CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205437Orig1s007

Trade Name:	OTEZLA
Generic or Proper Name:	apremilast
Sponsor:	Celgene Corporation
Approval Date:	July 19, 2019
Indication:	OTEZLA, an inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment of: • Adult patients with active psoriatic arthritis • Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy • Adult patients with oral ulcers associated with Behçet's Disease

CENTER FOR DRUG EVALUATION AND RESEARCH

205437Orig1s007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

APPROVAL LETTER

NDA 205437/S-007

SUPPLEMENT APPROVAL

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Attention: Vrunda Patel, PharmD
Senior Manager, Regulatory Affairs

Dear Dr. Patel:

Please refer to your supplemental new drug application (sNDA) dated September 21, 2018, received September 21, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Otezla (apremilast) Tablets, 10 mg, 20 mg, and 30 mg.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of adult patients with oral ulcers associated with Behçet's disease.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ngoc-Linh Do, Regulatory Project Manager, at 301-348-1896.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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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/

NIKOLAY P NIKOLOV
07/19/2019 11:05:09 AM
Signed under the authority, delegated by Dr. Sally Seymour, Division Director, DPARP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OTEZLA safely and effectively. See full prescribing information for OTEZLA.

OTEZLA® (apremilast) tablets, for oral use
Initial U.S. approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	07/2019
Dosage and Administration (2.1)	07/2019
Warnings and Precautions (5.2, 5.3)	07/2019

----------INDICATIONS AND USAGE----------

OTEZLA, an inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment of:

- Adult patients with active psoriatic arthritis (1.1)
- Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (1.2)
- Adult patients with oral ulcers associated with Behçet's Disease (1.3)

----------DOSAGE AND ADMINISTRATION----------

- To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg twice daily according to the following schedule (2.1)
  - Day 1: 10 mg in morning
  - Day 2: 10 mg in morning and 10 mg in evening
  - Day 3: 10 mg in morning and 20 mg in evening
  - Day 4: 20 mg in morning and 20 mg in evening
  - Day 5: 20 mg in morning and 30 mg in evening
  - Day 6 and thereafter: 30 mg twice daily
- Dosage in Severe Renal Impairment:
  - Recommended dose is 30 mg once daily (2.2)
  - For initial dosage titration, titrate using only morning schedule listed in Table 1 and skip afternoon doses (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg, 20 mg, 30 mg (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to apremilast or any excipients in formulation (4)

----------WARNINGS AND PRECAUTIONS----------

- Diarrhea, Nausea, and Vomiting: Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting (5.1)
- Depression: Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior (5.2)
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of OTEZLA (5.3)
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended because loss of efficacy may occur (5.4, 7.1)

----------ADVERSE REACTIONS----------

- Psoriatic Arthritis: The most common adverse reactions (≥5%) are diarrhea, nausea, and headache (6.1)
- Psoriasis: The most common adverse reactions (≥5%) are diarrhea, nausea, upper respiratory tract infection, and headache, including tension headache (6.1)
- Behçet's Disease: The most common adverse reactions (≥10%) are diarrhea, nausea, headache, and upper respiratory tract infection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

Severe Renal Impairment: Increased systemic exposure of OTEZLA has been observed, reduction in dose to 30 mg once daily is recommended (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriatic Arthritis

OTEZLA is indicated for the treatment of adult patients with active psoriatic arthritis.

1.2 Psoriasis

OTEZLA is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.3 Oral Ulcers Associated with Behçet's Disease

OTEZLA is indicated for the treatment of adult patients with oral ulcers associated with Behçet's Disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Psoriatic Arthritis, Psoriasis, and Behçet's Disease

The recommended initial dosage titration of OTEZLA from Day 1 to Day 5 is shown in Table 1. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

OTEZLA can be administered without regard to meals. Do not crush, split, or chew the tablets.

Table 1: Dosage Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	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	30 mg	30 mg

2.2 Dosage Adjustment in Patients with Severe Renal Impairment

OTEZLA dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CLcr) of less than 30 mL per minute estimated by the Cockcroft–Gault equation) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. For initial dosage titration in this group, it is recommended that OTEZLA be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped.

3 DOSAGE FORMS AND STRENGTHS

OTEZLA is available as diamond shaped, film coated tablets in the following dosage strengths:

- 10-mg pink tablet engraved with "APR" on one side and "10" on the other side
- 20-mg brown tablet engraved with "APR" on one side and "20" on the other side
- 30-mg beige tablet engraved with "APR" on one side and "30" on the other side.

4 CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea, Nausea, and Vomiting

There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

5.2 Depression

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Behçet's disease: During the placebo-controlled period of the phase 3 study, 1% (1/104) of patients treated with OTEZLA reported depression/depressed mood compared to 1% (1/103) treated with placebo. None of these reports of depression was serious or led to study discontinuation. No instances of suicidal ideation or behavior were reported during the placebo-controlled period of the phase 3 study in patients treated with OTEZLA (0/104) or treated with placebo (0/103).

5.3 Weight Decrease

During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

During the controlled period of the phase 3 study in Behçet's disease, weight decrease >5% of body weight was reported in 4.9% (5/103) of subjects treated with OTEZLA 30 mg twice daily compared to 3.9% (4/102) patients treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered *[see Adverse Reactions (6.1)]*.

5.4 Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Diarrhea, Nausea, and Vomiting *[see Warnings and Precautions (5.1)]*
- Depression *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*
- Drug Interactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Psoriatic Arthritis Clinical Trials

OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis *[see Clinical Studies (14.1)]*. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days *[see Dosage and Administration (2.1)]*. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented in Table 2 occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

Table 2: Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo for up to Day 112 (Week 16)

	Placebo		OTEZLA 30 mg BID	
Preferred Term	Day 1 to 5 (N=495) n (%)[c]	Day 6 to Day 112 (N=490) n (%)	Day 1 to 5 (N=497) n (%)	Day 6 to Day 112 (N=493) n (%)
Diarrhea[a]	6 (1.2)	8 (1.6)	46 (9.3)	38 (7.7)
Nausea[a]	7 (1.4)	15 (3.1)	37 (7.4)	44 (8.9)
Headache[a]	9 (1.8)	11 (2.2)	24 (4.8)	29 (5.9)
Upper respiratory tract infection[b]	3 (0.6)	9 (1.8)	3 (0.6)	19 (3.9)
Vomiting[a]	2 (0.4)	2 (0.4)	4 (0.8)	16 (3.2)
Nasopharyngitis[b]	1 (0.2)	8 (1.6)	1 (0.2)	13 (2.6)
Abdominal pain upper[b]	0 (0.0)	1 (0.2)	3 (0.6)	10 (2.0)

[a] Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.
[b] Of the reported adverse drug reactions none were serious.
[c] n (%) indicates number of patients and percent.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:
Immune system disorders: Hypersensitivity
Investigations: Weight decrease
Gastrointestinal Disorders: Frequent bowel movement, gastroesophageal reflux disease, dyspepsia
Metabolism and Nutrition Disorders: Decreased appetite*

Nervous System Disorders: Migraine
Respiratory, Thoracic, and Mediastinal Disorders: Cough
Skin and Subcutaneous Tissue Disorders: Rash
*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

Psoriasis Clinical Trials
The safety of OTEZLA was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days *[see Dosage and Administration (2.1)]*. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Table 3: Adverse Reactions Reported in ≥1% of Subjects on OTEZLA and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
Diarrhea	32 (6)	160 (17)
Nausea	35 (7)	155 (17)
Upper respiratory tract infection	31 (6)	84 (9)
Tension headache	21 (4)	75 (8)
Headache	19 (4)	55 (6)
Abdominal pain*	11 (2)	39 (4)
Vomiting	8 (2)	35 (4)
Fatigue	9 (2)	29 (3)
Dyspepsia	6 (1)	29 (3)
Decreased appetite	5 (1)	26 (3)
Insomnia	4 (1)	21 (2)
Back pain	4 (1)	20 (2)
Migraine	5 (1)	19 (2)
Frequent bowel movements	1 (0)	17 (2)
Depression	2 (0)	12 (1)
Bronchitis	2 (0)	12 (1)
Tooth abscess	0 (0)	10 (1)
Folliculitis	0 (0)	9 (1)
Sinus headache	0 (0)	9 (1)

*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with OTEZLA.

Behçet's Disease Clinical Trials
OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled study (BCT-002) in adult patients with Behçet's Disease (BD) with active oral ulcers. A total of 207 patients were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days *[see Dosage and Administration (2.1)]*. After Week 12, all patients received treatment with OTEZLA 30 mg twice daily. Patients ranged in age from 19 to 72, with a mean age of 40 years.

Diarrhea, nausea, headache, and upper respiratory tract infection were the most commonly reported adverse reactions. The proportion of patients with BD who discontinued treatment due to any adverse reaction during the placebo-controlled period of the study, was 2.9% for patients treated with OTEZLA 30 mg twice daily and 4.9% for placebo-treated patients.

Table 4: Adverse Reactions Reported in ≥5% of Patients on OTEZLA and with at least 1% Greater Frequency than Patients on Placebo; up to Week 12

Preferred Term	Placebo (N=103) n (%)	OTEZLA 30 mg twice daily (N=104) n (%)
Diarrhea[a]	21 (20.4)	43 (41.3)
Nausea[a]	11 (10.7)	20 (19.2)
Headache	11 (10.7)	15 (14.4)
Upper respiratory tract infection	5 (4.9)	12 (11.5)
Abdominal pain upper	2 (1.9)	9 (8.7)
Vomiting[a]	2 (1.9)	9 (8.7)
Back pain	6 (5.8)	8 (7.7)
Viral upper respiratory tract infection	5 (4.9)	7 (6.7)
Arthralgia	3 (2.9)	6 (5.8)

[a] There were no serious adverse reactions of diarrhea, nausea or vomiting.

7 DRUG INTERACTIONS

7.1 Strong CYP450 Inducers

Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary
Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Based on findings from animal reproduction studies, OTEZLA may increase the risk for fetal loss. In animal embryo-fetal development studies, the administration of apremilast to pregnant cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. When administered to pregnant mice, during organogenesis there were no apremilast-induced malformations up to exposures 4.0-times the MRHD (see Data). Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In an embryo-fetal developmental study, pregnant cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation Days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during Weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an area under the curve [AUC] basis at doses ≥50 mg/kg/day). No abortifacient effects were observed at a dose approximately 1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

In an embryo-fetal development study in mice, apremilast was administered at doses of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study in mice, apremilast was administered at doses of 10, 20, 40, or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose

approximately 1.3-times the MRHD (10 mg/kg/day).

Apremilast distributed across the placenta into the fetal compartment in mice and monkeys.

In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥4.0-times the MRHD (on an AUC basis at doses ≥80 mg/kg/day). No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

8.2 Lactation

Risk Summary
There are no data on the presence of apremilast in human milk, the effects on the breastfed infant, or the effects on milk production. However, apremilast was detected in the milk of lactating mice. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed infant from OTEZLA or from the underlying maternal condition.

Data
In mice, following a single oral administration of 10 mg/kg to dams on postpartum day 13, apremilast concentrations in milk were approximately 1.5-times that of simultaneously collected blood samples.

8.4 Pediatric Use

The safety and effectiveness of OTEZLA in pediatric patients less than18 years of age have not been established.

8.5 Geriatric Use

Of the 1493 subjects who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis subjects were 65 years of age and older, including 19 subjects 75 years and older. No overall differences were observed in the safety profile of elderly subjects ≥65 years of age and younger adult subjects <65 years of age in the clinical studies.

Of the 1257 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis subjects were 65 years of age and older, including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects ≥65 years of age and younger adult subjects <65 years of age in the clinical trials.

8.6 Renal Impairment

Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

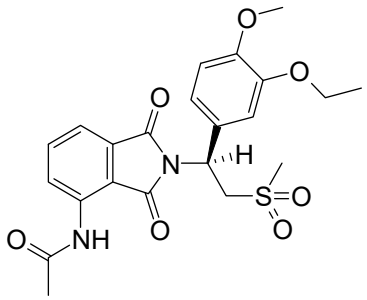
10 OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

The active ingredient in OTEZLA tablets is apremilast. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is known chemically as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide. Its empirical formula is $C_{22}H_{24}N_2O_7S$ and the molecular weight is 460.5.

The chemical structure is:



OTEZLA tablets are supplied in 10-, 20-, and 30-mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide yellow (20 and 30 mg only) and iron oxide black (30 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.3 Pharmacokinetics

Absorption
Apremilast 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. Co-administration with food does not alter the extent of absorption of apremilast.

Distribution
Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution (Vd) is 87 L.

Metabolism
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. It is extensively metabolized in humans with up to 23 metabolites identified in plasma, urine and feces. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. In vitro, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

Elimination
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 radio-labeled 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.

Specific Populations
Hepatic Impairment: The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment.

Renal Impairment: The pharmacokinetics of apremilast is not affected by mild or moderate renal impairment. In 8 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 *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Age: A single oral dose of 30-mg apremilast was studied in young adults and elderly healthy subjects. The apremilast exposure in elderly subjects (65 to 85 years of age) was about 13% higher in AUC and about 6% higher in C_{max} than in young subjects (18 to 55 years of age) *[see Use in Specific Populations (8.5)]*.

Gender: In pharmacokinetic studies in healthy volunteers, the extent of exposure in females was about 31% higher and C_{max} was about 8% higher than that in male subjects.

Race and Ethnicity: The pharmacokinetics of apremilast in Chinese and Japanese healthy male subjects is comparable to that in Caucasian healthy male subjects. In addition, apremilast exposure is similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans.

Drug Interactions
In vitro data: Apremilast is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and not an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4. Apremilast is a substrate, but not an inhibitor of P-glycoprotein (P-gp) and is not a substrate or an inhibitor of organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP).

Drug interaction studies were performed with apremilast and CYP3A4 substrates (oral contraceptive containing ethinyl estradiol and norgestimate), CYP3A and P-gp inhibitor (ketoconazole), CYP450 inducer (rifampin) and frequently co-administered drug in this patient population (methotrexate).

No significant pharmacokinetic interactions were observed when 30-mg oral apremilast was administered with either oral contraceptive, ketoconazole, or methotrexate. Co-administration of the CYP450 inducer rifampin (600 mg once daily for 15 days) with a single oral dose of 30-mg apremilast resulted in reduction of apremilast AUC and C_{max} by 72% and 43%, respectively *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8-times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).

14 CLINICAL STUDIES

14.1 Psoriatic Arthritis

The safety and efficacy of OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1493 adult patients with active PsA (≥3 swollen joints and ≥3 tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized. Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion of at least 2 cm in diameter was required in Study PsA- 3. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n=496), OTEZLA 20 mg (n=500), or OTEZLA 30 mg (n=497) given orally twice daily. Titration was used over the first 5 days *[see Dosage and Administration (2.1)]*. Patients were allowed to receive stable doses of concomitant methotrexate [MTX (≤25 mg/week)], sulfasalazine [SSZ (≤2 g/day)], leflunomide [LEF (≤20 mg/day)], low dose oral corticosteroids (equivalent to ≤10 mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PsA-1, PsA-2 and PsA-3. There was an additional stratification of BSA >3% with psoriasis in study PsA-3. The patients who were therapeutic failures of >3 agents for PsA (small molecules or biologics), or >1 biologic TNF blocker were excluded.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Placebo-controlled efficacy data were collected and analyzed through Week 24. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomized 1:1 in a blinded fashion

to either OTEZLA 20 mg twice daily or 30 mg twice daily following the titration schema *[see Dosage and Administration (2.1)]*. OTEZLA patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomized to either 20 mg twice daily or 30 mg twice daily.

Patients with subtypes of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (27.0%), distal interphalangeal (DIP) joint arthritis (6.0%), arthritis mutilans (3.0%), and predominant spondylitis (2.1%). The median duration of PsA disease was 5 years. Patients received concomitant therapy with at least one DMARD (65.0%), MTX (55.0%), SSZ (9.0%), LEF (7.0%), low dose oral corticosteroids (14.0%), and NSAIDs (71.0%). Prior treatment with small-molecule DMARDs only was reported in 76.0% of patients and prior treatment with biologic DMARDs was reported in 22.0% of patients, which includes 9.0% who had failed prior biologic DMARD treatment.

Clinical Response in Patients with Psoriatic Arthritis

The percent of patients achieving ACR 20, 50 and 70 responses in Studies PsA-1, PsA-2, and PsA-3 are presented in Table 5 below. OTEZLA ± DMARDs, compared with Placebo ± DMARDs resulted in a greater improvement in signs and symptoms of psoriatic arthritis as demonstrated by the proportion of patients with an ACR 20 response at Week 16.

Table 5: Proportion of Patients With ACR Responses in Studies PsA-1, PsA-2 and PsA-3

	PsA-1		**PsA-2**		**PsA-3**	
N[a]	**Placebo ± DMARDs N=168**	**OTEZLA 30 mg twice daily ± DMARDs N=168**	**Placebo ± DMARDs N=159**	**OTEZLA 30 mg twice daily ± DMARDs N=162**	**Placebo ± DMARDs N=169**	**OTEZLA 30 mg twice daily ± DMARDs N=167**
ACR 20 Week 16	19%	38% [b]	19%	32% [b]	18%	41% [b]
ACR 50 Week 16	6%	16%	5%	11%	8%	15%
ACR 70 Week 16	1%	4%	1%	1%	2%	4%

[a] N is number of randomized and treated patients.
[b] Statistically significantly different from placebo ($p<0.05$).

