspepsia.

There were no apparent differences in mean clinical laboratory measurements prior to the first dose of study drug and at the end of the study. Sporadic out-of-range values occurred in some subjects for various clinical laboratory measurements; however, no laboratory parameter results were considered clinically significant. There were no apparent trends in mean or individual vital signs measurements. Subject (b) (6) experienced a mild TEAE of tachycardia, which occurred on Period 2, Day 4 and was detected during the subject's early termination vital sign assessments. The subject was discontinued by the investigator due to behavioral issues. The subject had a reported normal baseline ECG, and no concomitant treatments were required, and the event resolved.

Reviewer's Comments:
There were no new safety signals identified in the current study which is limited by the design of this clinical pharmacology study in healthy volunteers.

Study CC-10004-CP-035 (Celgene)
Study CC-10004-CP-035 (hereafter referred to as 035) was a two-part study. The study objective for Part 1 was to assess pharmacokinetics (PK) and exposure of apremilast following multiple-dose administration of QD apremilast formulation relative to the BID reference IR tablet under the fed condition with a standard meal. The study objective for Part 2 was to estimate the PK and

exposure of apremilast following single dose administration of a QD apremilast formulation relative to the BID reference IR tablet under the fasting condition and to estimate the effect of food on the PK of a single oral dose of a QD apremilast formulation.

Part 1:
Part 1 was a multicenter, phase 1, open-label, randomized, multiple-dose two-period, two-sequence, crossover study in healthy subjects. The study consisted of a screening phase (Days -21 through -2), baseline (Day -1), two treatment periods (Treatment Periods 1 and 2), and a follow-up phone call. Each period was 10 days in duration (Days 1 through 10) for sample collection up to 72 hours post Day 7 morning dose.

Healthy adult subjects were confined to the study center from Day -1 of Treatment Period 1 through Day 10 of Treatment Period 2. On Day 1 of Treatment Period 1, eligible subjects were randomized to one of two sequences (Table 17), to receive multiple doses of apremilast 30 mg IR tablet BID (IR) or 75 mg apremilast XR daily formulation (APRE XR) on Days 1 through 7 of each treatment period. Subjects underwent a washout period of at least six days that began after the last dose of study drug of Period 1.

Table 17: Part 1 Treatment Assignment: Study CC-10004-CP-035

	Treatment Period 1	**Treatment Period 2**
Sequence 1 (n=62)	Treatment A IR tablet BID	Treatment B APRE XR table QD
Sequence 2 (n=62)	Treatment B APRE XR table QD	Treatment A IR tablet BID

Source: CC-10004-CP-035 Study Report, page 17, Table 3. BID=twice daily; QD=once daily; Treatment A=apremilast 30 mg IR BID; Treatment B=APRE XR 75 mg QD

Part 2:
Part 2 was a single center, open-label, randomized, four-period, four-sequence crossover study. A Williams-Square design was used to evaluate the PK and exposure of apremilast following single dose administration of APRE XR tablet relative to the IR tablet (Reference IR) under the fasting condition and to evaluate the effect of food on the QD apremilast formulation.
Part 2 consisted of a screening phase (Days -21 through -2), baseline (Day -1), four treatment periods, and a follow-up phone call. Each period was four days in duration (Days 1 through 4) for dosing and sample collection for up to 72 hours post Day 1 of Period 1, 2, 3, and 4. Subjects were confined at the study center from Day -1 (baseline) of Treatment Period 1 through Day 4 of Treatment Period 4. On Day 1 of Treatment Period 1, eligible subjects were randomized to one of four sequences to receive 30 mg IR tablet BID and 75 mg APRE XR QD formulation across four treatment periods following an overnight fast (Table 18).

Table 18: Part 1 Treatment Assignment: Study CC-10004-CP-035

	Period 1	**Period 2**	**Period 3**	**Period 4**

Sequence 1 (n=5)	Treatment C IR tablet BID (fasting)	Treatment F APRE XR QD (high fat)	Treatment D APRE XR QD (fasting)	Treatment E IR tablet BID (standard meal)
Sequence 2 (n=5)	Treatment D APRE XR QD (fasting)	Treatment C IR tablet BID (fasting)	Treatment E IR tablet BID (standard meal)	Treatment F APRE XR QD (high fat)
Sequence 3 (n=5)	Treatment E IR tablet BID (standard meal)	Treatment D APRE XR QD (fasting)	Treatment F APRE XR QD (high fat)	Treatment C IR tablet BID (fasting)
Sequence 4 (n=5)	Treatment F APRE XR QD (high fat)	Treatment E IR tablet BID (standard meal)	Treatment C IR tablet BID (fasting)	Treatment D APRE XR QD (fasting)

Source: CC-10004-CP-035 Study Report, page 18, Table 4. BID=twice daily; QD=once daily; IR=immediate release;

Subject Disposition and Baseline Demographics:
A total of 100 healthy adult male or female subjects were planned for Part 1 and a total of 20 healthy adult male or female subjects were planned for Part 2. As a result of Hurricane Matthew on October 5, 2015, 42 subjects were discontinued early in Part 1. Of those subjects, 19 were discharged on Period 2 Day 9 (thus these subjects completed the Period 2 Day 7 dosing and PK collection) and were not replaced. An additional 24 subjects were recruited as replacement subjects. In Part 1, 69 of the 124 subjects enrolled, randomized, and completed the study, with 88 subjects completing all Day 7 PK assessments. In Part 2, 18 of the 20 subjects enrolled, randomized, and completed the study. Overall, 144 subjects were enrolled in the study and 87 subjects completed the study.

In general, the healthy volunteers were predominately male (63%), White (56%) with a mean age of 37 years and mean BMI of 26.4.

Extent of Exposure:
A total of 106/144 (74%) subjects completed dosing in this study. In Part 1, 88 of 124 subjects completed dosing and in Part 2, 18 of 20 subjects completed dosing. As noted above, several subjects did not complete the study and therefore did not receive all prespecified doses. All 144 subjects in Parts 1 and 2 of the study were included in the safety and PK populations.

Adverse Events:
During Part 1 of the study, apremilast was generally well-tolerated when given as multiple oral doses the reference 30 mg IR BID or APRE XR 75 mg QD formulation for seven days with subjects in the fed state. Similarly, during Part 2 of the study, apremilast was generally well-tolerated when given as single oral doses of the reference 30 mg IR BID or APRE XR 75 mg QD formulation with subjects in the fasted state, or single oral doses of APRE XR75 mg QD following a standard or high-fat meal.

In Part 1, the incidence of TEAEs was similar after multiple doses of APRE XR 75 mg QD as compared to the 30 mg IR BID tablet. In Part 2, the incidence of TEAEs was also similar following the 30 mg IR BID with subjects in the fasted state, APRE XR 75 mg QD with subjects in the fasted state, or when APRE XR 75 mg QD was administered following a standard or high-fat meal. No effect of food was observed during Part 2 of the study.