OTEZLA 30 mg twice daily resulted in improvement for each ACR component, compared to placebo at Week 16 in Study PsA-1 (Table 6). Consistent results were observed in Studies PsA-2 and PsA-3.

Table 6: ACR Components Mean Change from Baseline at Week 16 in Study PsA- 1

	Placebo (N*=168)	OTEZLA 30 mg twice daily (N*=168)
Number of tender joints[a]		
Sample Size	166	164
Baseline	23	23
Mean Change at Week 16	-2	-7
Number of swollen joints[b]		
Sample Size	166	164
Baseline	13	13
Mean Change at Week 16	-2	-5
Patient's assessment of pain[c]		
Sample Size	165	159
Baseline	61	58
Mean Change at Week 16	-6	-14

Patient's global assessment of disease activity[c]		
Sample Size	165	159
Baseline	59	56
Mean Change at Week 16	-3	-10
Physician's global assessment of disease activity[c]		
Sample Size	158	159
Baseline	55	56
Mean Change at Week 16	-8	-19
HAQ-DI[d] score		
Sample Size	165	159
Baseline	1.2	1.2
Mean Change at Week 16	-0.09	-0.2
CRP[e]		
Sample Size	166	167
Baseline	1.1	0.8
Mean Change at Week 16	0.1	-0.1

Mean changes from baseline are least square means from analyses of covariance.
[a] Scale 0-78.
[b] Scale 0-76.
[c] VAS=Visual Analog Scale; 0=best, 100=worst.
[d] HAQ-DI=Health Assessment Questionnaire-Disability Index; 0=best, 3=worst; measures the subject's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
[e] CRP=C-reactive protein; Reference range 0-0.5 mg/dL.
* N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

Treatment with OTEZLA resulted in improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis.

Physical Function Response

OTEZLA 30 mg twice daily demonstrated a greater improvement compared to placebo in mean change from baseline for the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 16 [-0.244 vs. -0.086, respectively; 95% CI for the difference was (-0.26, -0.06)] in Study PsA-1. The proportions of HAQ-DI responders (≥0.3 improvement from baseline) at Week 16 for the OTEZLA 30 mg twice daily group were 38%, compared to 27%, for the placebo group in Study PsA-1. Consistent results were observed in Studies PsA-2 and PsA-3.

14.2 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque psoriasis [body surface area (BSA) involvement of ≥10%, static Physician Global Assessment (sPGA) of ≥3 (moderate or severe disease), Psoriasis Area and Severity Index (PASI) score ≥12, candidates for phototherapy or systemic therapy]. Subjects were allowed to use low-potency topical corticosteroids on the face, axilla and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.

Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to OTEZLA 30 mg BID or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved PASI-75 at Week 16 and the proportion of subjects who achieved a sPGA score of clear (0) or almost clear (1) at Week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. Approximately 30% of all subjects had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of subjects had not received prior phototherapy, conventional systemic nor biologic therapy. A total of 18% of subjects had a history of psoriatic arthritis.

Clinical Response in Subjects with Plaque Psoriasis

The proportion of subjects who achieved PASI -75 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 7.

Table 7: Clinical Response at Week 16 in Studies PSOR-1 and PSOR-2

	Study PSOR-1		Study PSOR-2	
	Placebo	OTEZLA 30 mg BID	Placebo	OTEZLA 30 mg BID
N[a]	N=282	N=562	N=137	N=274
PASI[b] -75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[c] of Clear or Almost Clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

[a] N is number of randomized and treated patients.
[b] PASI=Psoriasis Area and Severity Index.
[c] sPGA=Static Physician Global Assessment.

The median time to loss of PASI-75 response among the subjects re-randomized to placebo at Week 32 during the Randomized Treatment Withdrawal Phase was 5.1 weeks.

14.3 Oral Ulcers Associated with Behçet's Disease

A multicenter, randomized, placebo-controlled trial (BCT-002) enrolled a total of 207 adult patients with BD with active oral ulcers. Patients were previously treated with at least one nonbiologic BD medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for BD. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for BD was not allowed.

Patients were randomized 1:1 to receive either OTEZLA 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks. After Week 12, all patients received OTEZLA 30 mg twice daily.

Efficacy was assessed based on the number and pain of oral ulcers.

Patients ranged in age from 19 to 72, with a mean age of 40 years. The mean duration of BD was 6.84 years. All subjects had a history of recurrent oral ulcers that were currently active. Subjects had a history of skin lesions (98.6%), genital ulcers (90.3%), musculoskeletal manifestations (72.5%), ocular manifestations (17.4%), central nervous system (9.7%), gastrointestinal (GI) manifestations (9.2%) and vascular involvement (1.4%). The mean baseline oral ulcer counts were 4.2 and 3.9 in the OTEZLA and placebo groups, respectively.

Measures of Oral Ulcers

Improvements in measures of oral ulcers at Week 12 are presented in Table 8.

Table 8: Clinical Response of Oral Ulcers at Week 12 in the BCT-002 Study (ITT[a] Population)

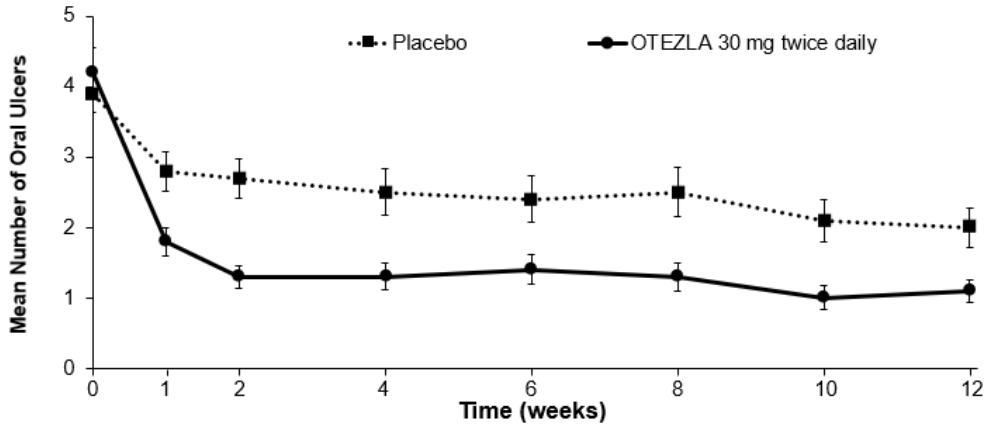
Endpoint	Placebo N=103	OTEZLA 30 mg twice daily N=104	Treatment Difference[b] (95% CI[c])
Change[d] from baseline in the pain of oral ulcers as measured by VAS[e] at Week 12	-18.7	- 42.7	-24.1 (-32.4, -15.7)
Proportion[f] of subjects achieving oral ulcer complete response (oral ulcer-free) at Week 12	22.3%	52.9%	30.6%[g] (18.1%, 43.1%)
Proportion[f] of subjects achieving oral ulcer complete response (oral ulcer-free) by Week 6, and who remained oral ulcer-free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase	4.9%	29.8%	25.1%[g] (15.5%, 34.6%)

Daily average[h,i] number of oral ulcers during the 12-week Placebo-controlled Treatment Phase	2.6	1.5	-1.1 (-1.6, -0.7)

[a] ITT=intent to treat.
[b] OTEZLA – Placebo.
[c] CI=confidence interval.
[d] Mean changes from baseline are least square means from mixed-effects model for repeated measures, adjusting for sex, region, and baseline pain of oral ulcers as measured by the visual analog scale.
[e] VAS=visual analog scale; 0=no pain, 100=worst possible pain.
[f] Patients for whom data are not available to determine response status are considered non-responders.
[g] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the Cochran-Mantel-Haenszel weights.
[h] Mean daily averages are least squares means from analysis of covariance, after adjusting for sex, region, and baseline number of oral ulcers.
[i] Based on oral ulcer counts measured at baseline and at Weeks 1, 2, 4, 6, 8, 10, and 12.

Figure 1 displays the mean number of oral ulcers for each treatment group at each visit, while Figure 2 displays the mean oral ulcer pain on a visual analog scale for each treatment group at each visit.

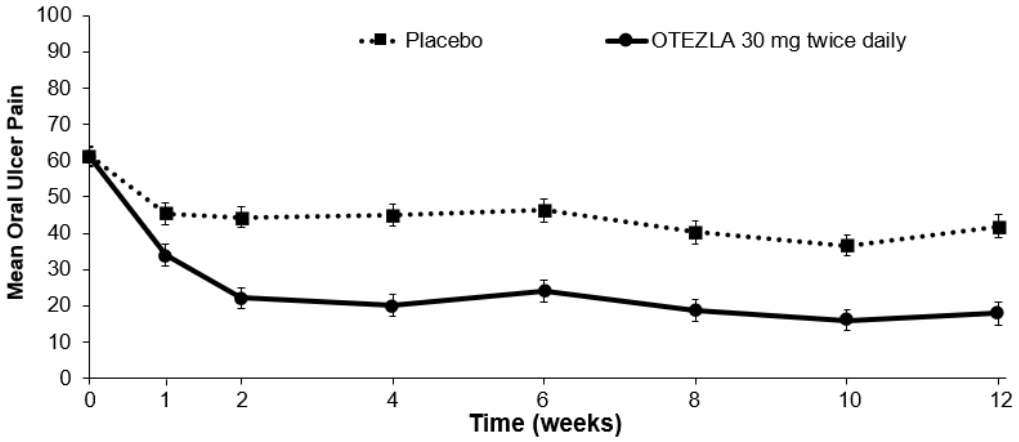
Figure 1: Mean (± SE) Number of Oral Ulcers by Time Point Through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	103	98	97	93	91	86	83	82
OTEZLA 30 mg twice daily, n	104	101	101	101	98	94	94	97

ITT = intent-to-treat; SE = standard error.

Figure 2: Mean (± SE) Oral Ulcer Pain on a Visual Analog Scale by Time Point Through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	101	95	96	91	90	85	82	81
OTEZLA 30 mg twice daily, n	102	95	97	99	97	92	93	95

ITT=intent-to-treat; SE=standard error.
Oral ulcer pain was assessed on a 100-mm Visual Analog Scale with 0 = no pain and 100 = worst possible pain. Mean baseline Visual Analog Scale pain scores were 61.2 and 60.8 in the OTEZLA 30 mg twice daily treatment group and placebo treatment group, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

OTEZLA is available as diamond-shaped, film-coated tablets in the following dosage strengths: 10-mg pink tablet engraved with "APR" on one side and "10" on the other side; 20-mg brown tablet engraved with "APR" on one side and "20" on the other side; 30-mg beige tablet engraved with "APR" on one side and "30" on the other side.

Tablets are supplied in the following strengths and package configurations:

Package configuration	Tablet strength	NDC number
Bottles of 60	30 mg	59572-631-06
Two-week starter pack	13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (14) 30-mg tablets	59572-630-27
28-count carton	Two 30-mg blister cards containing (14) 30-mg tablets	59572-631-28
28-day starter pack	13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (42) 30-mg tablets	59572-632-55

Storage and Handling
Store tablets below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

- **Diarrhea, Nausea, and Vomiting**
  Instruct patients to contact their healthcare provider if they experience severe diarrhea, nausea, or vomiting. Prescribers should advise patients of the potential complications of severe diarrhea, nausea, or vomiting. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting *[see Warnings and Precautions (5.1)]*.

- **Depression**
  Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur *[see Warnings and Precautions (5.2)]*.
- **Weight Decrease**
  Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered *[see Warnings and Precautions (5.3)]*.
- **Drug Interactions**
  The use of strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended *[see Warnings and Precautions (5.4), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.
- Instruct patients to take OTEZLA only as prescribed.
- Advise patients OTEZLA can be taken with or without food.
- Advise patients that the tablets should not be crushed, split, or chewed.
- Advise patients about the side effects associated with OTEZLA *[see Adverse Reactions (6.1)]*.
- **Pregnancy**
  Inform patients that there is a pregnancy registry for pregnant women who have taken OTEZLA during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll or visit https://mothertobaby.org/ongoing-study/otezla/ *[see Use in Specific Populations (8.1)]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy.

Manufactured for: Celgene Corporation
Summit, NJ 07901

OTEZLA® is a registered trademark of Celgene Corporation.

Pat. http://www.celgene.com/therapies

APRPI.007 07/19

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplement
Application Number(s)	205437/ s7
Priority or Standard	Standard
Submit Date(s)	9/21/2018
Received Date(s)	9/21/2018
PDUFA Goal Date	7/21/2019
Division/Office	DPARP/ODE2
Review Completion Date	See electronic signature page
Established/Proper Name	Apremilast
(Proposed) Trade Name	Otezla
Pharmacologic Class	PDE-4 inhibitor
Applicant	Celgene Corporation
Doseage form	10 mg, 20 mg, 30 mg tablets
Applicant proposed Dosing Regimen	30 mg twice daily. To reduce risk of gastrointestinal symptoms, there is a titration to the recommended dose of 30 mg twice daily over (b) (4) days (as per current USPI)
Applicant Proposed Indication(s)/Population(s)	Adult patients with oral ulcers associated with Behçet's Disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Adult patients with oral ulcers associated with Behçet's Disease
Recommended Dosing Regimen	30 mg twice daily. To reduce risk of gastrointestinal symptoms, titirate to the recommended dose of 30 mg twice daily over (b) (4) days (as per current USPI)

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Reviewers of Multi-Disciplinary Review and Evaluation

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Clinical Reviewer	Nadia Habal, MD, MPH
Clinical Team Leader	Rachel Glaser, MD
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Statistical Team Leader	Peiling Yang, PhD
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OSE/DEPI	N/A
OSE/DMEPA	N/A
OSE/DRISK	N/A
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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	L. Steven Leshin	DPARP/ODE2/OND	Sections: 5, 11.1	**Select one:** __X_ Authored ___ Approved
	Signature: Lawrence S. Leshin -S Digitally signed by Lawrence S. Leshin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222013, cn=Lawrence S. Leshin -S Date: 2019.07.18 17:49:59 -04'00'			
Nonclinical Team Leader	Carol Galvis	DPARP/ODE2/OND	Sections: 5, 11.1	**Select one:** ___ Authored __X_ Approved
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S DN: c=US, o=U.S.Government, ou=HHS, ou=FDA, ou=People, cn=Carol Galvis -S, 0.9.2342.19200300.100.1.1=2000329778 Date: 2019.07.18 18:35:57 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lei He (Jianmeng Chen to sign on behalf of Lei)	OTS/OCP/DCP II	Section: 6	**Select one:** __X_ Authored ___ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2019.07.19 08:29:41 -04'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen	OTS/OCP/DCP II	Section: 6	**Select one:** ___ Authored __X__ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2019.07.19 08:30:34 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Nadia Habal	DPARP/ODE2/OND	Sections: 1-13, 15 Except for efficacy and statistics sections	**Select one:** _X__ Authored ___ Approved
	Signature: Nadia Habal -S	Digitally signed by Nadia Habal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nadia Habal -S, 0.9.2342.19200300.100.1.1=0014318202 Date: 2019.07.19 10:01:30 -04'00'		
Clinical Team Leader	Rachel Glaser	DPARP/ODE2/OND	Sections: 1-3, 8	**Select one:** ___ Authored __X_ Approved
	Signature: Rachel Glaser -S	Digitally signed by Rachel Glaser -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rachel Glaser -S, 0.9.2342.19200300.100.1.1=0013432915 Date: 2019.07.18 19:08:20 -04'00'		
Statistical Reviewer	Cesar Torres	DB2/OB/OTS	Sections: 7, 8	**Select one:** _X__ Authored ___ Approved
	Signature: Cesar Torres -S	Digitally signed by Cesar Torres -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Cesar Torres -S, 0.9.2342.19200300.100.1.1=2002015842 Date: 2019.07.19 08:58:59 -04'00'		
Statistical Team Leader	Peiling Yang	DB2/OB/OTS	Sections: 7, 8	**Select one:** ___ Authored _X__ Approved
	Signature: Peiling Yang -S	Digitally signed by Peiling Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peiling Yang -S, 0.9.2342.19200300.100.1.1=1300147876 Date: 2019.07.19 08:25:39 -04'00'		
Designated Signatory (DPARP)	Nikolay Nikolov	DPARP/ODE2/OND	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S	Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2019.07.18 17:12:33 -04'00'		

1 Executive Summary

1.1. Product Introduction

Celgene corporation submitted supplement 7 to NDA 205437 for apremilast for the treatment of adult patients with oral ulcers associated with Behçet's Disease (BD). 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.

Apremilast is available as a 10 mg, 20 mg, and 30 mg immediate release tablet. The dosing regimen is 30 mg twice daily. To reduce risk of gastrointestinal symptoms, there is a titration to the recommended dose of 30 mg twice daily according to the following schedule:

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	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	30 mg	30 mg

It is approved for the treatment of adult patients with active psoriatic arthritis and patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The studies supporting this supplement, BCT-001 and BCT-002 were done in adult patients with active ulcers from Behçet's Disease. Study BCT-001 had a 12 week placebo-controlled period followed by a 12 week blinded extension period and the primary endpoint of the study was the mean number of oral ulcers at week 12. Study BCT-002 had a 12 week placebo-controlled period followed by 52 weeks open label and the primary endpoint was AUC for the number of oral ulcers from baseline through week 12. In each study, there was substantial evidence of efficacy based on analysis results from the primary efficacy endpoint. Analysis results of secondary efficacy endpoints in each study were also supportive of efficacy.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk profile of apremilast for oral ulcers associated with Behçet's Disease is favorable. The efficacy is supported by data from two clinical studies, BCT-001 and BCT-002. The benefit included an average decrease of 1.1 in 12-week average oral ulcer count and an average decrease of 24.2 in change from baseline to Week 12 in oral ulcer pain visual analog scale. The risks of apremilast treatment in this patient population appear to be qualitatively similar as those seen in psoriasis and psoriatic arthritis. Apremilast offers an alternative treatment option for oral ulcers of Behçet's Disease given that there are currently no FDA approved therapies for this condition and treatment is based on consensus treatment and off-labeled use of other medications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Behçet's Disease (syndrome) is an auto inflammatory disorder. • The prevalence of Behçet's Disease in the US is approximately one case out of every 170,000. •Patients must present with: recurrent oral ulcerations >three times in one year. Additionally, patients must present any two of the following: recurrent genital ulcerations, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules), positive pathergy test.	Oral ulcers are the most frequent manifestation of the disease.
Current Treatment Options	• Current treatment approach is based on consensus treatment. • Oral ulcers of Behçet's Disease are typically treated with the off-labeled use of corticosteroids, colchicine, dapsone, and thalidomide.	There are currently no approved therapies for Behçet's Disease or the associated oral ulcers .
Benefit	• Average decrease of 1.1 in 12-week average oral ulcer count. • Average decrease of 24.2 in change from baseline to Week 12 in oral ulcer pain visual analog scale (VAS). • Average decrease of 10.0 in change from baseline to Week 12 in Behçet's Syndrome Activity Score.	The data from the clinical program in this supplemental NDA provide evidence of apremilast being effective for the treatment of oral ulcers associated with Behçet's Disease, when compared to placebo.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Average decrease of 0.7 in change from baseline to Week 12 in Patient's Perception of Disease Activity. • Average decrease of 0.8 in change from baseline to Week 12 in Clinician's Overall Perception of Disease Activity. • Increase of 24.2% in probability of achieving complete response by Week 6 and maintaining it for at least 6 additional weeks. • Hazard ratio of 2.1, with respect to time to oral ulcer resolution. • Increase of 29.6% in probability of complete response at Week 12. • Decrease of 2.8 in change from baseline to Week 12 in Behçet's Disease Quality of Life Score.	
Risk and Risk Management	• Diarrhea, nausea, vomiting, depression, and weight decrease are labeled risks of apremilast treatment.	The overall safety profile of apremilast for oral ulcers of Behçet's Disease is consistent with known safety profile of apremilast in psoriasis and psoriatic arthritis.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

□	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO) • Changes from baseline in BD QoL score at week 12 • Behçet's disease Current Activity Form • Change from baseline in oral ulcer pain visual analog scale • Behçet's Syndrome Activity Score	Section 8.1.4 15.4 Additional Clinical Outcome Assessment Analyses
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	

2 Therapeutic Context

2.1. Analysis of Condition

Behçet's Disease (syndrome) is an auto inflammatory disorder. It is classified among vasculitides by the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, in the group of variable vessel vasculitis.[1] It is more common along the ancient "Silk Route" from eastern Asia to the Mediterranean; however, it may affect any ethnic origin. The prevalence of Behçet's Disease in the US is approximately one case out of every 170,000.[2] The mean age of onset is in the third decade of life. There are no currently available specific laboratory or radiological tests to diagnose Behçet's Disease. The diagnosis is based on having positive clinical criteria referred to as the International Clinical Criteria for Behçet's Disease. Patients must present with: recurrent oral ulcerations (apthous or herpetiform) at least three times in one year. Additionally, patients must present any two of the following: recurrent genital ulcerations, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules), positive pathergy test read by a physician within 24-48 hours of testing.[3] Clinical manifestations may also include arthritis, gastrointestinal and neurologic involvement. Behçet's Disease is characterized by a relapsing and remitting course. Oral ulcers are the most frequent manifestation of the disease.[4]

2.2. Analysis of Current Treatment Options

The treatment of Behçet's Disease is largely based on treatment of the clinical manifestations. Currently, there are no FDA approved medications for Behçet's Disease. The choice of therapy is limited by the scarceness of therapy trials and is based largely on case reports, case series, and several randomized clinical trials. Interferon alpha has been used to treat mucocutaneous, articular, and ocular manifestations of Behçet's Disease. Infliximab has been used to treat refractory uveoretinitis, entero-Behçet, neuroBehçet, vascular Behçet's, and arthritis.[5] The

[1] J. C. Jennette, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. 08 October 2012.
[2] http://www.behcets.com/site/c.8oIJJRPsGcISF/b.9196317/k.904C/Behcets_Disease.htm
[3] F. Davatchi et al. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. 26 February 2013.
[4] F. Davatchi et al. Behçet's disease: epidemiology, clinical manifestations, and diagnosis. 04 Feb 2016.
[5] Z. Saleh. Update on the therapy of Behçet disease. Ther Adv Chronic Dis. 2014 May; 5(3): 112–134.

treatment of Behçet's Disease oral ulcers are typically the off-labeled use of corticosteroids, colchicine, dapsone, and thalidomide. In 2018, there was an update of the EULAR recommendations for the management of Behçet's syndrome. For mucocutaneous involvement, they recommend the following: Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions, especially when the dominant lesion is erythema nodosum or genital ulcer. Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris. Drugs such as azathioprine, thalidomide, interferon-alpha, TNF-alpha inhibitors or apremilast should be considered in selected cases.[6]

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On March 21, 2014, under NDA 205437, apremilast was approved as a new molecular entity for the treatment of adult psoriatic arthritis.

On September 23, 2014, under NDA 206088, apremilast was approved for the treatment of plaque psoriasis.

3.2. Summary of Presubmission/Submission Regulatory Activity

On April 29, 2009, in written responses provided to the Applicant, the FDA stated that at least 100 Behçet's Disease patients should be followed for one year of treatment with apremilast. On December 4, 2012 in comments before the type B, end of phase two meeting, the FDA said that more than one single controlled study will be required, and (b) (4) . On January 17, 2013, apremilast was given an Orphan Drug Designation for the indication: "treatment of Behçet's Disease."

(b) (4)

On March 1, 2018, in a type B, pre-NDA meeting, the FDA suggested that the indication "for the treatment of oral ulcers associated with BD" may be more appropriate (b) (4) The FDA further expressed concerns with the interpretability of the primary endpoint, Area Under the Curve for the number of oral ulcers from baseline through Week 12, and recommended that the applicant prioritize the assessment of more meaningful and intertable

[6] Hatemi G, Christensen R, Bang D, et al 2018 update of the EULAR recommendations for the management of Behçet's syndrome Annals of the Rheumatic Diseases 2018;77:808-818.

endpoints, such as (1) complete response (CR) rate; (2) change from baseline in the pain of oral ulcers at Week 12; and (3) the proportion of patients achieving CR by Week 6 and remaining oral ulcer free for at least six additional weeks during the placebo-controlled treatment phase.

On May 23, 2018, a breakthrough therapy designation request was denied because the reduction of number of oral ulcers does not measure irreversible morbidity, mortality, or symptoms that represent serious consequences of the disease.

With this submission, the applicant also requested a Priority review. However, the Division concluded that the applicant has not addressed the requirements detailed in the Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics[7], to support a Priority review of this application. Specifically, the clinical program was not designed to assess the serious nature of oral ulcers or other manifestations of BD.

[7] https://www.fda.gov/media/86377/download

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

4.1. Office of Scientific Investigations (OSI)

No OSI inspections were deemed necessary for this supplemental NDA as there were no concerns with the design, conduct and results from the clinical program supporting this application.

4.2. Product Quality

This efficacy supplement is approvable from CMC standpoint. For details, see primary review by Chong Ho Kim in DARRTS dated 6/12/2019.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no new pharmacology/toxicology studies or information submitted or needed to support this supplement. Refer to the original phamacology/toxicology NDA review, dated November 20, 2013, for previously submitted information.

6 Clinical Pharmacology

6.1. Executive Summary

OTEZLA (apremilast), an inhibitor of phosphodiesterase 4 (PDE4), has been approved for the treatment of adult patients with active psoriatic arthritis (PsA) and patients with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy. Celgene submitted the supplemental submission on September 21, 2018 seeking the marketing approval of apremilast for the treatment of oral ulcers associated with Behçet's Disease (BD). The proposed dosage form and dosing regimen are same as those approved for the treatment of PsA and PsO.

The NDA 205437 Supplement-07 application consists of two clinical studies in subjects with active BD with oral ulcers, including one Phase 2 study (Study BCT-001) and one Phase 3 study (Study BCT-002). Exploratory assessment of apremilast pharmacokinetics (PK) in BD patients was performed as optional in a subset of subjects (n=14) in Study BCT-002. There were no proposed labeling changes in the clinical pharmacology sections.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

OTEZLA (apremilast) is a PDE4 inhibitor and has been approved for the treatment of adult patients with PsA and PsO. Refer to the approved labeling of OTEZLA regarding apremilast PK in subjects with PsA and PsO.

Study BCT-002 is a phase 3, multicenter, randomized, parallel-group study to evaluate the efficacy and safety of apremilast in the treatment of subjects with active BD (n=207), in which apremilast PK in BD patients was assessed as optional in a subset of subjects (n=14) as exploratory objectives. In Study BCT-002, approximately 204 eligible subjects were randomized 1:1 (102 subjects per group) to receive apremilast 30 mg twice daily (BID) or placebo in the 12-week Placebo-controlled Treatment Phase and followed by the 52-week Active Treatment Phase with apremilast 30 BID. For 14 subjects who agreed to participate in the PK substudy, PK samples were collected at Week 16 at predose (prior to morning dose), and 1, 2, 3, 5, 8, 12 hours postdose. Concentrations of apremilast in plasma were measured using a validated liquid chromatography-tandem mass spectrometry assay (Validation Report CC-10004-DMPK-024, reviewed in the original NDA205437 submission for the treatment of PsA by Dr. Sheetal Agarwal dated 11/20/2013). Apremilast PK in patients with BD was analytized using non-compartmental analysis, and the PK parameters are shown Table 1.

Table 1. Apremilast PK Parameters (Geometric Mean (Geometric CV%)) at Week 16 in Patients with Behçet's Disease (Study CC-10004-BCT-002)

	APR 30 BID		
Pharmacokinetic Parameter (unit)	**Japanese (n = 7)**	**non-Japanese (n = 7)**	**Total (n = 14)**
AUC_{0-t} (ng•h/mL)	2071 (49.5)	3100 (29.6)	2534 (44.9)
AUC_{0-12} (ng•h/mL)	2076 (49.5)	3120 (30.0)	2545 (45.2)
C_{max} (ng/mL)	374.2 (31.3)	380.9 (27.9)	377.6 (28.4)
T_{max} (h)[a]	1.08 (1.00, 2.00)	2.00 (1.00, 3.00)	1.88 (1.00, 3.00)
$t_{1/2}$ (h)	4.23 (26.9)	8.07 (64.8)	5.84 (59.9)
CL/F (L/h)	14.45 (49.5)	9.6 (30.0)	11.8 (45.2)
V_z/F (L)	88.3 (46.1)	112.0 (58.0)	99.4 (51.8)

AUC_{0-12} = area under the plasma concentration-time curve from time zero to 12 hours post-dose; AUC_{0-t} = area under the plasma concentration-time curve from time zero to last quantifiable time point; CL/F = apparent clearance of drug from plasma after extravascular administration; C_{max} = maximum observed plasma concentration, $t_{1/2}$ = terminal phase elimination half-life; T_{max} = time to maximum observed plasma concentration; V_z/F = apparent volume of distribution during the terminal phase.

[a] Median (range)

Source: Report CC-10004-BCT-002, Table 40

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen for the treatment of patients with BD is the same as the approved dosing regimen for PsA and PsO: titrate to the recommended dose of 30 mg BID.

Therapeutic Individualization

Same as the approved dosing regimen for PsA and PsO.

Outstanding Issues

None

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 2: Key Design Features of Clinical Studies

Protocol	Patient population	Design/ Primary Endpoint	Duration	Treatment arms: sample size/ dose
BCT-001	Adult patients with active ulcer disease from Behçet's Disease	R, DB, PC, PG study/ *The mean number of oral ulcers at Week 12*	*24 weeks tx duration:* 84-day PC period, followed by 85-day blinded extension period	56 PBO, 55 APR After dose escalation per label, dose 30 mg bid
BCT-002	Same as above	R, DB, PC, PG study/ *AUC for the number of oral ulcers from baseline through Week 12*	*64 weeks tx duration:* 12 weeks PC period, followed by OL 52 weeks	103 PBO, 104 APR Same dose as above

Abbreviations: R=randomized, DB=double blind, PC=placebo-controlled, PG=parallel group, AUC=area under the curve, tx=treatment, PC=placebo-controlled, OL=open label, PBO=placebo, APR=apremilast, bid=twice daily

7.2. Review Strategy

NDA 205437/s7 was reviewed for content, format, overall data quality and found acceptable during the filing review. Datasets were submitted in legacy format. The quality of data submitted for review was adequate to support a substantive review of the application.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Integrated Overview

For many of the efficacy endpoints in Studies BCT-001 and BCT-002, the statistical analysis plans prespecified a Last Observation Carried Forward (LOCF) missing data imputation procedure for the primary analysis. Since the use of a single imputation approach such as LOCF is typically not appropriate due to scientific and statistical considerations[8], in this review the Agency's statistical reviewer presents results of post-hoc sensitivity analyses for these endpoints. These sensitivity analyses typically make use of a multiple imputation procedure.

8.1.2. Study BCT-001

Trial Design

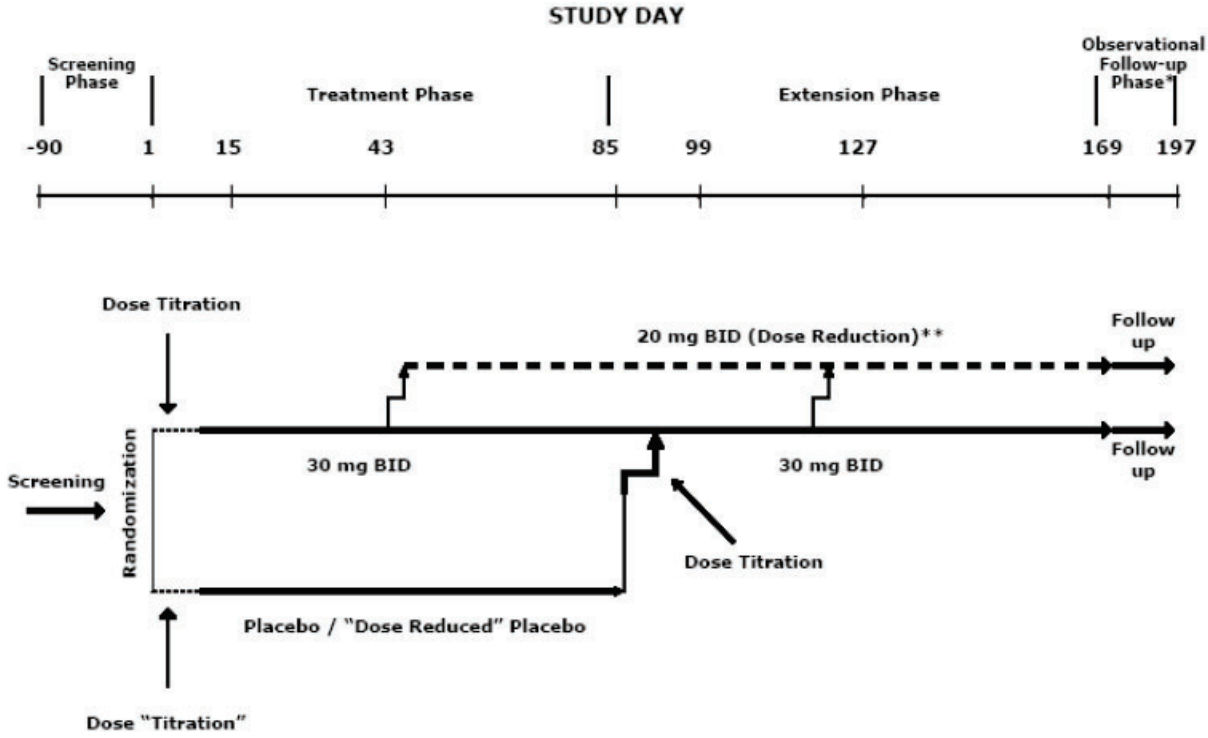
Study BCT-001 was a multicenter, randomized, placebo-controlled, double blind, parallel group study in Behçet's Disease patients with at least two oral ulcers at randomization. The primary objective of this study was to evaluate the efficacy of apremilast in the treatment of oral ulcers after 84 days of treatment.

Randomization was stratified by gender. The treatment duration was 24 weeks, which consisted of a 12-week placebo-controlled period followed by a 12-week blinded extension period. Study drug remained blinded during the extension phase to preserve the blind from the treatment phase. There was also a four-week posttreatment observational follow-up phase.

111 patients were randomized 1:1 to apremilast 30 mg twice daily or placebo after dose escalation as per label. Patients were dosed orally (PO) twice per day (BID) with 10 mg apremilast or identically appearing placebo on Days 1 and 2, followed by 20 mg BID apremilast or placebo on Days 3 and 4, and 30 mg BID apremilast or placebo on Days 5 to 7. Thereafter, patients took apremilast 30 mg BID or matching placebo through Day 84. After the dose-titration period (ie, starting at Day 8), patients who were unable to tolerate study drug were permitted to dose-reduce to 20 mg BID apremilast or matching placebo, after the investigator consulted with Celgene. Each patient was allowed to reduce their dose only once during the study. During the extension phase, patients who had received placebo during the treatment phase (including those who were "dose reduced" on placebo) were switched to apremilast 30 mg BID, following the titration scheme utilized for patients randomized to apremilast in the treatment phase. Patients who had been randomized to apremilast continued

[8] National Research Council. 2010. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: The National Academies Press. https://doi.org/10.17226/12955

to receive apremilast at the same dosage at which they completed the treatment phase (30 mg BID or 20 mg BID).