Overall, 80 of 144 (56%) subjects reported a total of 372 TEAEs in the study (Table 19). The majority of TEAEs in this study were mild in severity and no events were considered severe or serious.

Table 19: Summary of Treatment-emergent Adverse Events-Number (%) of Subjects by Treatment: Study CC-10004-CP-035

	Part 1			Part 2				
	A N=108	B N=107	Total N=124	C N=20	D N=19	E N=18	F N=19	Total N=20
Number of Subjects	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**	**n (%) E**
Subjects with ≥1 TEAE	50 (46) 184	47 (44) 162	72 (58) 346	2 (10) 10	4 (21) 8	3 (17) 3	2 (11) 5	8 (40) 26
Subjects with ≥1 SAE	0	0	0	0	0	0	0	0
Subjects discontinued due to TEAE	3 (3) 7	5 (5) 18	8 (7) 25	2 (10) 8	3 (16) 7	2 (11) 2	2 (11) 2	6 (30) 22
Deaths	0	0	0	0	0	0	0	0

Source: CC-10004-CP-035 Study Report, page 65, Table 20. TEAE=treatment emergent adverse events; SAE=serious adverse event; E=number of TEAEs; n=number of subjects with TEAE; %=n/N*100. Note: Part 1 Treatment A: apremilast 30 mg IR BID; Treatment B: apremilast XR 75 mg QD. Part 2: Treatment C: apremilast 30 mg IR BID, fasting; Treatment D: apremilast XR 75 mg QD, fasting; Treatment E: apremilast 30 mg IR BID, standard meal; Treatment F: apremilast XR 75 mg QD, high-fat meal.

Part 1:
In Part 1, the incidence and types of TEAEs were similar after multiple doses of the apremilast 30 mg IR BID and the APRE XR formulation. The TEAE with the highest incidence during this part of the study was headache (43 of 124 [35%] subjects) followed by diarrhea (21 of 124 [17%] subjects), nausea (16 of 124 [12.9%] subjects), and myalgia (15 of 124 [12%] subjects). All other PTs occurred in less than 10 percent of the subjects.

During the study, eight subjects in Part 1 discontinued due to TEAEs.

- Subject (b) (6) who received APRE XR 75 mg was withdrawn due to TEAEs of abdominal pain, myalgia, arthralgia, diarrhea, headache, pruritus, vomiting, and nausea prior to receiving the Treatment Period 1, Day 6 dose of APRE XR 75 mg. The subject received no further doses and was later discharged from the study.
- Subject (b) (6) had received APRE XR 75 mg and was withdrawn on Treatment Period 1, Day 4 because of a TEAE of staphylococcal infection. The subject received no further doses and was later discharged from the study.
- Subject (b) (6) who was treated with APRE XR 75 mg was withdrawn from on Treatment Period 1, Day 5 because of TEAEs of nausea, myalgia, diarrhea, headache, and pruritus. The subject received no further doses and was later discharged from the study.

- Subject (b) (6) who received APRE XR was withdrawn on Treatment Period 1, Day 3 due to TEAEs of headache, diarrhea, and photophobia. The subject received no further doses and was later discharged from the study.
- Subject (b) (6) had received apremilast IR 30 mg BID was withdrawn after the morning dose on Treatment Period 1, Day 5 because of a TEAE of headache. The subject received no further doses and was later discharged from the study.
- Subject (b) (6) was treated with apremilast IR 30 mg BID and was withdrawn prior to the morning dose on Treatment Period 1, Day 5 because of TEAEs of dizziness, feeling abnormal, arthralgia, fatigue, and affect lability. The subject received no further doses and was later discharged from the study.
- Subject (b) (6) who received APRE XR 75 mg was withdrawn because of a TEAE of nausea prior to dosing on Treatment Period 2, Day 3.
- Subject (b) (6) was treated with apremilast IR 30 mg BID and withdrawn because of a TEAE of nausea prior to receiving the scheduled doses of IR drug on Treatment Period 1, Day 4. In addition, the subject did not receive the scheduled evening doses of the Reference IR on Treatment Period 1, Days 2 and 3, because of a TEAE of nausea.

Part 2:
In Part 2, the incidence and types of TEAEs were generally similar after single doses of apremilast 30 mg IR BID in the fasted state, APRE XR 75 mg QD in the fasted state, and following a standard meal, or high-fat meal. The TEAE with the highest incidence during this part of the study was headache (4 of 20 [20%] subjects) followed by nausea (3 of 20 [15%] subjects). All other PTs were reported by fewer than three subjects each. TEAEs of headache were not reported by subjects during the apremilast 30 mg IR BID fasted treatment and nausea was not reported for APRE XR 75 mg group following a standard meal.

During Part 2 of the study, one subject discontinued due to a TEAE.

- Subject (b) (6) was withdrawn because of a TEAE of abdominal pain after receiving the morning and evening doses of apremilast IR 30 mg BID while fasting in Treatment Period 2 and prior to dosing in Treatment Period 3.

Reviewer's Comments:
There were no new safety signals identified in the current study which is limited by the design of this clinical pharmacology study in healthy volunteers.

Study 20200369 (Amgen)
Study 20200369 was a two-part study to assess the relative bioavailability of apremilast XR 75 mg QD tablet after single and repeated doses in healthy adult subjects.

<u>Part 1:</u>

Part 1 was a two-period, two-sequence study and enrolled approximately 202 healthy male and female subjects randomized equally between treatment arms. Each subject received two treatments:

- APRE XR: apremilast XR 75 mg oral tablet, administered QD.
- Apremilast IR: apremilast IR 30 mg oral tablet, administered BID.

On Period 1 Day 1, subjects were randomized to Sequence 1 (BA) or Sequence 2 (AB). In Sequence 1 (BA), subjects received apremilast IR on Period 1 Day 1 and Period 1 Days 4 through 8, followed by apremilast XR on Period 2 Day 1 and Period 2 Days 4 through 8. In Sequence 2 (AB), subjects received apremilast XR on Period 1 Day 1 and Period 1 Days 4 through 8, followed by apremilast IR on Period 2 Day 1 and Period 2 Days 4 through 8.
The study was planned to enroll approximately 202 subjects in Part 1. A total of 211 subjects entered the study and 197 subjects completed the study. Data for all subjects were included in the PK and safety analyses.

Part 2:
Part 2 was a two-period, two-sequence study and enrolled approximately 20 healthy adult male and female subjects equally between treatment arms. Each subject received two treatments:

- APRE XR 75 mg oral tablet, single dose administered under fed conditions.
- APRE XR 75 mg oral tablet, single dose administered under fasted conditions.

On Period 1 Day 1, subjects were randomized to Sequence 3 (CD) or Sequence 4 (DC). In Sequence 3 (CD), subjects received APRE XR under fed conditions on Period 1 Day 1 followed by APRE XR under fasted conditions on Period 2 Day 1. In Sequence 4 (DC), subjects received APRE XR under fasted conditions on Period 1 Day 1 followed by APRE XR under fed conditions on Period 2 Day 1. APRE XR was administered under fed conditions following an overnight fast of at least 10 hours where subjects consumed the entirety of a standard high fat breakfast within 20 minutes followed by dose administration 30 minutes after the start of the meal. APRE XR was administered under fasting conditions following an overnight fast of at least 10 hours.