Note: Dose reduction was permitted after the dose-titration period (ie, starting at Day 8).

Trial location

There were three study sites in Turkey and three study sites in the United States.

Diagnostic criteria

The diagnosis was based on the International Study Group Criteria For The Diagnosis Of Behçet's Disease (1990) which is:

In the absence of other clinical explanations, patients must have Recurrent Oral Ulceration (apthous or herpetiform) observed by the physician or patient recurring at least three times in one 12-month period. In addition, at least two of the following criteria must be met:

1) Recurrent Genital Ulceration:
   Aphthous ulceration or scarring observed by physician or patient.
2) Eye Lesions:
   Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination; or:

Retinal vasculitis observed by ophthalmologist.

3) Skin Lesions:
   Erythema nodosum, pseudofolliculitis, or papulopustular lesions; or: acneiform nodules in postadolescent patients not on corticosteroid treatment.
4) Positive result on Pathergy Testing: read by a physician at 24 to 48 hours.

Inclusion

1) Males and Females ≥18 years old
2) Females of childbearing potential (FCBP) had to have a negative urine pregnancy test at screening and at Baseline (Day 1). In addition, FCBP who engaged in activity in which conception was possible had to use 2 forms of contraception while on study drug and for at least 28 days after the last dose of study drug: one highly effective (ie, hormonal, intrauterine device, tubal ligation, vasectomized partner) and one additional form (eg, latex condom, diaphragm, cervical cap, sponge). If one highly effective form of contraception could not be used, then 2 forms of barrier contraception had to be used (ie, latex condom with any of the following: sponge, diaphragm with spermicide, or cervical cap with spermicide)
3) Male patients (including those who had a vasectomy) who engaged in activity in which conception was possible had to use barrier contraception (latex condoms) while on study drug and for at least 28 days after last dose of study drug
4) Met the international study group criteria for BD
5) Laboratory criteria: Hemoglobin > 9 g/dL; White blood cell count ≥ 3000 /uL (≥ 3.0 X 10^9/L) and ≤14,000/uL (≥14 X 10^9/L); Platelet count ≥ 100,000 /uL (≥ 100 X 10^9/L); Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L); Total bilirubin ≤ 2.0 mg/dL; Aspartate transaminase and alanine transaminase <1.5 X upper limit of normal
6) Had active ulcer disease (oral and/or genital) in the 28-day period prior to screening, with or without current treatment
7) Had two or more oral ulcers at the time of randomization (Baseline; Day 1)

Exclusion

1) Pregnant or breast feeding
2) Any condition, including the presence of laboratory abnormalities, that placed the patient at unacceptable risk if he/she were to participate in the study or confounded the ability to interpret data from the study
3) Systemic fungal infection
4) History of active mycobacterial infection with any species (including Mycobacterium tuberculosis) within three years prior to Screening Visit
5) History of recurrent bacterial infection (at least three major infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within the past two years)
6) Mycobacterium tuberculosis infection as indicated by a positive purified protein derivative (PPD) skin test. Patients with a positive PPD were excluded. If a QuantiFERON® test was performed instead of the PPD test, only those with a negative

QuantiFERON test were allowed in the study
7) History of incompletely treated Mycobacterium tuberculosis infection
8) Clinically significant abnormality on chest x-ray at screening
9) Use of any investigational medication within four weeks or five pharmacokinetic/ pharmacodynamic half-lives (whichever was longer) prior to randomization
10) Clinically significant abnormality on 12-lead ECG at screening
11) History of human immunodeficiency virus infection
12) History of congenital or acquired immunodeficiency
13) Hepatitis B surface antigen positive at screening; antibodies to hepatitis C at screening
14) Malignancy or history of malignancy (except for treated [ie, cured] basal cell skin carcinomas > three years prior to screening)
15) Any active major organ involvement of BD, including ocular, central nervous system, lung, vascular, or GI involvement. Previous major organ involvement wasnallowed if it occurred at least one year prior to screening and was not active. Patients with mild BD-related inflammatory eye disease not requiring immunosuppressive therapy were allowed. Patients with arthritis were also allowed
16) Receiving concomitant immune-modulating therapy or topical corticosteroids. Patients receiving such agents may have been eligible to enroll following a washout period
17) Low dose systemic corticosteroids (≤ 10 mg/day prednisone or equivalent) were allowed during the study, if the dose was stable for at least four weeks prior to randomization
18) Patients using ocular corticosteroids

Patient discontinuation criteria

1) Adverse events that in the judgment of the investigator could cause severe or permanent harm or would rule out continuation of study drug, including, but not limited to: WBC of ≥ 20,000/ µL (≥ 20 X 10^9/L) or any clinically significant ECG finding
2) Lack of therapeutic effect, which could include the development or worsening of major organ involvement
3) Patient withdrew consent or was lost to follow-up
4) Death
5) Major protocol violation

Concurrent medications

Oral or topical analgesics had to be discontinued for 24 hours prior to each study visit in order to avoid interference with the pain assessments. Chronic medications were to be dosed on a stable regimen.

Rescue

Flare in this study was defined as development of new manifestations of Behçet's Disease or worsening of existing disease, fulfilling one or more of the following five criteria:

1) Organ involvement: any major organ involvement (eg, central nervous system, gastrointestinal tract)
2) Oral/genital ulcers: ≥ 100% increase in the number of oral or genital ulcers from Day 1

or a minimum increase of three in the number of oral or genital ulcers, whichever is greater
3) Arthritis: ≥ 50% increase in the number of swollen joints, or a minimum increase of three swollen joints, whichever is greater
4) Skin lesions (non-oral/genital ulcers): ≥ 50% increase in the total score of the Physician's Global Assessment of Skin Lesions, or a minimum increase of two in the total score of the Physician's Global Assessment of Skin Lesions, whichever is greater
5) New onset or worsening of existing Behçet Disease-related inflammatory eye disease requiring initiation of immunosuppressive therapy.

Patients who developed major organ involvement (Criterion 1) and/or new onset or worsening of existing Behçet Disease-related inflammatory eye disease requiring initiation of immunosuppressive therapy (Criterion 5) were to be discontinued from the study. Patients who experienced other types of flare (Criteria 2, 3 or 4) could remain in the study at the investigator's discretion.

Safety variables of this study

The safety variables included: adverse events, deaths, number of patients who had new onset of uveitis or worsening of existing uveitis (defined as initiation of immunosuppressive therapy), number of new manifestations of BD that were not present at Day 1, assessment of flare throughout the study, laboratory abnormalities, and changes from baseline or abnormalities in vital signs or electrocardiogram (ECG).

Study Endpoints

The primary endpoint was the mean number of oral ulcers at Week 12.

The secondary endpoints were:

1) AUC of the number of oral ulcers, genital ulcers, or oral plus genital ulcers from Day 1 to Day 85
2) The sum of the number of oral ulcers, genital ulcers, or oral plus genital ulcers from Day 1 to Day 85
3) Pain of oral ulcers
4) Number of genital ulcers
5) Pain of genital ulcers
6) "Behçet's Disease Current Activity Form" score
7) Proportion of patients who are oral ulcer-free (complete response), or whose oral ulcers are reduced by >50% (partial response) from Day 1.

Statistical Analysis Plan

Analysis Populations

The following analysis populations were defined in the Statistical Analysis Plan (SAP):

- Intent-to-Treat Population: This population included all randomized patients who had at least one oral ulcer evaluation (baseline or otherwise). As stated in the SAP, this population was to be used for the primary efficacy analysis. Patients were to be analyzed as randomized.
- Per-Protocol Population: This population included all randomized patients who received at least one dose of study medication, had a baseline oral ulcer evaluation, at least one post-treatment oral ulcer evaluation, and had no major protocol violations that would potentially substantially affect the results of the primary efficacy endpoint. Patients were to be analyzed as randomized.
- Safety Population: This population included all randomized patients who received at least one dose of investigational product. Patients were to be analyzed as treated. Furthermore, patients who received mixed treatments would be included in the apremilast arm for analysis. Analyses for this population would be restricted to the placebo-controlled period.
- Apremilast Subjects as Treated Population: This population included all randomized patients who were initially randomized to or switched to apremilast, and received at least one dose of apremilast after initial randomization or switch. Patients would be analyzed according to treatment sequence received.

Estimands

Estimands were not defined in the SAP.

Primary Endpoint

The primary endpoint was number of oral ulcers at Day 85. To evaluate the primary endpoint, an Analysis of Covariance (ANCOVA) model was to be used, including the following variables in the model: treatment, gender, and number of oral ulcers at baseline. For patients with missing data, a Last Observation Carried Forward (LOCF) approach was to be used. The test for a treatment effect difference was to be performed at a two-sided significance level of 0.05.

Multiplicity Control Procedure

There was no prespecified multiplicity control procedure to control the study-wise type I error across the primary and secondary endpoints. Because of this, results of only select analyses of the secondary endpoints are presented in this review. A brief description of some prespecified analyses is provided.

Secondary Endpoints

Secondary endpoints to be evaluated during the placebo-controlled period included the following:

- Change from baseline to Day 85 in the pain of oral ulcers, as measured by a Visual Analog Scale (VAS)
- Number of genital ulcers at Day 85
- Change from baseline to Day 85 in the pain of genital ulcers, as measured by a VAS
- AUC of the number of oral ulcers, genital ulcers, or oral + genital ulcers from Day 1 to Day 85
- Sum of the number of oral ulcers, genital ulcers, or oral + genital ulcers from Day 1 to Day 85
- Ulcer response (achieving oral ulcer-free status (complete response), or achieving oral ulcer count reduction of ≥ 50% (partial response)) from Day 1 to Day 85
- Change from baseline to Day 85 in Behçet's Disease Current Activity Form score
- Change from baseline to Day 85 in Behçet's Disease Quality of Life Measure (BD QoL) score
- Changes from baseline to Day 85 in Behçet's Disease Multidimensional Health Assessment Questionnaire (BD MDHAQ) score
- Changes from baseline to Day 85 in the 8 domains and the 2 component scores (physical and mental) of the Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) score

Complete response and partial response endpoints were to be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusting for gender, at the two-sided significance level of 0.05. An ANCOVA model was to be used to analyze number of oral + genital ulcers at Day 85. All other secondary endpoints were to be analyzed using descriptive statistics.

Safety Analyses

In general, safety analyses were to be descriptive in nature. No inferential statistical testing was planned on the safety data.

Protocol Amendments

Protocol Amendment 1 on June 17, 2009 deleted the biomarker portion of the study and the PK portion of the study (including intensive and population PK).

Protocol Amendment 2 on April 09, 2010 deleted some study visit days and deleted the pathergy test. In addition, all pregnancy tests were changed to be urine tests, not serum tests, and were to be performed at screening, baseline, end of study or early termination, and four weeks after last dose of study drug.

The changes contained in the protocol amendments are not expected to have an impact on the assessment of efficacy or safety.

8.1.3. Study Results BCT-001

Compliance with Good Clinical Practices

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Financial Disclosure

There were no relevant financial disclosures for this study.

Patient Disposition

A total of 238 patients were screened for inclusion in this study. Of these patients, 111 were randomized and 127 were screen failures. Fifty six patients were randomized to the placebo group and 55 were randomized to apremilast 30 mg BID (APR group). Ninety five (86%) patients completed the treatment phase of the study. Five (9%) patients in the placebo group and four (7%) patients in the APR group discontinued due to an adverse event (AE). The proportion of patients withdrawing for lack of therapeutic effect was three (5%) in the placebo group and (0%) in the APR group. Two patients required a dose reduction to 20 mg BID of APR.

All 95 patients who completed the treatment phase of the study entered the extension phase. 91 patients completed the extension phase. Four patients discontinued during the extension phase due to an adverse event, one in the placebo/APR 30 BID arm and three in the APR 30 BID/APR 30 BID arm.

Protocol Violations/Deviations

During the placebo-controlled period (intention to treat population), protocol violations were reported for 11 (10%) patients, eight (14%) in the placebo group and three (5%) in the APR group. The most common protocol violation was prohibited concomitant medication (eight), which occurred more frequently in the placebo group (seven) than in the APR group (one).
In the intention to treat population, there were more protocol deviations overall in the APR group than in the placebo group. The most common protocol deviation was study drug compliance 36 (64%) in the placebo group versus 43 (78%) in the APR group. In the APR group, 25 patients (45%) had a missing safety assessment vs 15 (27%) in the placebo group. In addition, 25 patients (45%) had mishandled samples in the APR group vs 19 (34%) in the placebo group. In the APR group, 16 patients (29%) had out of window safety assessments vs 10 (18%) in the placebo group.

There was no protocol deviation that had a potential impact on the analyses.

Table 3: Demographic Characteristics for Study BCT-001 (ITT population)

Demographic Parameters	**Study BCT-001** (N=111)	
	Placebo (N=56) n (%)	APR 30 BID (N=55) n (%)
Sex		
Male	18 (32)	16 (29)
Female	38 (68)	39 (71)
Age		
Mean years (SD)	34.7 (10.97)	34.3 (9.11)
Median (years)	34	34
Min, max (years)	(18, 64)	(19, 59)
Age Group		
< 40 years	37 (66)	40 (73)
40 to ≤ 65	19 (34)	15 (27)
Race		
White	55 (98)	53 (96)
Black or African American	0	2 (3.6)
Other	1 (1.8)	0
Ethnicity		
Hispanic or Latino	1 (1.8)	1 (1.8)
Not Hispanic or Latino	55 (98)	54 (98)
Region		
Turkey	53 (95)	50 (91)
United States	3 (5)	5 (9)
Weight (kg)		
Mean (SD)	68.7 (12.5)	67.3 (12.2)
Median	67.3	68
(Min, Max)	(45, 99)	(44, 95)

Adapted from Study BCT-001

In Table 3 you can see the Demographic Characteristics for Study BCT-001. The sex, age and race, ethnicity and region were generally similar between the treatment groups and representative of the expected patient population for BD.

Other Baseline Characteristics

Clinical disease characteristics at baseline are shown in Table 4. There were more patients with currently active arthralgia and genital ulcers in the placebo group. There were also more patients with a history of uveitis in the placebo group. Aside from these, the baseline clinical disease characteristics were generally similar across the randomized groups.

Table 4 : Study 001, Baseline Disease Characteristics

Disease Characteristic	Apremilast (N = 55)	Placebo (N = 56)	Total (N = 111)
Duration of BD in years, mean (sd)	4.9 (4.0)	5.7 (6.1)	5.3 (5.1)
Has History of Genital Ulcers, N (%)	50 (90.9%)	48 (85.7%)	98 (88.3%)
Currently Active, N (%)	18 (32.7%)	25 (44.6%)	43 (38.7%)
Missing, N (%)	3 (5.5%)	3 (5.4%)	6 (5.4%)
Has History of Skin Lesions[1], N (%)	53 (96.4%)	53 (94.6%)	106 (95.5%)
Currently Active, N (%)	49 (89.1%)	50 (89.3%)	99 (89.2%)
Missing, N (%)	0 (0.0%)	1 (1.8%)	1 (0.9%)
Has History of Arthralgia, N (%)	34 (61.8%)	37 (66.1%)	71 (64.0%)
Currently Active, N (%)	27 (49.1%)	32 (57.1%)	59 (53.2%)
Missing, N (%)	1 (1.8%)	0 (0.0%)	1 (0.9%)
Has History of Arthritis, N (%)	19 (34.5%)	16 (28.6%)	35 (31.5%)
Currently Active, N (%)	11 (20.0%)	11 (19.6%)	22 (19.8%)
Missing, N (%)	1 (1.8%)	0 (0.0%)	1 (0.9%)
Has History of Nausea/Vomiting/Abdominal Pain, N (%)	2 (3.6%)	2 (3.6%)	4 (3.6%)
Currently Active, N (%)	1 (1.8%)	2 (3.6%)	3 (2.7%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Has History of Diarrhea/Bleeding, N (%)	2 (3.6%)	1 (1.8%)	3 (2.7%)
Currently Active, N (%)	2 (3.6%)	1 (1.8%)	3 (2.7%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Has History of Anterior Uveitis, Posterior Uveitis, or Cells in Vitreous, N (%)	6 (10.9%)	12 (21.4%)	18 (16.2%)
Currently Active, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Required Immunosuppressives, N (%)	2 (3.6%)	7 (12.5%)	9 (8.1%)
History of Retinal Vasculitis Observed by Ophthalmologist, N (%)	1 (1.8%)	1 (1.8%)	2 (1.8%)
Currently Active, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Required Immunosuppressives, N (%)	1 (1.8%)	0 (0.0%)	1 (0.9%)
History of Central Nervous System Involvement, N (%)	1 (1.8%)	1 (1.8%)	2 (1.8%)
Currently Active, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of Major Vessel Involvement, N (%)	1 (1.8%)	0 (0.0%)	1 (0.9%)
Currently Active, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of Other, N (%)	2 (3.6%)	8 (14.3%)	10 (9.0%)
Currently Active, N (%)	1 (1.8%)	6 (10.7%)	7 (6.3%)
Missing, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Excluding oral/genital ulcers
Source: FDA Statistical Reviewer

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

For the purpose of study analysis (not study conduct), compliance was defined as taking between 75% and 120% of intended study drug. One patient (2%) in the APR group took less than 75% of intended study drug.