Subject Disposition
Part 1:
Overall, 211 healthy male and female subjects were enrolled in Part 1 of the study. A total of 197 (93%) subjects completed the study. A total of 104 subjects were randomized into treatment sequence BA, with 101 (97%) subjects completing the study. One subject discontinued for noncompliance and two subjects discontinued because of a TEAE.
A total of 107 subjects were randomized into treatment sequence AB, with 96 (90%) subjects completing the study. Four subjects discontinued for noncompliance, five subjects discontinued because of a TEAE, and two subjects discontinued for other reasons (one subjected tested positive for an illicit substance and one subject discontinued voluntarily because of an adverse event).

Part 2:

A total of 20 healthy male and female subjects were enrolled in Part 2 of the study. A total of 20 subjects completed the study. A total of ten subjects were randomized into treatment sequence CD and ten subjects into treatment sequence DC.

Adverse Events:

Part 1 Day 1:

Overall, 126 TEAEs were reported in 69 (33%) subjects during the study, with most events (120 of 126 events) considered mild in severity. Of these adverse events, 56 adverse events in 39 (19%) subjects occurred following Day 1 doses of APRE XR and 70 adverse events in 50 (25%) subjects occurred following Day 1 doses of apremilast IR. One subject experienced a single TEAE that led to discontinuation.

A total of 55 (26%) subjects experienced a total of 102 TEAEs with the majority considered mild in severity. None of the events were considered severe or life-threatening and there were no deaths or SAEs reported in the study. The two most reported (≥5%) TEAEs were headache (18%) and nausea (8%). The three most reported (≥2%) TEAEs included headache (35 [17%] subjects [17%]) subjects; nausea (15 [7%] subjects); and diarrhea (9 [4%] subjects). Gastrointestinal and musculoskeletal adverse events were reported more frequently following treatment with single doses of apremilast IR compared to single doses of apremilast XR.

Part 1 Day 8:

Overall, 213 TEAEs were reported in 104 (50%) subjects during the study with the majority considered mild in severity. Of these adverse events, 95 adverse events in 59 (29%) subjects occurred following repeated doses of APRE XR and 118 adverse events in 71 (35%) subjects occurred following repeated doses of apremilast IR. Six (3%) subjects experienced six TEAEs that led to discontinuation. A total of 90 (43%) subjects experienced a total of 179 TEAES with the majority considered mild in severity. None of the events were considered severe or life-threatening and there were no deaths or SAEs reported in the study.

The two most frequently reported (≥5%) TEAEs were headache reported in 62 (30%) subjects and nausea reported in 21 (10%) subjects. The three most reported (≥2%) TEAEs included headache (30%), nausea (10%), and diarrhea (7%).

Part 2:

A total of 26 TEAEs were reported in 10 (50%) subjects during the study with the considered mild in severity. None of the subjects experienced a TEAE that led to discontinuation. Overall, eight (40%) subjects experienced a total of 15 TEAEs with the majority considered mild in severity. Of these adverse events, six adverse events in four subjects occurred following administration of APRE XR under fed conditions and nine adverse events in six subjects occurred following administration of APRE XR under fasted conditions. None of the events were considered severe or life-threatening and there were no deaths or SAEs reported in the study. The most reported treatment-emergent adverse events were headache (35%) reported in seven subjects and nausea 25%) reported in five subjects.

Reviewer's Comments:
There were no new safety signals identified in the current study which is limited by the design of this clinical pharmacology study in healthy volunteers.

7.2.2. Safety in the Postmarket Setting

Apremilast extended release is currently not marketed.

7.3. Statistical Issues

None.

7.4. Division of Dermatology and Dentistry Concurrence for the Indication of Plaque Psoriasis

Regulatory History:
OTEZLA (apremilast) was approved for marketing on March 21, 2014, for the treatment of adult patients with active psoriatic arthritis (PsA) under NDA 205437. On September 23, 2014, it was approved for the treatment of adult patients with active moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (NDA 206088, administratively closed on October 7, 2014), and was also approved on July 19, 2019, for the treatment of adult patients with oral ulcers associated with Behçet's disease. The approved dose regimen for these indications is 30 mg twice daily.

The following efficacy supplements have been approved by the Division of Dermatology and Dentistry (DDD) for the indication of plaque psoriasis:

- In April 2020, sNDA 205437-008 Prior Approval Efficacy Supplement was approved to support the inclusion of psoriasis of the scalp efficacy claims in Section 14.2, and safety data in Section 6.1 of the prescribing information for the treatment of subjects with moderate to severe plaque psoriasis of the scalp.
- In December 2021, sNDA 205437-011 Prior Approval Efficacy Supplement was approved to support the inclusion of efficacy claims for adult subjects with mild to moderate plaque psoriasis in Section 14.4 of the prescribing information, and to expand the indication from moderate to severe plaque psoriasis to plaque psoriasis (mild to severe).
- In July 2023, sNDA 205437-012 Prior Approval Efficacy Supplement was approved to support the inclusion of efficacy claims for subjects with moderate to severe plaque psoriasis of the genital area in Sections 14.2 of the prescribing information.

On April 25, 2024, Otezla was approved for pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy to support the inclusion of efficacy claims for pediatric subjects with moderate to severe plaque psoriasis in Sections 14.3 of the prescribing information. The approved pediatric dose regimen

is 20 mg twice daily for subjects weighing ≥ 20 to < 50 kg and 30 mg twice daily for subjects weighing ≥ 50 kg.

The Applicant has submitted data supporting the bioequivalence of a once daily (QD) extended release (XR) tablet formulation of apremilast to the 30 mg twice daily immediate release (IR) dose for the indications of PsA, plaque psoriasis, and Behçet's disease under the current NDA.

Context of Use in Psoriasis:
Psoriasis is a common, chronic, inflammatory multi-system disorder, which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3%, of which an estimated 80 percent have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.

Apremilast is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels and in turn modulates inflammatory responses. The specific mechanism(s) by which apremilast exerts its therapeutic action is not well defined. It provides an oral systemic option for the treatment of adult patients with plaque psoriasis including scalp and genital psoriasis, and pediatric patients 6 years of age and older weighing at least 20 kg with moderate to severe psoriasis, who are candidates for phototherapy or systemic therapy.

Clinical Concurrence Review Comments:
The current application includes data from Study 20200369, an open-label, randomized, crossover study that evaluated the relative bioavailability (BA) of the apremilast 75 mg XR tablets after single and repeated doses compared with the currently approved apremilast 30 mg twice daily IR tablet (Part 1), and the effect of food on the PK of the apremilast 75 mg XR tablet after a single dose (Part 2) in healthy adult subjects. The primary endpoints for Part 1 of the study include Cmax and AUC parameters following apremilast dosing on day 1 of each study period and following apremilast dose administration on day 8 of each study period. While repeat dose PK parameters Cmax and AUC were within 80-125%; for single dose parameters, only Cmax is within 80-125% CI. According to the Sponsor, the repeat-dose assessment is more representative of a real-world treatment setting for apremilast, and the results from this assessment are the most clinically relevant data from this study. Additionally, results from supportive exposure-response (E-R) analyses, conducted to link the systemic exposure of the apremilast 75 mg XR tablets to efficacy using data from previous studies of the 30 mg twice daily IR tablets, confirm that the steady-state AUC is the key driver of efficacy for apremilast and that the observed steady-state AUC for the apremilast 75 mg XR tablets will result in efficacy responses comparable to those seen with the 30 mg IR formulation. The Clinical Pharmacology review team concludes that the provided study data is sufficient to demonstrate bioequivalence between apremilast 75 mg once daily XR and apremilast 30 mg twice daily IR

tablets. Additionally, no new safety concerns were identified in this study. Refer to the Clinical Pharmacology section of this Unireview.

DDD Recommendation for Regulatory Action:
Approval. Based on the above considerations, DDD concludes that the Applicant has provided sufficient data to support the use of apremilast XR tablets as a once daily oral treatment option for adult patients with plaque psoriasis, and pediatric patients 6 years of age and older weighing at least 50kg with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy.

A PMC will be issued for the development of an equivalent once daily XR formulation to the 20 mg twice daily apremilast IR dose approved for pediatric patients 6 years of age and older weighing ≥ 20 to < 50 kg, as well as a PMR study conducted to demonstrate bioequivalence between the 20 mg twice daily IR formulation and once daily XR formulation (dosage to be determined) in this population.

Authors:

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Clinical Reviewer	Clinical Team Leader	Deputy Director for Safety

7.5. Conclusions and Recommendations

The clinical pharmacology data demonstrated bioequivalence between the apremilast IR 30 mg BID formulation and the apremilast 75 mg extended-release dosing formulation. There were no new safety signals identified in review of the safety data for submitted clinical pharmacology studies. Taken together, these data provide the basis for justification of the extrapolation between the two formulations regarding the efficacy and safety for the currently approved indications.

The review team recommends approval of OTEZLA XR 75 mg formulation.

8 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for this Application.

9 Pediatrics

Apremilast IR tablets are currently approved for pediatrics with active psoriatic arthritis and moderate to severe PsO who are candidates for phototherapy or systemic therapy 6 years of age and older and weighing at least 20 kg. The current extended-release formulation is equivalent to IR 30 mg BID and, therefore, if the extended-release formulation is approved for adult indications, it can also be approved for pediatrics 6 years of age and older and weighing at least 50 kg.

There are 2 initial Pediatric Study Plans (iPSPs) for the apremilast QD XR formulation. These iPSPs apply to the PsA and PsO indications for apremilast. An iPSP is not required for oral ulcers associated with Behçet's disease, as apremilast has an orphan designation for this indication and is therefore exempt from the requirements of the Pediatric Research Equity Act (PREA).

A summary of the regulatory interactions between the Applicant and the Agency are outlined below in Table 20.

Table 20: Summary of Applicant's Interactions with FDA Related to iPSPs for Apremilast Once-Daily and Extended-Release Formulations

Date	Activity	Related Correspondence	Description
July 11, 2017	Agreed iPSP for QD XR in PsA	Celgene iPSP Submission to IND 121919/0157 (21 Apr 2017) FDA Written Response (11 May 2017) Celgene Submission of Agreed iPSP to IND 121919/0165 (22 Jun 2017) FDA Issuance of Agreed iPSP (11 Jul 2017)	An iPSP for the QD XR formulation in pediatric patients with PsA was agreed with the Agency in July 2017. The plan outlined a full waiver for the PsA indication because necessary studies were considered impossible or highly impracticable due to the rarity of the condition in children

August 17, 2017	Agreed iPSP for QD XR in Moderate to Severe PsO	Celgene iPSP Submission to IND 121919/ 0594 (10 Mar 2017)
		
		FDA Written Response (12 Jun 2017)
		
		Celgene Submission of Agreed iPSP to IND 121919/0611 (14 Jul 2017)
		
		FDA Issuance of Agreed iPSP (17 Aug 2017)
		
		FDA Issuance of Agreed iPSP (17 Aug 2017)
			An iPSP for the QD XR formulation in pediatric patients with moderate to severe PsO was agreed with the Agency in August 2017. The plan outlined the following:
			• Partial waiver of the requirement to perform pediatric studies in children from birth to <6 years of age, because necessary studies are impossible or highly impracticable, as there are too few children with the condition to study.
			• Deferral of development of a pediatric QD XR formulation for use in children 6 to 17 years of age until:
			  • The results from postmarketing studies testing the PK, safety, and efficacy of the BID IR formulation in pediatric moderate to severe PsO subjects 6 to 17 years of age are available (Studies CC-10004-PPSO-001 [PMR 2791-1] and CC-10004-PPSO-003 [PMR 2791-2]).
			  • The NDA for the apremilast QD XR formulation for adult patients is approved.

Date	Activity	Related Correspondence	Description
			• If the appropriate pediatric dosage for the IR formulation is determined to be the same as the approved adult dosage of 30 mg BID for some or all children in the 6 to 17 years age group the adult QD XR formulation will be fully extrapolated to those pediatric patients, as relative bioavailability study CC-10004-CP-035 demonstrated equivalent steady-state AUC between the 75 mg XR formulation given QD and the 30 mg IR formulation given BID. • If Studies CC-10004-PPSO-001 and CC-10004-PPSO-003 demonstrate that the appropriate pediatric dosage for the IR formulation is different from the approved adult dosage of 30 mg BID for some or all children in the 6 to 17 years age group, a pediatric QD XR formulation that provides equivalent exposure to the 20 mg IR tablet given BID will be evaluated in clinical PK bioavailability studies in healthy adults.

03 May 2023	Agreed Amended iPSP
	for QD XR in PsO
		Amgen iPSP Amendment to IND 070270/0739 (16 Sep 2022)
		
		FDA Written Response (15 Dec 2022)
		
		Amgen Submission of Agreed Amended iPSP to IND 070270/0744 (31 Jan 2023)
		
		FDA Issuance of Agreed Amended iPSP (03 May 2023)
			An amended iPSP for the QD XR formulation in pediatric patients with PsO was agreed with the FDA in May 2023. The amended plan included the following changes:
			• Updates to reflect the most current information for the apremilast program:
			  • Change of the sponsor from Celgene Corporation to Amgen Inc.
			  • Updates to the status of pediatric PsO studies (Study CC-10004-PPSO-001 and Study CC-10004-PPSO-003)
			  • Other updates to the regulatory and development history for apremilast;
			• Incorporation of the mild to moderate plaque psoriasis population in the iPSP based on the December 2021 expansion of the plaque psoriasis indication for Otezla in adults.
			• Updates to the technical development activities for the pediatric XR formulation.
			• Modification of the pilot relative bioavailability study (b) (4) to a pilot study evaluating a single XR formulation, based on the selected dosage form technology.
			• Extension of the timelines for the pediatric development plan, primarily due to Celgene's discontinuation of XR formulation development, time needed for Amgen's assessment and decision on pursuing the QD XR program, and the December 2020 deferral extension for pediatric PMR 2791-2 (Study CC-10004-PPSO-003).