Concomitant Medications/Procedures

Seven patients (13%) in the placebo group and one (2%) in the APR group received prohibited concomitant medication during the placebo-controlled period. During the placebo-controlled period, 85 (77%) patients received concomitant medications: 44 (79%) in the placebo group and 41 (75%) in the APR group. The most common medications were anti-inflammatory: 20 (36%) in the placebo group and 26 (47%) in the APR group, consisting of naproxen, meloxicam and flurbiprofen. Drospirenone w/ethinylestradiol was taken by 15 patients (27%) in the placebo group and 11 (20%) in the APR group. Paracetamol was taken by 11 patients (20%) in the placebo group and 7 (13%) in the APR group. Lansoprazole was taken by six patients (11%) in the placebo group and five (9%) in the APR group. The types of concomitant medications used were generally similar across treatment arms during the placebo-controlled period. In the Apremilast-exposure period , antibacterials for systemic use were mostly in the APR/APR group with 16 patients (32%), vs the PBO/APR group which had two patients (4%). Otherwise, concomitant medication use was consistent during the placebo-controlled period.

Seven patients had concomitant procedures in the placebo-controlled period, one (2%) in the placebo group (renal stone removal) and six (11%) in the APR group: one vaginal biopsy, one chest x-ray, one upper GI endoscopy, one electrocauterisation, one suture insertion, and one tooth extraction.

In the apremilast exposure period, there were six additional procedures in the APR/APR group: two colonoscopies, one endodontic procedure, one benign breast lump removal, one nuclear magnetic resonance imaging, and one tooth extraction. In the PBO/APR group, one patient had tooth extraction and polypectomy.

Table 5:Study 001, Concomitant Medication Use for Musculo-Skeletal System (Baseline and Placebo-Controlled Period)

Medication	Period	Apremilast (N = 55)	Placebo (N = 56)	Total (N = 111)
Naproxen Sodium	Baseline	5 (9.1%)	1 (1.8%)	6 (5.4%)
	Placebo-Controlled	9 (16.4%)	5 (8.9%)	14 (12.6%)
Meloxicam	Baseline	1 (1.8%)	1 (1.8%)	2 (1.8%)
	Placebo-Controlled	5 (9.1%)	4 (7.1%)	9 (8.1%)
Flurbiprofen	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	5 (9.1%)	3 (5.4%)	8 (7.2%)
Indometacin	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	2 (3.6%)	3 (2.7%)
Dexketoprofen Trometamol	Baseline	0 (0.0%)	1 (1.8%)	1 (0.9%)
	Placebo-Controlled	0 (0.0%)	3 (5.4%)	3 (2.7%)
Dexketoprofen	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	2 (3.6%)	0 (0.0%)	2 (1.8%)
Colchicine	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	1 (1.8%)	2 (1.8%)
Diclofenac Potassium	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	1 (1.8%)	2 (1.8%)
Etodolac	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	1 (1.8%)	2 (1.8%)
Ibuprofen	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	1 (1.8%)	2 (1.8%)
Camphor with Menthol	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Celecoxib	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Diclofenac Diethylamine	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Diclofenac Sodium	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Metaxalone	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Naproxen	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Piroxicam	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Thermo-Rheumon	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Trolamine Salicylate	Baseline	1 (1.8%)	0 (0.0%)	1 (0.9%)
	Placebo-Controlled	1 (1.8%)	0 (0.0%)	1 (0.9%)
Acemetacin	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	1 (1.8%)	1 (0.9%)
Fenyramidol	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	1 (1.8%)	1 (0.9%)
Lornoxicam	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Placebo-Controlled	0 (0.0%)	1 (1.8%)	1 (0.9%)
Parafon	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	0 (0.0%)	0 (0.0%)
Phenprobamate	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: FDA Statistical Reviewer

Table 6: Study 001, Concomitant Medication Use for Systemic Hormonal Preparations, Excluding Sex Hormones and Insulins (Baseline and Placebo-Controlled Period)

Medication	Period	Apremilast (N = 55)	Placebo (N = 56)	Total (N = 111)
Prednisone	Baseline	2 (3.6%)	0 (0.0%)	2 (1.8%)
	Placebo-Controlled	2 (3.6%)	1 (1.8%)	3 (2.7%)
Methylprednisolone	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	1 (1.8%)	1 (0.9%)
Prednisolone	Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Placebo-Controlled	0 (0.0%)	1 (1.8%)	1 (0.9%)

Source: FDA Statistical Reviewer

Efficacy Results – Primary Endpoint

The primary endpoint in study 001 was number of oral ulcers at Day 85. There was a statistically significant difference in this endpoint, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -1.6 oral ulcers (95% CI: -2.4 to -0.9) Table 7.

Table 7: Study 001, Number of Oral Ulcers at Day 85, LOCF, ITT

	Study 001	
	Apremilast (N =55)	Placebo (N = 56)
Adjusted number of oral ulcers at Day 85	0.4	2.0
Adjusted mean difference[a] (95% CI) p-value	-1.6 (-2.4 to -0.9) $p < 0.001$	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

The Agency's statistical reviewer conducted a *post-hoc* sensitivity analysis, in which a multiple imputation procedure was performed assuming that among those with the same treatment, gender, and baseline number of oral ulcers, missingness was at random (MAR). 25 multiply imputed datasets were generated for this analysis. For each multiply imputed dataset, a linear regression model was used, with Huber-White sandwich standard errors to relax the homoskedasticity assumption.

With this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -1.7 oral ulcers (95% CI: -2.5 to -0.8) Table 8.

Table 8: Study 001, Number of Oral Ulcers at Day 85, MI, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Adjusted number of oral ulcers at Day 85	0.4	2.1
Adjusted mean difference[a] (95% CI) p-value	-1.7 (-2.5 to -0.8) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Note: Huber-White sandwich standard errors were used to calculate the 95% confidence interval and p-value.
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

To assess the robustness of the MAR assumption in this analysis, a tipping point analysis was performed comparing apremilast to placebo, without adjusting for any covariates. The differences in mean outcome between the completers and non-completers were δ_a and δ_p for the apremilast and placebo arms, respectively. The results are shown in Table 9.

Table 9 : Study 001, Number of Oral Ulcers at Day 85, Tipping Point Analysis, ITT

		δ_a				
		0	1	2	3	4
δ_p	0	-1.6 (-2.5, -0.7) p < 0.001	-1.5 (-2.4, -0.6) p < 0.001	-1.4 (-2.3, -0.5) p = 0.001	-1.3 (-2.2, -0.4) p = 0.002	-1.2 (-2.2, -0.3) p = 0.004
	-1	-1.4 (-2.3, -0.5) p = 0.001	-1.3 (-2.2, -0.4) p = 0.002	-1.2 (-2.1, -0.3) p = 0.003	-1.1 (-2.1, -0.2) p = 0.007	-1.1 (-2.0, -0.1) p = 0.013
	-2	-1.2 (-2.1, -0.3) p = 0.004	-1.1 (-2.0, -0.2) p = 0.007	-1.0 (-1.9, -0.1) p = 0.012	-0.9 (-1.9, 0.0) p = 0.022	-0.9 (-1.8, 0.1) p = 0.038

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Note: Huber-White sandwich standard errors were used to calculate the 95% confidence interval and p-value.
Source: FDA Statistical Reviewer

This table demonstrates that for the results to tip from statistical significance to lack of statistical significance, the mean difference between non-completers and comparable completers in the apremilast arm would have to be 4 oral ulcers at Day 85, while simultaneously the mean difference between non-completers and comparable completers in the placebo arm would have to be -2 oral ulcers at Day 85. Though this tipping point analysis is slightly limited by the fact that it does not adjust for the same covariates as in the previous analysis, the results for this tipping point analysis lead the Agency's review team to conclude that the analyses of this endpoint are statistically robust with respect to violations of missingness mechanism assumptions.

Data Quality and Integrity

No clear issues were uncovered in data quality or data integrity.

Efficacy Results – Secondary and other relevant endpoints

The following results are from analyses of endpoints that were not included in the multiplicity control procedure.

Complete Response

Complete response was defined as not having oral ulcers at Day 85. The Clinical Study Report did not present results from a formal statistical comparison between apremilast and placebo, with respect to this endpoint. The unadjusted observed response rates were 70.9% and 28.6%, respectively (Table 10).

Table 10: Study 001, Complete Response, LOCF, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Unadjusted Complete Response Rate at Day 85	70.9%	28.6%
Adjusted mean difference[a] (95% CI)	Not Reported	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 001 CSR page 71

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. With this sensitivity analysis, the adjusted mean difference in complete response rates between apremilast and placebo was 42.3% (95% CI: 24.7% to 59.9%) (Table 11Table 11).

Table 11: Study 001, Complete Response, MI, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Adjusted Complete Response Rate at Day 85	69.9%	27.6%
Adjusted mean difference[a] (95% CI)	42.3% (24.7% to 59.9%)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Note: Huber-White sandwich standard errors were used to calculate the 95% confidence interval and p-value.
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

Partial Response

Partial response was defined as having a reduction of at least 50% in number of oral ulcers at Day 85, compared to the baseline number of oral ulcers. In the Clinial Study Report, the reported adjusted difference in partial response rates was 39.1% (95% CI: 23.6% to 54.5%) (Table 12).

Table 12: Study 001, Partial Response, LOCF, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Unadjusted Partial Response Rate at Day 85	70.9%	28.6%
Adjusted mean difference[a] (95% CI)	39.1% (23.6% to 54.5%)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 001 CSR page 71

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. With this sensitivity analysis, the adjusted mean difference in complete response rates between apremilast and placebo was 36.2% (95% CI: 19.7% to 52.8%) (Table 13).

Table 13: Study 001, Partial Response, MI, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Adjusted Partial Response Rate at Day 85	88.1%	51.9%
Adjusted mean difference[a] (95% CI)	36.2% (19.7% to 52.8%)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Note: Huber-White sandwich standard errors were used to calculate the 95% confidence interval and p-value.
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

Area Under the Curve (AUC) for Oral Ulcer Count From Day 1 to Day 85

In the Clinial Study Report, the reported adjusted difference in this endpoint was -90.1 (95% CI: -125.3 to -54.8) (Table 14).

Table 14: Study 001, AUC for Oral Ulcer Count From Day 1 to Day 85, LOCF, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Adjusted AUC for Oral Ulcer Count From Day 1 to Day 85	67.7	157.8
Adjusted mean difference[a] (95% CI)	-90.1 (-125.3 to -54.8)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 001 CSR page 73

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. With this sensitivity analysis, the adjusted mean difference between apremilast and placebo was -87.5 (95% CI: -122.7 to -52.4) (Table 15). A straightforward linear transformation provides

the following interpretation of these results: the adjusted mean difference between apremilast and placebo with respect to the 12-week average oral ulcer count is -1.0 (95% CI: -1.4 to -0.6).

Table 15: Study 001, AUC for Oral Ulcer Count From Day 1 to Day 85, MI, ITT

	Study 001	
	Apremilast (N = 55)	Placebo (N = 56)
Adjusted AUC for Oral Ulcer Count From Day 1 to Day 85	64.8	152.3
Adjusted mean difference[a] (95% CI)	-87.5 (-122.7 to -52.4)	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Note: Huber-White sandwich standard errors were used to calculate the 95% confidence interval and p-value.
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

Dose/Dose Response

Dose response was not evaluated in study 001.

Durability of Response

The study was not designed for controlled evaluations of the durability of response with apremilast.

Persistence of Effect

There are no data to support a persistence of effect after treatment discontinuation.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Analyses of secondary or exploratory COA (PRO) endpoints were not performed, beyond what is described above.

Additional Analyses Conducted on the Individual Trial

The results of the sample estimates (with respect to AUC for Oral Ulcer Count From Day 1 to Day 85) of treatment effects in subgroups are presented in Table 16. The sample sizes were not sufficient to conduct multi-way subgroup analyses. Therefore, results were presented for marginal subgroups. These subgroup analysis results by demographic subgroups were largely consistent with findings in the overall population.

Table 16: Subgroup Analysis for Gender, Region, Age, and Race, for AUC for Number of Oral Ulcers from Day 1 to Day 85

Subgroup	N	Sample Treatment Effect Estimate (95% CI)
Overall	111	-87.5 (-122.7 to -52.4)
Female	77	-93.2 (-135.1 to -51.3)
Male	34	-74.6 (-139.2 to -10.0)
USA	8	-87.3 (-232.0 to 57.3)
Turkey	103	-87.7 (-124.4 to -51.0)
< 40 Years Old	77	-76.8 (-119.0 to -34.6)
≥ 40 Years Old	34	-115.5 (-179.6 -51.4)
White	108	-87.8 (-123.7 to -52.0)
Other Race	3	-42.4 (-277.5 to 192.8)

Abbreviations: CI = confidence interval
Source: FDA Statistical Reviewer

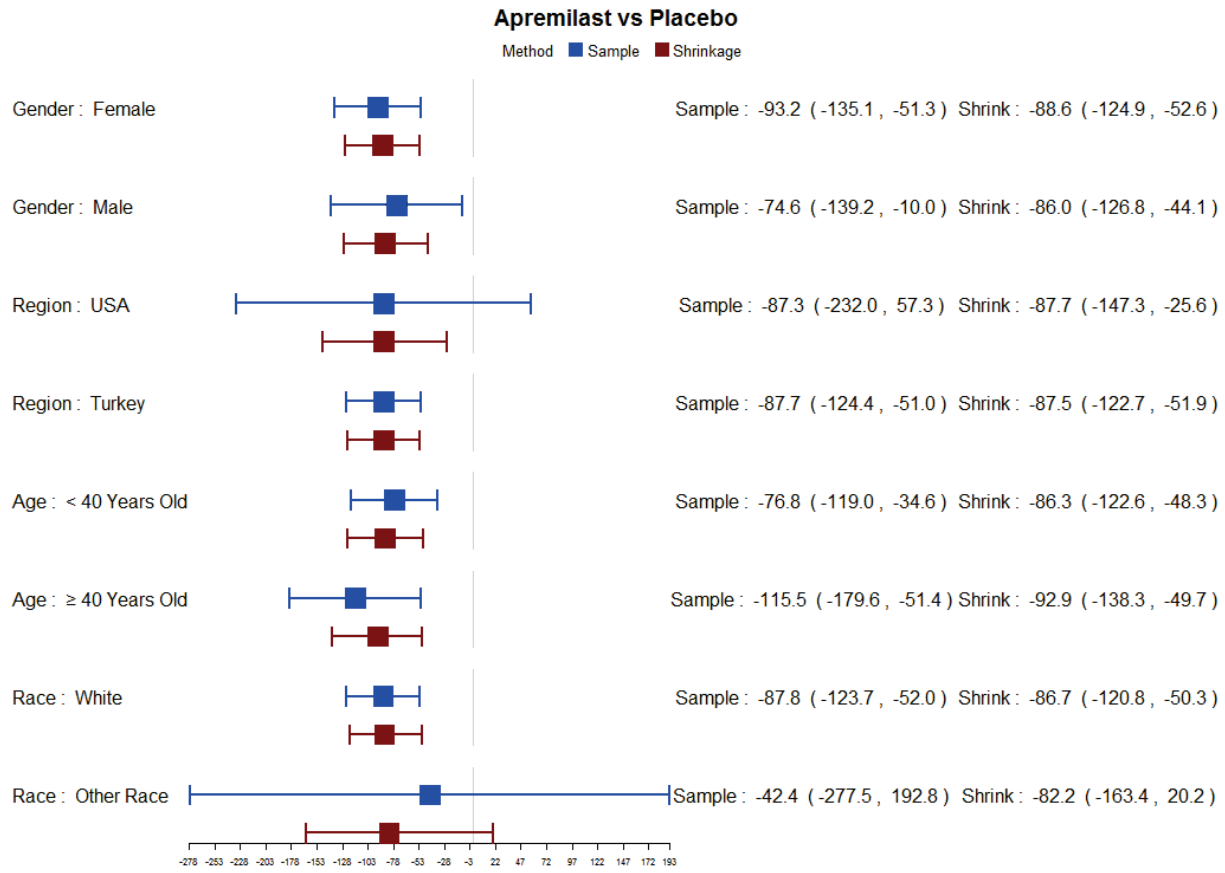
In the traditional subgroup analyses, there were random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. Therefore, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates in Table 16. The total variability in the sample estimates is the sum of the within-subgroup variability of the sample estimator and the across-subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. The greater the ratio is, the smaller the weight on the overall estimate (the less the shrinkage). The same flat prior distribution was used to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i \in \{1, 2, \dots\}$, Y_i represents the observed sample estimate of treatment effect in subgroup level i, assuming $Y_i \sim N(\mu_i, \sigma_i^2)$, where

- σ_i^2 are the observed values of the variance for the subgroup sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(-100, 90000)$, ${}^{1}/_{\tau^2} \sim Gamma(0.001, 0.001)$

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in Figure 1.