02 Jun 2023	Type B Pre-NDA Meeting (preliminary Meeting comments (07 Jun 2023 meeting cancelled)	Amgen Meeting Request to IND 121919/0219 (12 Apr 2023) FDA Meeting Granted Letter (17 Apr 2023) Amgen Meeting Package to IND 121919/0220 (28 Apr 2023) FDA Preliminary Meeting Comments (02 Jun 2023) Amgen Response to FDA to IND 121919/0223 (07 Jun 2023) FDA Response to Amgen (06 Jun 2023)	In June 2023, a Type B pre-NDA interaction was held with the FDA to align on plans for registration of the new 75 mg apremilast XR tablet formulation for QD oral administration. The meeting package noted that the agreed pediatric study plan for this formulation outlined a full PREA waiver for the PsA indication due to the rarity of the condition in children. During this interaction, the FDA indicated that the Agency's thinking on granting default PREA waivers for PsA has evolved. Given the high degree of disease similarity between adults and pediatric patients with PsA, efficacy can be extrapolated from adults with PsA to pediatric patients with juvenile PsA (JPsA)

Date	Activity	Related Correspondence	Description
		Meeting Cancellation (07 Jun 2023)	based on bridging of PK exposures and information to support an expectation of similarity in E-R between the two populations. The Agency recommended that Amgen conduct a PK study in JPsA patients. It was stated that assessment of safety from the PK study could be supplemented by safety information from other relevant pediatric indications. The Agency requested that Amgen submit an updated pediatric plan either with the NDA for the 75 mg XR tablet if the NDA will be submitted in 2023 or to the IND if the NDA will be submitted after 2023. In subsequent email communications, Amgen came to an agreement with the Agency to pursue a JPsA indication for apremilast in patients 6 years of age and older using an approach similar in principle to that described by the Agency. Amgen agreed to pursue the JPsA indication for both the immediate-release formulation (OTEZLA) and the new extended-release formulation. For the IR formulation, it was agreed that Amgen will use data from completed apremilast studies in adults with PsA, adults with PsO, and pediatric patients with PsO to select dosages for JPsA patients, justify full extrapolation of efficacy from adults with PsA to children with JPsA, and support the safety of apremilast in the JPsA population. A PK study in JPsA patients was not considered to be necessary. For the XR formulation, the same bioequivalence approach outlined in the agreed QD XR iPSP for the psoriasis indication will be utilized for JPsA. Based on the agreements a live discussion with the FDA was not required and the meeting was cancelled.
08 Dec 2023	Amended iPSP for QD XR in PsA	Amgen iPSP Amendment to IND 121919/0224 (26July 2023) FDA Written Response (25 Oct 2023) Amgen iPSP Withdrawal Proposal (03 Nov 2023) FDA Agreement to Withdraw (27 Nov 2023) Amgen Withdrawal of iPSP Amendment to IND 121919/0225 (08 Dec 2023)	As per the advice provided by the Agency in the Jun 2023 Type B interaction for the QD XR formulation, Amgen submitted an amended QD XR iPSP for JPsA in July 2023. The iPSP was revised to include the JPsA development plans for the IR and XR formulations in alignment with the plan agreed with FDA in the June 2023 Type B interaction. In the Agency's Written Response for the iPSP amendment (25 Oct 2023), the Agency indicated that, while the proposed extrapolation approach may be reasonable, it was premature to agree with the detailed information of the proposal. The Agency recommend that Amgen remove the details of the modeling and simulation strategies and submit another amended iPSP to the IND after the safety and efficacy data in pediatric moderate to severe plaque psoriasis (NDA 205437/013) have been reviewed by the Agency. Alternatively, based on the planned timing of the QD XR NDA resubmission, the updated pediatric plan may be submitted with the NDA. In subsequent email correspondence between Amgen and the Agency (Nov 2023), it was agreed that Amgen would withdraw the JPsA iPSP amendment and re-submit it after an Agency decision on the pediatric psoriasis efficacy supplement. It was agreed that the iPSP amendment would be submitted together with the NDA for the 75 mg XR formulation in 2024. In accordance with this agreement, Amgen formally withdrew the iPSP amendment (08 Dec 2023).
25 Apr 2024	Otezla sNDA for Pediatric Moderate to Severe PsO	Amgen sNDA Submission to NDA 205437/013 (25 Oct 2023) FDA Approval Letter (25 Apr 2024)	On 25 Apr 2024, Otezla was approved for the treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy.

Date	Activity	Related Correspondence	Description
24 Sep 2024	Otezla sNDA for JPsA	Amgen sNDA Submission to NDA 205437/0323 (24 Sep 2024)	On 24 Sep 2024, an efficacy supplement was submitted to expand the PsA indication for Otezla to include the treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA.
30 Oct 2024	Resubmission of Amended iPSP for QD XR in PsA	Amgen iPSP Amendment Resubmission to NDA 210745/0017 (Oct 2024)	In accordance with the November 27, 2023, agreement with the Agency to re-submit the amendment to the QD iPSP for JPsA together with the QD XR NDA in 2024, the current submission for NDA 210745 includes the proposed iPSP amendment. The revised iPSP includes the JPsA development plans for both the IR and XR formulations in alignment with the plan agreed with the Agency in the June 2023 Type B interaction. The iPSP amendment has been updated as compared to the iPSP amendment submitted in July 2023, mainly to include updates to the development timeline for the pediatric QD XR formulation. The timeline presented in this amended iPSP applies to development of the pediatric QD XR formulation for both the JPsA and PsO indications.

Source: Applicant's other-ped-correspondence, page 3, Table 1. AUC = area under the plasma concentration-time curve; BID = twice daily; E-R = exposure-response; IND = investigational new drug application; iPSP = initial pediatric study plan; IR = immediate-release; NDA = new drug application; PK = pharmacokinetic(s); PREA =Pediatric Research Equity Act; PsA = psoriatic arthritis; PsO = plaque psoriasis; QD = once daily; XR = extended-release

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing information
Proposed major labeling changes are as follows:

- (b) (4)
-

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

11 Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies (REMS) are required.