Figure 1: Study 001 Subgroup Analysis for Gender, Region, Age, and Race, for AUC for Number of Oral Ulcers from Day 1 to Day 85



Abbreviations: Shrink = Shrinkage
Source: FDA Statistical Reviewer

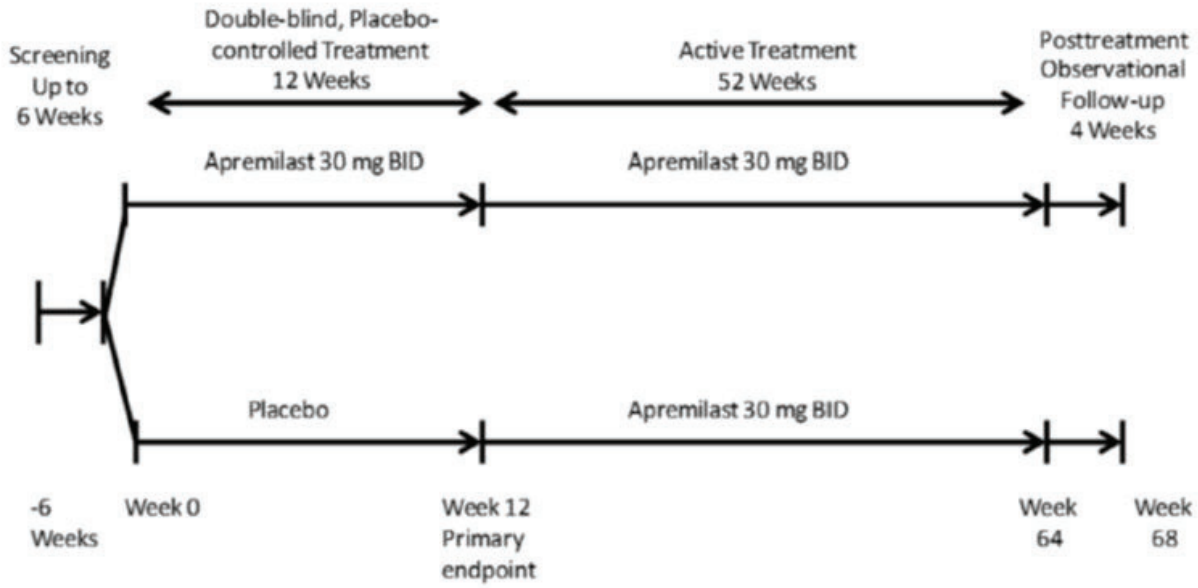
8.1.4. Study BCT-002

Trial Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, followed by an active treatment phase in patients with active BD. The primary objective of the study was to evaluate the efficacy of apremilast in the treatment of oral ulcers in active BD. Randomization was stratified by gender, history of uveitis, and region (Japan and Other). The treatment duration was 64 weeks, which consisted of a 12 week placebo-controlled period followed by a 52 week active treatment phase. There was also a four week posttreatment observational follow-up phase.

There were 207 patients randomized 1:1 to apremilast 30 mg twice daily or placebo after dose escalation as per label. During Weeks 12 to 64, all patients received apremilast 30 mg twice daily. During Weeks 12 to 64, the investigational product (IP) remained blinded, to prevent

study personnel and patients from knowing the IP assignment in the placebo-controlled treatment phase. To maintain the blind regarding the initial treatment assignment, all patients received dose titration cards at Visit 9. Although only patients initially randomized to placebo were dose titrated during their first week of the active treatment phase, all patients entering this phase received identically-appearing titration/treatment cards.



BID = twice daily.

Trial location

The study was conducted at 53 sites in Europe (France, Germany, Greece, and Italy), Asia (Japan and the Republic of Korea), the United States, and the rest of the world (Israel, Lebanon, and Turkey).

Diagnostic criteria

The diagnosis was based on the International Study Group Criteria For The Diagnosis Of Behçet's Disease (1990)--the same as in study BCT-001.

Inclusion

1) Males and Females ≥18 years old
2) Females of childbearing potential (FCBP) had to have a negative urine pregnancy test at visits 1 and 2. In addition, FCBP who engaged in activity in which conception was possible had to use contraception while on study drug and for at least 28 days after the last dose of study drug: one highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy OR Male or female condom (latex condom or non-latex condom NOT made out of natural [animal] membrane); PLUS one additional barrier

method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide

3) Male patients (including those who had a vasectomy) who engaged in activity in which conception was possible had to use barrier contraception (latex or non-latex condoms) NOT made out of natural [animal] membrane) while on IP and for at least 28 days after the last dose of IP
4) Met the international study group criteria for BD
5) Laboratory criteria: Hemoglobin > 9 g/dL; White blood cell count ≥ 3000 /uL (≥ 3.0 X 10^9/L) and <14,000/uL (>14 X 10^9/L); Platelet count ≥ 100,000 /uL (≥ 100 X 10^9/L); Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L); Total bilirubin < 2.0 mg/dL; Aspartate transaminase and alanine transaminase <1.5 times upper limit of normal
6) Oral ulcers that occurred at least three times in the previous 12-month period, including oral ulcers at the Screening Visit
7) Had at least two oral ulcers at Visit 1 (Screening Visit), and:
   a) at least two oral ulcers at Visit 2 (day of randomization), when Visit 2 occurs at least 14 days after Visit 1, or
   b) at least three oral ulcers at Visit 2, when Visit 2 occurs at any time between 1 day and 42 days after Visit 1
8) Candidate for systemic therapy, for the treatment of oral ulcers
9) Had prior treatment with at least one non-biologic BD therapy, such as, but not limited to, topical corticosteroids, or systemic treatment

<u>Exclusion</u>

1) Pregnant or breast feeding
2) Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study or places the patient at unacceptable risk if he/she were to participate in the study
3) Systemic or opportunistic fungal infection
4) Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections
5) Clinically significant abnormality on chest x-ray or 12-lead ECG at screening
6) Prior history of suicide attempt at any time in the patient's lifetime prior to Visit 2 (Baseline Visit; day of randomization) or major psychiatric illness requiring hospitalization within three years prior to Visit 2
7) History of human immunodeficiency virus infection or congenital or acquired immunodeficiency
8) Malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas skin or treated (ie, cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within the previous five years of Visit 1
9) Behçet's Disease-related active major organ involvement, including: pulmonary, central nervous system, vascular, GI involvement, and ocular lesions (eg, uveitis) requiring immunosuppressive therapy; however: Previous major organ involvement is allowed if it

occurred at least one year prior to Visit 1 (Screening Visit) and is not active at time of enrollment

Patients with mild BD-related ocular lesions not requiring systemic immunosuppressive therapy were allowed. Patients with BD-related arthritis and BD-skin manifestations were also allowed

10) Previous exposure to biologic therapies for the treatment of BD oral ulcers, but previous biologic therapy exposure is allowed for other indications, including other manifestations of BD
11) Prior use of apremilast
12) Use of any investigational medication within four weeks prior to Visit 2 or five pharmacokinetic/pharmacodynamic half-lives (whichever is longer)
13) Current use of strong cytochrome P450 enzyme inducers
14) Having received intra-articular or parenteral corticosteroids within six weeks prior to Visit 2
15) Having received concomitant immune modulating therapy (except oral or topical corticosteroids) within:

- Seven days prior to Visit 2 (Baseline Visit; day of randomization) for colchicine
- Ten days prior to Visit 2 for azathioprine and mycophenolate mofetil
- Four weeks prior to Visit 2 for cyclosporine, methotrexate, cyclophosphamide, thalidomide, and dapsone
  Note: Oral and topical corticosteroids must have been tapered as appropriate and discontinued prior to the day of Visit 2
- At least five terminal half-lives for all biologics, including, but not limited to, those listed below; within:
  -Four weeks prior to Visit 2 for etanercept
  -Eight weeks prior to Visit 2 for infliximab
  -Ten weeks prior to Visit 2 for adalimumab, golimumab, certolizumab, abatacept, and tocilizumab
  -Six months prior to Visit 2 for secukinumab

Patient discontinuation criteria

The following events were considered sufficient reasons for discontinuing a patient from the investigational product and/or from the study: adverse event, lack of efficacy, non-compliance with IP, withdrawal by patient, death, lost to follow-up, and protocol violation.

Permitted Concomitant Medications

- Corticosteroid eye drops for BD-related or other ocular diseases were allowed at any time during this study
- Oral/topical analgesics (lidocaine gel), chlorhexidine, used according to product prescribing information, were allowed throughout the study except for 24 hours prior to clinic visits to avoid interference with the pain assessments of oral or genital ulcers
- Use of topical corticosteroids for ulcers and skin disease were allowed until the day

of randomization AND/OR after the Week 12 visit (Visit 9) and assessments for any non-responders (patients who fail to achieve at least a partial response (≥ 50% improvement [reduction] in the number of oral ulcers from baseline)

- Use of colchicine was allowed at any time after the Week 12 visit and assessments for any non-responders or for any patients who experience a worsening of BD
- Patients could take any medication that was not restricted by the protocol or that did not confound the efficacy and safety assessments in the study

Prohibited Concomitant Medications

- Topical corticosteroids for ulcers and skin disease during the first 12 week placebo-controlled treatment phase of the study (through Visit 9)
- Use of colchicine during the 12-week placebo-controlled treatment phase of the trial
- Systemic therapy, other than colchicine, including, but not limited to, systemic corticosteroids (including low doses), cyclosporine, methotrexate, cyclophosphamide, hydroxychloroquine, thalidomide, dapsone, azathioprine, and mycophenolate mofetil for the treatment phases of the study
- Biologic agents, including, but not limited to, adalimumab, infliximab, etanercept, and rituximab for the treatment phases of the study

Study Endpoints

The primary endpoint was the area under the curve (AUC) for the number of oral ulcers from baseline through Week 12.

The secondary endpoints were:

1) Complete response rate for oral ulcers at Week 12 (defined as the proportion of patients who were oral ulcer-free)
2) Change from baseline in the pain of oral ulcers as measured by visual analog scale at Week 12
3) Complete response rate for genital ulcers at Week 12 for patients who had genital ulcers at baseline (defined as the proportion of patients who were genital ulcer-free)
4) Change from baseline in the pain of genital ulcers, as measured by VAS at Week 12 in patients who had genital ulcers at baseline
5) Change from baseline in disease activity as measured by Behçet's Disease Current Activity Scores (BD Current Activity Form [BDCAF]) at Week 12
6) Change from baseline in the BD QoL score at Week 12
7) Change from baseline in Behçet's Syndrome Activity Score (BSAS) at Week 12
8) Time to oral ulcer resolution (complete response), i.e., the first instance when a patient had a complete response, during the placebo-controlled treatment phase
9) Proportion of patients with no oral ulcers following complete response, i.e., the first time when a patient had a complete response, during the placebo-controlled treatment phase

10) Number of oral ulcers following loss of complete response, i.e., the first instance when a patient had a reappearance of oral ulcers following a complete response, during the placebo-controlled treatment phase
11) Time to recurrence of oral ulcers following loss of complete response, i.e., the first instance when a patient had a reappearance of oral ulcers following a complete response, during the placebo-controlled treatment phase
12) Change from baseline in the total score of the static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis, and erythema nodosum) of BD at Week 12 in patients who had BD skin lesions at baseline
13) Proportion of patients achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after start of dosing, and who remained oral ulcer-free for at least six additional weeks during the 12-week placebo-controlled treatment phase

The safety endpoints were safety and tolerability, as defined by the following: type, frequency, severity, and relationship of AEs to apremilast, number of patients who prematurely discontinued investigational product (IP) due to any AE, and frequency of clinically significant changes in vital signs and/or laboratory findings.

Statistical Analysis Plan

Analysis Populations

The following analysis populations were defined in the Statistical Analysis Plan (SAP):

- Intent-to-Treat Population: This population included all randomized patients who received at least one dose of investigational product. As stated in the SAP, this population was to be used for the primary efficacy analysis. Patients were to be analyzed as randomized.
- Per-Protocol Population: This population included all randomized patients who received at least one dose of study medication, had a baseline oral ulcer evaluation, had at least one post-treatment oral ulcer evaluation, and had no important protocol violations during the 12-week placebo-controlled period.
- Safety Population: This population included all randomized patients who received at least one dose of investigational product. Patients were to be analyzed as treated.
- Apremilast Subjects as Treated Population: This population included all randomized patients who received apremilast at randomization or were switched to apremilast. Patients would be analyzed according to treatment sequence received.

Estimands

Estimands were not defined in the SAP.

Primary Endpoint

The primary endpoint was area under the curve (AUC) for the number of oral ulcers from baseline through Week 12. To evaluate the primary endpoint, an Analysis of Covariance (ANCOVA) model was to be used, including the following variables in the model: treatment, gender, region, and number of oral ulcers at baseline. The test for a treatment effect difference was to be performed at a two-sided significance level of 0.05.

For any missingness patterns that were not monotone, a Markov Chain Monte Carlo (MCMC) with a single chain method was to be used to impute sufficient missing oral ulcer counts by treatment to make 25 datasets having monotone patterns only. Imputed values that were negative were to be set to zero. Then, for monotone missingness patterns, a predictive mean matching method with treatment, sex, region, and oral ulcer counts from previous visits as covariates was to be used to impute the remaining missing oral ulcer counts to make datasets complete.

Multiplicity Control Procedure

To control the study-wise type I error rate, a hierarchical testing procedure was to be used. First, the primary endpoint was to be tested at the two-sided significance level of 0.05. If results for the primary analysis of this endpoint were found to be statistically significant, the first secondary efficacy endpoint was to be tested at the same significance level. If the primary analysis for this endpoint were also found to be statistically significant, the next secondary efficacy endpoint was to be tested at the same significance level, and so on. If at any point in the testing procedure, primary analysis results for any key efficacy endpoint were not found to be statistically significant, formal hypothesis testing would not be performed for any remaining endpoints in the analysis hierarchy. The order in which the key efficacy endpoints were to be tested is the following:

- AUC for the number of oral ulcers from baseline through Week 12
- Change from baseline in the pain of oral ulcers as measured by VAS at Week 12
- Change from baseline in Behçet's Syndrome Activity Score (BSAS) at Week 12
- Change from baseline in disease activity as measured by Behçet's Disease Current Activity scores (BD Current Activity Form) at Week 12
- Proportion of subjects achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after start of dosing, and who remain oral ulcer free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase
- Time to oral ulcer resolution (complete response), i.e., the first instance when a subject has a complete response, during the Placebo-controlled Treatment Phase
- Complete response rate for oral ulcers at Week 12
- Change from baseline in the BD QoL score at Week 12
- Complete response rate for genital ulcers at Week 12 for subjects who had genital ulcers at baseline

- Proportion of subjects with no oral ulcers following complete response, i.e., the first time when a subject has a complete response, during the Placebo-controlled Treatment Phase
- Time to recurrence of oral ulcers following loss of complete response, i.e., the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase
- Number of oral ulcers following loss of complete response, i.e., the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase
- Change from baseline in the total score of the Static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis and erythema nodosum) of BD at Week 12 in subjects who had BD skin lesions at baseline
- Change from baseline in the pain of genital ulcers as measured by VAS at Week 12 in subjects who had genital ulcers at baseline

Note that some of the endpoints in the analysis hierarchy conditioned on post-randomization variables. Results from analyses of such endpoints are generally difficult to interpret.

Key Secondary Endpoints

For binary endpoints, a CMH test was used, adjusting for gender and region. Non-responder imputation was used for missing data, except for secondary endpoint #13 in the Study Endpoints section above. For this endpoint, a LOCF approach was used for missing numbers of oral ulcers.

For continuous endpoints, an ANCOVA model was used, adjusting for treatment, gender, region, and baseline value. A LOCF approach was used for missing data.

A stratified log-rank test was used to evaluate time-to-event endpoints. The reported hazard ratios and associated 95% confidence intervals were calculated using a stratified Cox proportional hazards model. Stratification for the log-rank tests as well as the Cox proportional hazards models were done on gender and region. The Cox proportional hazards models also included baseline number of oral ulcers as a covariate.

Note that since it is difficult to interpret endpoints that condition on post-randomization events (such as secondary endpoints #9, 10, and 11 as described above), their results are not discussed in this review.

Safety

In general, safety analyses were descriptive in nature. No inferential statistical testing was planned for the safety data.

Protocol Amendments

Protocol Amendment 1 on February 2, 2016 allowed for inclusion of potential patients who had been previously exposed to biologic therapies for indications other than oral ulcers, including other manifestations of Behçet's Disease. In addition, it allowed patients to continue taking colchicine until seven days prior to randomization instead of at least four weeks prior to randomization. The amendment also allowed for tapering of topical and oral corticosteroids and subsequent discontinuation close to the day of randomization. Additionally, there was a clarification for the required number of oral ulcers as per the inclusion criteria. Finally, on the Static Physician's Global Assessment of Skin Lesions, the scoring of the number of nodules/ lesions was changed from one anatomical site at a time to any anatomical site with respect to the whole body.

The changes contained in this protocol amendment are not expected to have had an impact on the assessment of efficacy or safety.

8.1.5. Study Results BCT-002

Compliance with Good Clinical Practices

This trial was conducted in accordance with the ethical principles of Good Clinical Practice.

Financial Disclosure

One investigator in Study BCT-002 had disclosable financial interests/arrangements. (b) (6) (b) (6) . As defined in 21 CFR 54.2(f), the Significant payments of other sorts made to (b) (6) from 2016-2018 include a total of $169,149.82. (b) (6) . The steps taken to minimize the potential bias of clinical study results include the clinical trial design being placebo-controlled, randomized, and double-blind. The primary endpoint of this study was the area under the curve at Week 12 (AUC_{W0-12}) for the number of oral ulcers, which was calculated utilizing objective oral ulcer counts at each study visit from baseline through Week 12. (b) (6) (b) (6) . Given that no patients from this site were included in the study, the disclosable financial interests/arrangements did not have any impact on the study.