12 Postmarketing Requirements and Commitment

Apremilast XR represents a new dosage form and a new dosing regimen, and approval of this NDA would trigger the requirements of the PREA. In the amendment to the agreed iPSP submitted under current NDA submission, the Applicant requested a partial waiver of the requirement to perform pediatric studies in psoriatic arthritis patients from birth to less than 6 years of age and a deferral for the development of a pediatric extended-release formulation for psoriatic arthritis patients 6 to 17 years old. Similarly, in another amended Agreed iPSP, the Applicant request a partial waiver of the requirement to perform pediatric studies in psoriasis patients from birth to less than 6 years of age and request a deferral for the development of a pediatric extended-release formulation for 6 to 17 years old.

On July 1, 2025, the Agency hold a PeRC meeting to discuss the PREA post-marketing required (PMR). Based on the PeRC meeting discussion, the age appropriate XR formulation development includes one study which will be conducted as PREA PMR study with the following timelines which are acceptable to the Division:

- Develop an age appropriate extended-release formulation suitable for use in patients who weigh 20-50 kg.

  Estimated completion date: September 2026

- Conduct a relative bioavailability study in healthy adult subjects to determine an appropriate dose and dosing regimen for the extended-release apremilast formulation in pediatric patients aged 6-17 years weighing between 20 kg and 50 kg for the treatment of plaque psoriasis and psoriatic arthritis.

  a. Final Protocol Submission: August 2026
  b. Study Completion: May 2027
  c. Final Report Submission: February 2028

13 Division Director (DRTM) Comments

Otezla XR (apremilast) is an orally administered phosphodiesterase 4 (PDE4) inhibitor specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. Otezla IR was previously approved for the treatment of adult patients with active PsA; treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA; and adult patients with oral ulcers associated with BD.

In the current NDA submission, the Applicant is seeking approval of Otezla XR for the treatment of all the adult indications approved for Otezla IR and both pediatric indications approved for Otezla IR in pediatrics 6 years and older and weighing at least 50 kg. The Applicant conducted a relative bioavailability (BA) study in healthy adults to compare steady state PK characteristics between Otezla XR 75 mg following once daily dosing and Otezla IR 30 mg following twice daily dosing. The relative BA study demonstrated comparable PK exposure at steady state based on $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ with other justifications, including exposure response analysis in adults with active PsA and moderate to severe PsO, to support all the proposed indications in adults and pediatrics.

The review team found that the data and justification submitted under the current NDA are adequate to support the approval of Otezla XR for the treatment of adult patients with active PsA; treatment of adult patients with PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with moderate to severe PsO who are candidates for phototherapy or systemic therapy; treatment of pediatric patients 6 years of age and older and weighing at least 50 kg with active PsA; and adult patients with oral ulcers associated with BD.

A PREA PMR will be issued to the Applicant for the development of an age appropriate XR formulation in pediatric patients 6 years of age and older and weighing 20 kg to less than 50 kg and conducting a corresponding relative BA study in healthy subjects.

I agree with the review team's assessment and recommend for approval.

14 Appendices

14.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 20200369

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. OCP Appendices

14.2.1. Pharmacometrics Review

Exposure-Response Analysis: This analysis was designed to bridge existing knowledge of apremilast IR efficacy to the new XR tablet formulation by leveraging exposure-response modeling and observed XR exposure data from Study 20200369.

Objective: This exposure-response analysis for apremilast had three primary objectives related to comparing immediate release (IR) and extended release (XR) formulations:

1. Exposure-Response Relationship Evaluation:
    - Evaluate the relationship between different steady-state apremilast IR tablet exposure metrics ($C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$) and clinical response in adult patients
    - Assess efficacy endpoints including:
        1. Psoriasis (PsO): PASI-75 (≥75% reduction in Psoriasis Area and Severity Index) and sPGA (static Global Physician's Assessment)
        2. Psoriatic Arthritis (PsA): ACR20 (20% improvement in American College of Rheumatology criteria)
    - Confirm that $AUC_{0-24,ss}$ is the optimal predictor of clinical efficacy
2. XR Formulation Response Prediction for Psoriasis
    - Predict response rates (PASI-75 and sPGA) for the new apremilast 75 mg XR tablets given once daily (QD) in adults with moderate to severe plaque psoriasis
    - Compare predicted XR response rates to historical data from the approved 30 mg BID IR formulation
3. XR Formulation Response Prediction for Psoriatic Arthritis
    - Predict response rates (ACR20) for apremilast XR tablets in adults with psoriatic arthritis
    - Compare predicted XR response rates to historical data from the approved IR formulation

Data: The analysis dataset was derived from 4 Phase 2 and 3 clinical studies, all randomized, double-blind, and placebo controlled. Two psoriasis studies included Study 20200184 (CC-10004-PSOR-005), a Phase 2 dose-ranging study with placebo and apremilast 10/20/30 mg BID for 16 weeks, and Study 20200185 (CC-10004-PSOR-008), a Phase 3 study comparing apremilast 30 mg BID versus placebo for 48 weeks. Two psoriatic arthritis studies included Study 20200172 (CC-10004-PSA-001), a Phase 2 dose-ranging study with placebo, apremilast 20 mg BID, and 40 mg QD for 16 weeks, and Study 20200173 (CC-10004-PSA-002), a Phase 3 study comparing apremilast 20 or 30 mg BID versus placebo for 48 weeks. The exposure-response datasets included clinical efficacy endpoints (PASI-75, sPGA, and ACR20 responses) and apremilast exposure from previously developed population PK models (CC-10004-PSOR-008-PK and CC-10004-PSA-002-PK). sPGA response was defined as a score of clear (0) or almost clear (1) with ≥2-point reduction from baseline, PASI-75 as ≥75% reduction in PASI score from baseline,

and ACR20 as 20% improvement in ACR score from baseline. $AUC_{0\text{-}12h,ss}$ was converted to $AUC_{0\text{-}24h,ss}$ using linear extrapolation.

Method: Analysis was conducted via nonlinear mixed effects modeling with the nonlinear mixed effects modeling (NONMEM) software, (version 7.4 or later) (ICON Development Solutions, Hanover, MD). First -order conditional estimation with interaction (FOCEI) was used. Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed with R (version 3.5.3 or later).

The exposure-response models used a saturating Emax structure. The best-fitting model included a placebo component with exponential delay and an Emax-type drug effect model. Key parameters included placebo response (Plb_0), placebo onset delay (k_{plb}), basal response (Intercept), maximal drug effect (E_{max}), and exposure for 50% response (EC_{50}). A drug effect delay term (k_{drug}) was included for ACR20 but not for PASI-75 or sPGA responses. $AUC_{0\text{-}24h,ss}$ exposure was derived from previously developed population PK models.

$$P = f_{Placebo} + f_{DrugEffect}$$

$$f_{Placebo} = Intercept + Plb_0\left(1 - e^{-k_{plb}t}\right)$$

$$f_{DrugEffect} = \left(\frac{E_{max}\left(1 - e^{-k_{drug}t}\right)AUC_{0-24h,ss}}{EC_{50} + AUC_{0-24h,ss}}\right)$$

Model assessment was performed using alternate exposure metrics ($AUC_{0\text{-}24hr,ss}$, $C_{max,ss}$, or $C_{min,ss}$) to confirm $AUC_{0\text{-}24hr,ss}$ as the optimal predictor of apremilast efficacy. Model assessment included convergence, standard error estimation, and reasonable parameter estimates. Goodness-of-fit was evaluated using changes in the minimum value of the objective function (MVOF), with ΔMVOF ≥10.8 required for statistical significance ($p<0.001$) when adding one fixed effect parameter.