Patient Disposition

A total of 282 patients were screened for inclusion in this study, of whom 207 were randomized 1:1 to APR (104) or placebo (103) and were included in the ITT population. A total of 179 (86%) patients completed the placebo-controlled treatment phase . A higher proportion of patients in the APR treatment group compared with placebo completed the placebo-controlled treatment phase (92% versus 81%, respectively). The most frequently cited reasons for study discontinuation in the APR group and the placebo group were patient withdrawal (4% and 5%, respectively), AEs (3% and 4%, respectively), and lack of efficacy (0% and 8%, respectively). There were 178 patients who completed the placebo-controlled treatment phase (Week 12) and entered the active treatment phase (Weeks 12 to 64). One patient in the APR group withdrew. Of the 178 patients who entered the active treatment phase, 143 (80%) completed the active treatment phase and 35 (20%) discontinued treatment early.

Protocol Violations/Deviations

Compliance with applicable international GCP standards or relevant Celgene policies and procedures were identified. In the first incident, the treatment assignments for five patients were inadvertently unblinded due to vendor error, resulting from the inclusion of a "Randomized Treatment" field in a blinded Patient Summary Report. In the second incident, the treatment assignments for 20 patients were inadvertently unblinded due to several study team members receiving unblinded ad hoc serious adverse event (SAE) reconciliation listings from Celgene Drug Safety. In this case, the two unblinded data managers and an unblinded programmer were removed from the study and replaced. These departures likely did not impact data analysis, or the interpretation of study results.

During the placebo-controlled period (ITT population), there were eight (8%) protocol violations in the placebo group and four (4%) in the APR group. Three of the patients in the APR group and two in the placebo group had problems with inclusion/exclusion criteria. Two patients in the placebo group and one in the APR group had issues with IP compliance. During the placebo-controlled period, 87 (84%) patients in the placebo group and 78 (75%) patients in the APR group had at least one protocol deviation. The most frequently reported protocol deviations were related to study procedures/assessments, visit scheduling, IP issues/IP compliance, and informed consent issues (e.g., patients did not sign the most current version of the ICF). The deviations were similar between the treatment groups except that IP issues/IP compliance were greater in the placebo group: 35 (34%) patients versus 23 (22%) of patients in the APR group.

During the active treatment phase , there were more protocol violations in the PBO/APR group seven (8%) of patients versus the APR/APR group two (2%) of patients. There were 70 (84%) patients in the PBO/APR group and 83 (87%) patients in the APR/APR group who had at least one protocol deviation. The most frequently reported protocol deviations were consistent with the placebo-controlled phase and were generally balanced between the treatment arms except for concomitant medication, which was reported in 12 (14%) of the PBO/APR patients and 11 (12%) of the APR/APR patients.

There was no protocol deviation that had a potential impact on the analyses.

Table 17: Demographic Characteristics for Study BCT-002

Demographic Parameters	**Study BCT-002** (N=207)	
	Placebo (N= 103) n (%)	APR 30 BID (N=104) n (%)
Sex		
Male	40 (38.8)	40 (38.5)
Female	63 (61.2)	64 (61.5)
Age		
Mean years (SD)	40.6 (12.7)	39.4 (12.1)
Median (years)	40	37
Min, max (years)	19, 72	20, 67
Age Group		
< 40 years	45 (43.7)	58 (55.8)
≥ 40 to < 65	54 (52.4)	43 (41.3)
≥ 65 years	4 (3.9)	3 (2.9)
Race		
White	68 (66.0)	69 (66.3)
Black or African American	0	1 (1.0)
Asian	30 (29.1)	32 (30.8)
American Indian or Alaska Native	1 (1.0)	0
Native Hawaiian or Other Pacific Islander	1 (1.0)	0
Not Collected or Reported	3 (2.9)	2 (1.9)
Ethnicity		
Hispanic or Latino	3 (2.9)	2 (1.9)
Not Hispanic or Latino	100 (97.1)	102 (98.1)
Region		
North America	11 (10.7)	14 (13.5)
Europe	27 (26.2)	25 (24.0)
Asia	29 (28.2)	32 (30.8)
Rest of the World	36 (35.0)	33 (31.7)
Weight (kg)		
Mean (SD)	69.98 (16.4)	66.41 (16.0)
Median	68.00	63.25
(Min, Max)	(39.6, 120.0)	(40.0, 117.8)

Adapted from Study BCT-002 CSR Table 10

In Table 17, you can see the Demographic Characteristics for Study BCT-002. The sex, age and race, ethnicity and region were generally similar between the treatment groups and representative of the expected patient population for BD.

Other Baseline Characteristics

Clinical disease characteristics at baseline are shown in Table 18. There were more patients with a history of arthritis in the placebo group. The overall history and current activity of the BD manifestations were comparable between the treatment groups and representative of a patient population with active BD.

Table 18: Study 002, Baseline Disease Characteristics

Disease Characteristic	Apremilast (N = 104)	Placebo (N = 103)	Total (N = 207)
Duration of BD in years[1], mean (sd)	6.7 (7.4)	6.9 (8.0)	6.8 (7.7)
Recurrent Oral Aphthous Ulceration, N (%[2])	104 (100.0%)	103 (100.0%)	207 (100.0%)
Currently Active, N (%[3])	104 (100.0%)	103 (100.0%)	207 (100.0%)
Genital Ulcers, N (%[2])	96 (92.3%)	91 (88.3%)	187 (90.3%)
Currently Active, N (%[3])	18 (18.8%)	18 (19.8%)	36 (19.3%)
Acne-Like Lesions, N (%[2])	1 (1.0%)	1 (1.0%)	2 (1.0%)
Currently Active, N (%[3])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acneiform Lesions/Acne-Like Lesions, N (%[2])	50 (48.1%)	42 (40.8%)	92 (44.4%)
Currently Active, N (%[3])	35 (70.0%)	25 (59.5%)	60 (65.2%)
Erythema Nodosum, N (%[2])	41 (39.4%)	40 (38.8%)	81 (39.1%)
Currently Active, N (%[3])	15 (36.6%)	16 (40.0%)	31 (38.3%)
Folliculitis, N (%[2])	2 (1.9%)	0 (0.0%)	2 (1.0%)
Currently Active, N (%[3])	2 (100.0%)	--	2 (100.0%)
Papulopustular Lesions, N (%[2])	36 (34.6%)	32 (31.1%)	68 (32.9%)
Currently Active, N (%[3])	10 (27.8%)	17 (53.1%)	27 (39.7%)
Pathergy Test (Positive), N (%[2])	23 (22.1%)	19 (18.4%)	42 (20.3%)
Currently Active, N (%[3])	6 (26.1%)	3 (15.8%)	9 (21.4%)
Subcutaneous Thrombophlebitis, N (%[2])	3 (2.9%)	4 (3.9%)	7 (3.4%)
Currently Active, N (%[3])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other Skin Disease Characteristics, N (%[2])	4 (3.8%)	2 (1.9%)	6 (2.9%)
Currently Active, N (%[3])	2 (50.0%)	1 (50.0%)	3 (50.0%)
Arthralgia, N (%[2])	65 (62.5%)	72 (69.9%)	137 (66.2%)
Currently Active, N (%[3])	41 (63.1%)	50 (69.4%)	91 (66.4%)
Arthritis with Ankylosis, N (%[2])	1 (1.0%)	2 (1.9%)	3 (1.4%)
Currently Active, N (%[3])	1 (100.0%)	1 (50.0%)	2 (66.7%)
Arthritis without Ankylosis, N (%[2])	18 (17.3%)	27 (26.2%)	45 (21.7%)
Currently Active, N (%[3])	8 (44.4%)	9 (33.3%)	17 (37.8%)
Fibromyalgia, N (%[2])	4 (3.8%)	4 (3.9%)	8 (3.9%)
Currently Active, N (%[3])	3 (75.0%)	3 (75.0%)	6 (75.0%)
Myalgia, N (%[2])	9 (8.7%)	7 (6.8%)	16 (7.7%)
Currently Active, N (%[3])	4 (44.4%)	5 (71.4%)	9 (56.3%)
Other Musculoskeletal Disease Characteristics, N (%[2])	3 (2.9%)	2 (1.9%)	5 (2.4%)
Currently Active, N (%[3])	2 (66.7%)	0 (0.0%)	2 (40.0%)
Anterior Uveitis, Iridocyclitis, N (%[2])	10 (9.6%)	10 (9.7%)	20 (9.7%)
Currently Active, N (%[3])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Posterior Uveitis, N (%[2])	3 (2.9%)	4 (3.9%)	7 (3.4%)
Currently Active, N (%[3])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other Ocular Disease Characteristics, N (%[2])	5 (4.8%)	6 (5.8%)	11 (5.3%)
Currently Active, N (%[3])	0 (0.0%)	1 (16.7%)	1 (9.1%)
Behçet's Disease-related Headache, N (%[2])	10 (9.6%)	6 (5.8%)	16 (7.7%)
Currently Active, N (%[3])	5 (50.0%)	5 (83.3%)	10 (62.5%)
Stroke-Like Symptoms, N (%[2])	1 (1.0%)	0 (0.0%)	1 (0.5%)
Currently Active, N (%[3])	0 (0.0%)	--	0 (0.0%)
Aneurysms, N (%[2])	1 (1.0%)	0 (0.0%)	1 (0.5%)
Currently Active, N (%[3])	0 (0.0%)	--	0 (0.0%)
Thrombophlebitis, N (%[2])	1 (1.0%)	1 (1.0%)	2 (1.0%)
Currently Active, N (%[3])	0 (0.0%)	1 (100.0%)	1 (50.0%)

[1]Computed using data from 103 of the patients in the Apremilast arm and 102 of the patients in the Placebo Arm
[2]Percent of randomized patients
[3]Percent of randomized patients with disease characteristic
Source: FDA Statistical Reviewer

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Compliance was defined as taking between 75% and 120% of dispensed IP. This definition of compliance was only for the purpose of study analysis, not study conduct. In the placebo-controlled period, 100% of patients in the APR treatment group and 94% of patients in the placebo treatment group were considered treatment compliant.

During the apremilast-exposure period, 96% of patients overall were treatment compliant, including 97% of patients in the APR 30 BID/APR 30 BID treatment group and 95% of patients in the placebo/APR 30 BID treatment group.

Concomitant Medications
Overall, 83% of patients in the APR 30 BID treatment group and 83% of patients in the placebo treatment group reported concomitant medication use during the placebo-controlled period. The most commonly used concomitant medication was paracetamol in both the APR treatment group (20%) and the placebo treatment group (16%); all other concomitant medications were in less than 10% of patients.

Concomitant Procedures
Concomitant procedures during the placebo-controlled period were reported in eight (8%) of patients in the APR treatment group and seven (7%) of patients in the placebo group.

Concomitant procedures were reported in a total of 20% of patients during the active treatment phase, including 22% of patients in the APR 30 BID/APR 30 BID treatment group and 17% of patients in the placebo/APR 30 BID treatment group.

The reported individual concomitant procedures were comparable between the two groups.

Efficacy Results – Primary Endpoint

The primary endpoint in study 002 was AUC for number of oral ulcers from baseline until Day 85. There was a statistically significant difference in this endpoint, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -89.5 (95% CI: -126.4 to -52.6) (Table 19). A straightforward linear transformation provides the following interpretation of these results: the adjusted mean difference between apremilast and placebo with respect to the 12-week average oral ulcer count is -1.1 (95% CI: -1.6 to -0.7).

Table 19: Study 002, AUC for Number of Oral Ulcers from Baseline Until Day 85, MI, ITT

	Study 002	
	Apremilast (N = 104)	Placebo (N = 103)
Adjusted AUC	130.4	219.9
Adjusted mean difference[a] (95% CI) p-value	-89.5 (-126.4 to -52.6) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

To assess the robustness of the MAR assumption in this analysis, a tipping point analysis was performed comparing apremilast to placebo. For monotone missingness patterns within each arm, the number of oral ulcers at a given visit was assumed to be δ higher, on average, compared to the average number of observed ulcers at that visit among similar patients. The imputed number of oral ulcers was bounded below by zero. δ_a and δ_p correspond to the apremilast and placebo arms, respectively. After shifting the monotone imputed values, the same statistical model as in the primary analysis was fit to each imputed dataset. The results are shown in Table 20.

Table 20: Study 002, AUC for Number of Oral Ulcers from Baseline Until Day 85, Tipping Point Analysis, MI, ITT

		δ_a					
		0	1	2	3	4	5
δ_p	0	-89.5 (-126.4, -52.6) p < 0.001	-86.3 (-123.1, -49.4) p < 0.001	-83.0 (-119.9, -46.1) p < 0.001	-79.7 (-116.9, -42.5) p < 0.001	-76.5 (-114.1, -38.8) p < 0.001	-73.2 (-111.4, -35.0) p < 0.001
	-1	-82.7 (-119.3, -46.2) p < 0.001	-79.5 (-115.9, -43.0) p < 0.001	-76.2 (-112.8, -39.6) p < 0.001	-72.9 (-109.8, -36.1) p < 0.001	-69.6 (-107.0, -32.3) p < 0.001	-66.4 (-104.3, -28.5) p = 0.001
	-2	-77.0 (-113.4, -40.7) p < 0.001	-73.8 (-110.0, -37.5) p < 0.001	-70.5 (-106.9, -34.1) p < 0.001	-67.2 (-103.9, -30.5) p < 0.001	-64.0 (-101.1, -26.8) p = 0.001	-60.7 (-98.4, -22.9) p = 0.002
	-3	-72.7 (-108.9, -36.6) p < 0.001	-69.5 (-105.6, -33.4) p < 0.001	-66.2 (-102.4, -30.0) p < 0.001	-62.9 (-99.5, -26.4) p = 0.001	-59.7 (-96.7, -22.7) p = 0.002	-56.4 (-94.0, -18.8) p = 0.003
	-4	-69.6 (-105.7, -33.6) p < 0.001	-66.4 (-102.4, -30.4) p < 0.001	-63.1 (-99.2, -27.0) p = 0.001	-59.8 (-96.3, -23.4) p = 0.001	-56.6 (-93.5, -19.6) p = 0.003	-53.3 (-90.9, -15.7) p = 0.005
	-5	-67.4 (-103.4, -31.5) p < 0.001"	-64.2 (-100.1, -28.3) p < 0.001	-60.9 (-97.0, -24.8) p = 0.001	-57.6 (-94.0, -21.3) p = 0.002	-54.4 (-91.2, -17.5) p = 0.004"	-51.1 (-88.6, -13.6) p = 0.008

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
Source: FDA Statistical Reviewer

The results did not tip from statistical significance to lack of statistical significance, in any of the scenarios considered in this table. The results for this tipping point analysis lead the Agency's

review team to conclude that the analyses of this endpoint are statistically robust with respect to violations of missingness mechanism assumptions.

Data Quality and Integrity

No clear issues were uncovered in data quality or data integrity.

Efficacy Results – Secondary and other relevant endpoints

The results for the key secondary endpoints are presented in the order in which they were analyzed, according to the prespecified hierarchical testing procedure.

Change from Baseline in Oral Ulcer Pain Visual Analog Scale

In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -24.8 (95% CI: -32.8 to -16.8) (Table 21).

Table 21: Study 002, Change from Baseline in Oral Ulcer Pain Visual Analog Scale, LOCF, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=102)
Adjusted Change from Baseline	-40.7	-15.9
Adjusted mean difference[a] (95% CI) p-value	-24.8 (-32.8 to -16.8) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 002 CSR page 94

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. For each imputed dataset, a linear regression model was fit, adjusting for gender, region, and baseline score, and used Huber-White sandwich estimates for the standard errors. In this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -24.2 (95% CI: -32.8 to -15.6) (Table 22).

Table 22: Study 002, Change from Baseline in Oral Ulcer Pain Visual Analog Scale, MI, ITT

	Study 002	
	Apremilast (N=104)	Placebo(N=102)
Adjusted Change from Baseline[a]	-42.1	-17.9
Adjusted mean difference[bc] (95% CI)[bd] p-value[bd]	-24.2 (-32.8 to -15.6) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
[a]Least squares means based on a linear regression model adjusting for gender, region, and baseline score.
[b]Calculated using the aforementioned linear regression model.
[c]Apremilast minus Placebo
[d]Calculated using Huber-White sandwich standard errors.
Source: FDA Statistical Reviewer

Change From Baseline in Behçet's Syndrome Activity Scores

In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was -11.9 (95% CI: -16.2 to -7.7) (Table 23).

Table 23: Study 002, Change From Baseline in Behçet's Syndrome Activity Scores, LOCF, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=103)
Adjusted Change from Baseline	-17.4	-5.4
Adjusted mean difference[a] (95% CI) p-value	-11.9 (-16.2 to -7.7) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 002 CSR page 105

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. For each imputed dataset, a linear regression model was fit, adjusting for gender, region, and baseline score, and used Huber-White sandwich estimates for the standard errors. In this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was -10.0 (95% CI: -14.9 to -5.2) (Table 24).

Table 24: Study 002, Change From Baseline in Behçet's Syndrome Activity Scores, MI, ITT

	Study 002	
	Apremilast(N=104)	Placebo(N=103)
Adjusted Change from Baseline[a]	-20.4	-10.4
Adjusted mean difference[bc] (95% CI)[bd] p-value[bd]	-10.0 (-14.9 to -5.2) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
[a]Least squares means based on a linear regression model adjusting for gender, region, and baseline score.
[b]Calculated using the aforementioned linear regression model.
[c]Apremilast minus Placebo
[d]Calculated using Huber-White sandwich standard errors.
Source: FDA Statistical Reviewer

Change From Baseline in Behçet's Disease Current Activity Form at Week 12

The Behçet's Disease Current Activity Form consists of 3 components: Behçet's Disease Current Activity Index Score, Patient's Perception of Disease Activity, and the Clinician's Overall Perception of Disease Activity.