Results: The model using apremilast $AUC_{0\text{-}24h,ss}$ adequately described PASI-75 and sPGA response rates in moderate to severe psoriasis and ACR20 response rates in psoriatic arthritis across all dose levels and time points. For PASI-75, $AUC_{0\text{-}24h,ss}$ successfully described the data with parameters consistent with previous reports, while C_{max} showed no improvement (ΔMVOF≈0) and Cmin reduced performance (ΔMVOF≈7). For sPGA, $AUC_{0\text{-}24h,ss}$ was optimal, with C_{min} showing no improvement (ΔMVOF≈0) and Cmax reducing performance (ΔMVOF≈3). For ACR20, $AUC_{0\text{-}24h,ss}$ significantly outperformed both Cmax (ΔMVOF≈459) and Cmin (ΔMVOF≈450).

The PASI-75 and sPGA response models accurately estimated all parameters with relative standard errors within acceptable ranges (Table 21 and Table 22). The newly estimated EC50

values using $AUC_{0\text{-}24,ss}$ (3510 ng·hr/mL for PASI-75 and 2580 ng·hr/mL for sPGA) were consistent with previously estimated values using $AUC_{0\text{-}12,ss}$ after accounting for dosing interval differences. Similarly, the ACR20 model using $AUC_{0\text{-}24,ss}$ yielded parameter estimates consistent with previous models, with most RSE values below 50% (Table 23). The EC50_ACR20 (2370 ng·hr/mL) had an RSE of 97% but aligned with the previously used EC50 value of 1190 ng·hr/mL from the $AUC_{0\text{-}12,ss}$ model.

Table 21: Model Parameter Estimates for the Final PASI-75 E-R Model

Model Parameter	Typical Value (%RSE)
Baseline probability of response (SO_PASI75, logit)	6.26 (11%)
Placebo response slope (KPB_PASI75, 1/week)	0.248 (14%)
Maximum effect (EMAX_PASI75)	3.60 (15%)
$AUC_{0\text{-}24,ss}$ associated with 50% of maximum effect (EC50_PASI75, ng*hr/mL)	3510 (47%)
Model intercept (I_PASI75)	-9.09 (8%)

AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 h postdose at steady state; Emax = parameter that contributes to the maximum effect of the Emax model for apremilast; EC50 = parameter that contributes to the 50% of maximum effect of the Emax model for apremilast; E-R = exposure-response, I = a value in logit space chosen to represent 0% incidence; KPB = first order rate of the time effect; PASI-75 = ≥ 75% reduction in total Psoriasis Area and Severity Index; RSE = relative standard error
Source: Table 2; NDA 210745 Day 74 Letter Response; Page no. 7

Table 22: Model Parameter Estimates for the Final sPGA E-R Model

Model Parameter	Typical Value (%RSE)
Baseline probability of response (SO_SPGA, logit)	4.65 (12%)
Placebo response slope (KPB_SPGA, 1/week)	0.211 (19%)
Maximum effect (EMAX_SPGA)	2.41 (17%)
AUC0-24,ss associated with 50% of maximum effect (EC50_SPGA, ng*hr/mL)	2580 (57%)
Model intercept (I_SPGA)	-7.19 (10%)

AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 h postdose at steady state; Emax = parameter that contributes to the maximum effect of the Emax model for apremilast; EC50 = parameter that contributes to the 50% of maximum effect of the Emax model for

apremilast; E-R = exposure-response, I = a value in logit space chosen to represent 0% incidence; KPB = first order rate of the time effect; RSE = Relative standard error; sPGA = static Physician's Global Assessment
Source: Table 3; ER-Report-157815; Page no. 8

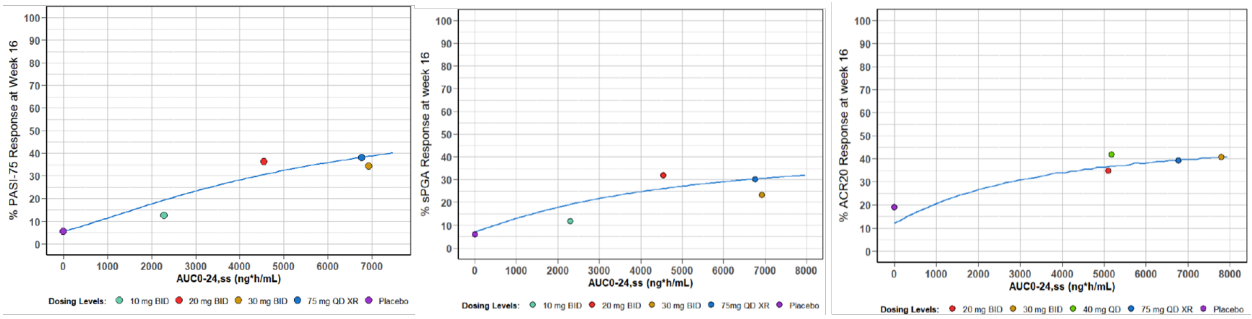
Table 23: Model Parameter Estimates for the Final ACR20 E-R Model

Model Parameter	Typical Value (%RSE)
Baseline probability of response (SO_ACR20, logit)	2.86 (22%)
Placebo response slope (KPB_ACR20, 1/week)	0.215 (17%)
Maximum effect (EMAX_ACR20)	3.10 (32%)
$AUC_{0\text{-}24,ss}$ associated with 50% of maximum effect (EC50_ACR20, ng*h/mL)	2370 (97%)
Between subject variability on EC50	0.309
Model intercept (I_ACR20)	-5.43 (11%)
Between subject variability on I	4.18
Rate of response (KDRUG_ACR20, 1/week)	0.0787 (48%)

AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 h postdose at steady state; Emax = parameter that contributes to the maximum effect of the Emax model for apremilast; EC50 = parameter that contributes to the 50% of maximum effect of the Emax model for apremilast; E-R = exposure-response, I = a value in logit space chosen to represent 0% incidence; KPB = first order rate of the time effect; RSE = Relative standard error; ACR20 = American College of Rheumatology criteria for 20% improvement;
Source: Table 4; ER-Report-157815; Page no. 8

The Figure 8 Model-Predicted Apremilast Exposure-PASI-75 Response (Left), Exposure-sPGA Response (Middle) and Exposure ACR20 Response (Right) in adults with Moderate to Severe Plaque Psoriasis and in Adults with Psoriatic Arthritis after 16 Weeks of Treatmentshows model-predicted exposure-response relationships for apremilast after 16 weeks of treatment in adults with moderate to severe plaque psoriasis (PASI-75 and sPGA) and psoriatic arthritis (ACR20). Each panel displays the model-predicted curve (line) with observed data points (circles) for immediate-release (IR) formulations at various doses and extended-release (XR) exposures overlaid. The left panel shows PASI-75 response versus $AUC_{0\text{-}24,ss}$ for doses of 10-30 mg BID, the middle panel shows sPGA response for placebo and 10-40 mg BID doses, and the right panel shows ACR20 response for placebo, 20-30 mg BID, and 40 mg QD doses. The model was able to capture the observed response data reasonably well.

Figure 8: Model-Predicted Apremilast Exposure-PASI-75 Response (Left), Exposure-sPGA Response (Middle) and Exposure ACR20 Response (Right) in adults with Moderate to Severe Plaque Psoriasis and in Adults with Psoriatic Arthritis after 16 Weeks of Treatment



$AUC_{0\text{-}24,ss}$ = area under the plasma concentration time curve from time 0 to 24 hours postdose at steady state; BID = twice daily; QD = once daily; XR = extended release;
PASI75 = ≥ 75% reduction in total Psoriasis Area Severity Index; sPGA = static Physicians Global Assessment; ACR20 = 20% improvement in American College of Rheumatology criteria;
Left Figure - Line: model predicted apremilast exposure-PASI-75 response relation. Circles: model-predicted apremilast IR $AUC_{0\text{-}24,ss}$ and observed PASI-75 response by dose level (10 mg BID, 20 mg BID, 30 mg BID) based on historical clinical data, and observed apremilast XR $AUC_{0\text{-}24,ss}$ overlaid over the model-predicted exposure-PASI-75 response curve.
Middle Figure - Line: model predicted apremilast exposure-sPGA response relation. Circles: model-predicted apremilast IR $AUC_{0\text{-}24,ss}$ and observed sPGA response by dose level (Placebo, 10 mg BID, 20 mg BID, 40 mg BID) based on historical clinical data, or observed apremilast XR $AUC_{0\text{-}24,ss}$ overlaid over the model-predicted exposure-sPGA response curve.
Right Figure - Line: model predicted apremilast exposure- ACR20 response relation. Circles: model predicted apremilast IR $AUC_{0\text{-}24,ss}$ (Table 24) and observed ACR20 response by dose level (Placebo, 20 mg BID, 30 mg BID, or 40 mg QD) based on historical clinical data, or observed apremilast XR $AUC_{0\text{-}24,ss}$ overlaid over the model-predicted exposure-ACR20 response curve
Source: Figure 1-1, 1-2, 1-3, Pharmacometrics report 157815, Page no. 7-9

Table 24: Summary of Model-Predicted Apremilast Steady State Exposure Metrics Segmented by Study and Treatment Arm

Exposure Metric	Study							
	20200172 20mg BID N = 161	20200172 30mg BID N = 157	20200173 20mg BID N = 38	20200173 40mg QD N = 43	20200184 10mg BID N = 79	20200184 20mg BID N = 66	20200184 30mg BID N = 70	20200185 30mg BID N = 560
Cmax,ss (ng/mL)								
Mean (SD)	292 (71)	443 (81)	289 (54)	420 (100)	128 (26)	254 (70)	390 (72)	386 (77)
Median (Min-Max)	279 (159-710)	443 (232-817)	275 (230-529)	415 (272-886)	120 (53-222)	240 (73-624)	370 (152-614)	361 (179-1,088)
Cmin,ss (ng/mL)								
Mean (SD)	133 (50)	203 (52)	128 (36)	75 (24)	62 (17)	124 (51)	191 (50)	189 (57)
Median (Min-Max)	114 (48-501)	218 (73-427)	114 (93-322)	76 (32-163)	57 (26-131)	112 (11-398)	176 (63-352)	169 (63-653)
AUC0-24h,ss (ng*h/mL)								
Mean (SD)	5,118 (1,455)	7,790 (1,580)	5,012 (1,074)	5,178 (1,257)	2,290 (502)	4,554 (1,489)	6,984 (1,447)	6,922 (1,616)
Median (Min-Max)	4,835 (2,405-14,737)	7,876 (3,837-15,091)	4,697 (4,107-10,394)	4,897 (3,066-11,203)	2,061 (970-4,263)	4,121 (867-12,611)	6,182 (2,588-11,544)	6,182 (2,919-21,195)

Source: Table 10-4; ER-Report-157815; Page no. 27

Comparison of model-predicted response rates between XR and IR tablet formulations (Table 25) showed minimal differences, with approximately 6% reduction in $AUC_{0\text{-}24,ss}$ for XR resulting in small decreases in response rates: PASI-75 (~1.2%), sPGA (~0.6%), and ACR20 (~0.7%).

Table 25: Comparison of Model Predicted PASI-75, sPGA, and ACR20 Response

Response	Formulation	Observed $AUC_{0-24,ss}$ (ng•h/mL)[b]	% of Subjects With Response at Week 16 % (90% CI)	Relative Response Change, IR-XR % (90% CI)
PASI-75	IR (30 mg BID)	7160	39.4	
	XR (75 mg QD)	6730[a]	38.2 (37.3, 39.0)	-1.2 (-1.9, -0.4)
sPGA	IR (30 mg BID)	7160	30.9	
	XR (75 mg QD)	6730[a]	30.3 (29.8, 30.7)	-0.6 (-1.1, -0.2)
ACR20	IR (30 mg BID)	7160	40.0	
	XR (75 mg QD)	6730[a]	39.3 (39.1, 39.7)	-0.7 (-0.9, -0.3)

ACR20 = 20% improvement in American College of Rheumatology criteria; AUC0-24,ss = area under the plasma concentration time curve from time 0 to 24 hours postdose at steady state; IR = immediate release; PASI75 = ≥ 75% reduction in total Psoriasis Area Severity Index; sPGA = static Physicians Global Assessment; XR = extended release
a 94.1% (90% CI: 89.6% -98.7%) of IR.
bAUC0-24h,ss: For XR shown is the GLSM calculated from observed data from study 20200369, For IR is estimated through from available PK models of apremilast in the relevant populations.
Source: Table 10-9; ER-Report-157815; Page no. 30

The exposure-response models demonstrated acceptable parameter estimates and successfully explained observed clinical data, with EC_{50} values of 3,510 ng·h/mL for PASI-75, 2,580 ng·h/mL for sPGA, and 2,370 ng·h/mL for ACR20. The exposure-response analysis for Apremilast demonstrated that $AUC_{0-24,ss}$ is the optimal predictor of clinical efficacy across all three endpoints (PASI-75, sPGA, and ACR20) for both psoriasis and psoriatic arthritis indications, compared to $C_{max,ss}$ and $C_{min,ss}$ in model performance metrics.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TAO LIU
08/28/2025 03:06:14 PM

TATIANA OUSSOVA
08/28/2025 03:11:30 PM

RAJ NAIR
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