In the primary analysis of Behçet's Disease Current Activity Index Score, there was a statistically significant difference, when comparing apremilast to placebo (p = 0.034). The adjusted mean difference between apremilast and placebo was -0.5 (95% CI: -1.0 to 0.0). In the primary analysis of Patient's Perception of Disease Activity, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was -1.0 (95% CI: -1.4 to -0.6). In the primary analysis of Clinician's Overall Perception of Disease Activity, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was -0.9 (95% CI: -1.3 to -0.5) (Table 25).

Table 25: Study 002, Change From Baseline in Behçet's Disease Current Activity Form at Week 12, LOCF, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=103)
Behçet's Disease Current Activity Index Score		
Adjusted Change from Baseline	-0.9	-0.4
Adjusted mean difference[a] (95% CI) p-value	-0.5 (-1.0 to 0.0) p = 0.034	
Patient's Perception of Disease Activity		
Adjusted Change from Baseline	-1.7	-0.7
Adjusted mean difference[a] (95% CI) p-value	-1.0 (-1.4 to -0.6) p < 0.001	
Clinician's Overall Perception of Disease Activity		
Adjusted Change from Baseline	-1.6	-0.7
Adjusted mean difference[a] (95% CI) p-value	-0.9 (-1.3 to -0.5) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 002 CSR pages 107 and 108

The Agency's statistical reviewer conducted a sensitivity analysis for each of the 3 components, using multiple imputation. For each component and for each imputed dataset, a linear regression model was fit, adjusting for gender, region, and baseline score, and used Huber-White sandwich estimates for the standard errors.

In the sensitivity analysis for Behçet's Disease Current Activity Index Score, there was not a statistically significant difference, when comparing apremilast to placebo (p = 0.132). The adjusted mean difference between apremilast and placebo was -0.4 (95% CI: -0.8 to 0.1). In the sensitivity analysis for Patient's Perception of Disease Activity, there was a statistically significant difference, when comparing apremilast to placebo (p = 0.002). The adjusted mean difference between apremilast and placebo was -0.7 (95% CI: -1.1 to -0.3). In the sensitivity analysis for Clinician's Overall Perception of Disease Activity, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was -0.8 (95% CI: -1.2 to -0.3) (Table 26).

Table 26: Study 002, Change From Baseline in Behçet's Disease Current Activity Form at Week 12, MI, ITT

	Study 002	
	Apremilast (N=104)	**Placebo (N=103)**
Behçet's Disease Current Activity Index Score		
Adjusted Change from Baseline	-1.1	-0.7
Adjusted mean difference[a] (95% CI) p-value	-0.4 (-0.8 to 0.1) p = 0.132	
Patient's Perception of Disease Activity		
Adjusted Change from Baseline	-1.8	-1.1
Adjusted mean difference[a] (95% CI) p-value	-0.7 (-1.1 to -0.3) p = 0.002	
Clinician's Overall Perception of Disease Activity		
Adjusted Change from Baseline	-1.8	-1.0
Adjusted mean difference[a] (95% CI) p-value	-0.8 (-1.2 to -0.3) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

Notably, results from the primary analysis for Behçet's Disease Current Activity Index Score appear to not be statistically robust, with the p-value of 0.034 likely due to overestimation of precision arising from the use of a Last Observation Carried Forward imputation procedure.

Maintenance of Complete Response

Maintenance of complete response was evaluated by testing the difference in probabilities between treatment arms of achieving complete response by Week 6 and remaining oral ulcer-free for at least 6 additional weeks during the 12-week controlled period. In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was 25.1% (95% CI: 15.5% to 34.6%) (Table 27).

Table 27: Study 002, Maintenance of Complete Response, LOCF, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=103)
Unadjusted Probability	29.8%	4.9%
Adjusted mean difference[ab] (95% CI)[a] p-value[c]	25.1% (15.5% to 34.6%) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Adjusted difference in proportions was the weighted average of the treatment differences across the 4 strata of combined gender and region factors with the CMH weights. Two-sided 95% CIs were based on normal approximation to the weighted average.
[b]Apremilast minus Placebo
[c]Two-sided p-value was based on the CMH test adjusting for gender and region.
Source: Study 002 CSR page 100

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. For each imputed dataset, a linear regression model was fit, adjusting for gender and region, and used Huber-White sandwich estimates for the standard errors. In this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was 24.2% (95% CI: 14.1% to 34.4%) (Table 28).

Table 28: Study 002, Maintenance of Complete Response, MI, ITT

	Study 002	
	Apremilast (N=104)	Placebo(N=103)
Adjusted Probability[a]	32.7%	8.4%
Adjusted mean difference[bc] (95% CI)[bd] p-value[bd]	24.2% (14.1% to 34.4%) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
[a]Least squares means based on a linear regression model adjusting for gender and region.
[b]Calculated using the aforementioned linear regression model.
[c]Apremilast minus Placebo
[d]Calculated using Huber-White sandwich standard errors.
Source: FDA Statistical Reviewer

Time to Oral Ulcer Resolution

Time to oral ulcer-free status was evaluated during the 12-week controlled period. Patients who were not observed to be oral ulcer-free at Week 12 were censored the earlier of Week 12 or the last oral assessment date. All censoring was assumed to be non-informative. In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted hazard ratio between apremilast and placebo was 2.4 (95% CI: 1.7 to 3.4) (Table 29), where hazard is defined as the instantaneous "risk" of achieving oral ulcer resolution.

Table 29: Study 002, Time to Oral Ulcer Resolution, No Imputation, ITT

	Study 002	
	Apremilast(N=104)	Placebo(N=103)
Adjusted hazard ratio[ab] (95% CI)[a] p-value[c]	2.4 (1.7 to 3.4) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval
[a]The adjusted hazard ratio and corresponding 95% CI were computed using a Cox proportional hazards model that adjusted for gender, region, and baseline number of oral ulcers.
[b]Apremilast compared to Placebo
[c]Two-sided p-value was based on the log-rank test adjusting for gender and region.
Source: Study 002 CSR page 97

The prespecified primary analysis implicitly assumed that non-monotone missing values of numbers of oral ulcers were positive. To allow for the possibility that patients achieved oral ulcer resolution at times of intermittent missingness, the Agency's statistical reviewer conducted a sensitivity analysis using the same multiply imputed datasets as those used in the primary analysis of the primary endpoint. In this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted hazard ratio between apremilast and placebo was 2.1 (95% CI: 1.5 to 3.0) (Table 30).

Table 30: Study 002, Time to Oral Ulcer Resolution, MI, ITT

	Study 002	
	Apremilast (N=104)	Placebo(N=103)
Adjusted hazard ratio[ab] (95% CI)[a] p-value[a]	2.1 (1.5 to 3.0) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; MI=multiple imputation
[a]The adjusted hazard ratio, corresponding 95% CI, and two-sided p-value were computed using a Cox proportional hazards model that adjusted for gender, region, and baseline number of oral ulcers.
[b]Apremilast compared to Placebo
Source: Study 002 CSR page 100

Complete Response Rate for Oral Ulcers at Week 12

For a given patient, complete response with respect to oral ulcers is defined as being oral ulcer free. In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo (p < 0.001). The adjusted mean difference between apremilast and placebo was 30.6% (95% CI: 18.1% to 22.3%) (Table 31).

Table 31: Study 002, Complete Response Rate for Oral Ulcers at Week 12, NRI, ITT

	Study 002	
	Apremilast (N = 104)	Placebo (N = 103)
Unadjusted Complete Response Rate	52.9%	22.3%
Adjusted mean difference[ab] (95% CI)[a] p-value[c]	30.6% (18.1% to 43.1%) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; NRI=nonresponder imputation
[a]Adjusted difference in proportions was the weighted average of the treatment differences across the 4 strata of combined gender and region

factors with the CMH weights. Two-sided 95% CIs were based on normal approximation to the weighted average.
[b]Apremilast minus Placebo
[c]Two-sided p-value was based on the CMH test adjusting for gender and region.
Source: Study 002 CSR page 96

Because it is possible for a patient with missing data at Week 12 to be a complete responder, the Agency's statistical reviewer conducted a sensitivity analysis to determine whether the primary analysis results were driven by the use of non-responder imputation. This analysis used the same multiply imputed datasets as for the primary analysis of the primary efficacy endpoint. For this sensitivity analysis, a linear regression model adjusting for gender, region, and baseline number of oral ulcers was used. Huber-White sandwich standard errors were used for the calculation of the 95% confidence interval and p-value. With this analysis, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was 29.6% (95% CI: 16.4% to 42.7%) (Table 32).

Table 32: Study 002, Complete Response Rate for Oral Ulcers at Week 12, MI, ITT

	Study 002	
	Apremilast (N=104)	Placebo(N=103)
Adjusted Complete Response Rate[a]	58.2%	28.6%
Adjusted mean difference[bc] (95% CI)[bd] p-value[bd]	29.6% (16.4% to 42.7%) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; NRI=nonresponder imputation
[a]Least squares means based on a linear regression model adjusting for gender, region, and baseline number or oral ulcers.
[b]Calculated using the aforementioned linear regression model.
[c]Apremilast minus Placebo
[d]Calculated using Huber-White sandwich standard errors.
Source: FDA Statistical Reviewer

Change From Baseline in Behçet's Disease Quality of Life Score at Week 12

In the primary analysis of this endpoint, there was a statistically significant difference, when comparing apremilast to placebo ($p < 0.001$). The adjusted mean difference between apremilast and placebo was -3.0 (95% CI: -4.5 to -1.4) (Table 33).

Table 33: Study 002, Change From Baseline in Behçet's Disease Quality of Life Score at Week 12, LOCF, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=103)
Unadjusted Change from Baseline	-3.5	-0.5
Adjusted mean difference[a] (95% CI) p-value	-3.0 (-4.5 to -1.4) p < 0.001	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: Study 002 CSR page 109

The Agency's statistical reviewer conducted a sensitivity analysis using multiple imputation. For each imputed dataset, a linear regression model was fit, adjusting for gender, region, and baseline score, and used Huber-White sandwich estimates for the standard errors. In this sensitivity analysis, there was a statistically significant difference, when comparing apremilast to placebo (p = 0.002). The adjusted mean difference between apremilast and placebo was -2.8 (95% CI: -4.6 to 1.0) (Table 34).

Table 34: Study 002, Change From Baseline in Behçet's Disease Quality of Life Score at Week 12, MI, ITT

	Study 002	
	Apremilast (N=104)	Placebo (N=103)
Unadjusted Change from Baseline	-4.4	-1.5
Adjusted mean difference[a] (95% CI) p-value	-2.8 (-4.6 to -1.0) p = 0.002	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; LOCF=last observation carried forward
[a]Apremilast minus Placebo
Source: FDA Statistical Reviewer

Complete Response Rate for Genital Ulcers at Week 12

In the primary analysis of this endpoint, there was not a statistically significant difference, when comparing apremilast to placebo (p = 0.110). The adjusted mean difference between apremilast and placebo was 28.4% (95% CI: -3.6% to 60.4%) (Table 35).

Table 35: Study 002, Complete Response Rate for Genital Ulcers at Week 12, NRI, ITT

	Study 002	
	Apremilast (N = 17)	Placebo (N = 17)
Unadjusted Complete Response Rate	70.6%	41.2%
Adjusted mean difference[ab] (95% CI)[a] p-value[c]	28.4% (-3.6% to 60.4%) p = 0.110	

Abbreviations: ITT=intention to treat: all subjects randomized; CI=confidence interval; NRI=nonresponder imputation
[a]Adjusted difference in proportions was the weighted average of the treatment differences across the 4 strata of combined gender and region factors with the CMH weights. Two-sided 95% CIs were based on normal approximation to the weighted average.
[b]Apremilast minus Placebo
[c]Two-sided p-value was based on the CMH test adjusting for gender.
Source: Study 002 CSR page 110

Because this endpoint was not statistically significant, all remaining endpoints in the analysis hierarchy were not statistically significant. Furthermore, a majority of the remaining endpoints in the analysis hierarchy condition on post-randomization variables, making interpretation of results from analyses of these endpoints difficult. For these reasons, results for the remaining endpoints in the analysis hierarchy are not presented in this review.

Dose/Dose Response

Dose response was not evaluated in study 002.

Durability of Response

The study was not designed for controlled evaluations of the durability of apremilast.

Persistence of Effect

There are no data to support a persistence of effect after treatment discontinuation.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

No relevant secondary or exploratory COA (PRO) endpoints were included in the multiplicity control procedure, beyond what is described above.

Additional Analyses Conducted on the Individual Trial

The results of the sample estimates of treatment effects in subgroups are presented in Table 36. The sample sizes were not sufficient to conduct multi-way subgroup analyses. Therefore, results were presented for marginal subgroups. These subgroup analysis results by demographic subgroups were largely consistent with findings in the overall population, based on AUC for number of oral ulcers from Day 1 to Day 85.

Table 36: Subgroup Analysis for Gender, Region, Age, and Race, for AUC for Number of Oral Ulcers from Day 1 to Day 85

Subgroup	N	Sample Treatment Effect Estimate (95% CI)
Overall	207	-89.5 (-126.4 to -52.6)
Female	127	-88.7 (-136.0 to -41.4)
Male	80	-90.9 (-149.5 to -32.2)
USA	25	-32.8 (-141.0 to 75.4)
Other Countries	182	-98.1 (-137.6 to -58.7)
< 40 Years Old	103	-88.5 (-140.7 to -36.3)
≥ 40 Years Old	104	-97.7 (-150.2 to -45.1)
White	137	-81.6 (-127.1 to -36.0)
Other Race	70	-104.9 (-167.8 to -42.0)

Abbreviations: CI = confidence interval
Source: FDA Statistical Reviewer

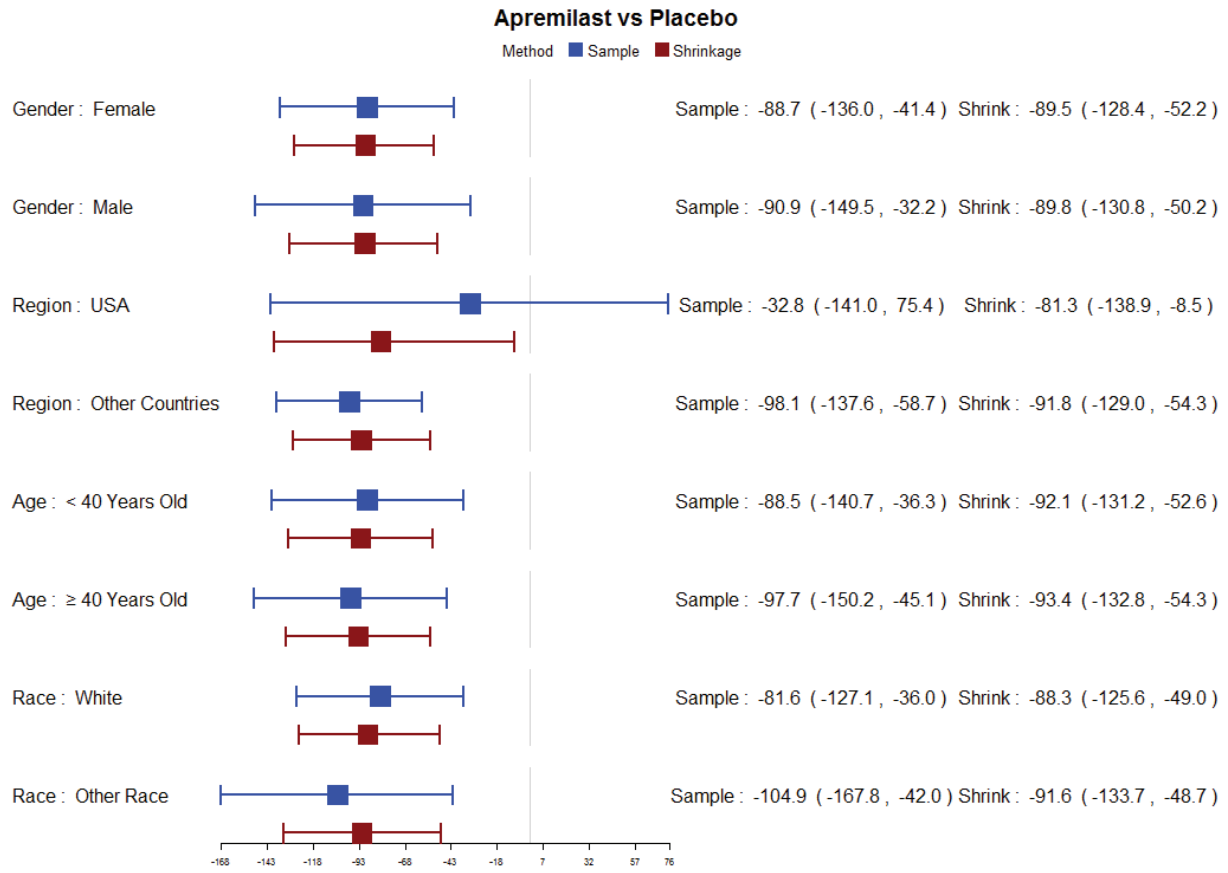
In the traditional subgroup analyses, there were random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. Therefore, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates in Table 36. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. The greater the ratio is, the smaller the weight on the overall estimate (the less the shrinkage). The same flat prior distribution was used to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i \in \{1, 2, \dots\}$, Y_i represents the observed sample estimate of treatment effect in subgroup level i, assuming $Y_i \sim N(\mu_i, \sigma_i^2)$, where

- σ_i^2 are the observed values of the variance for the subgroup sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(-100, 90000)$, $1/\tau^2 \sim Gamma(0.001, 0.001)$

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in Figure 2. The amount of shrinkage is relatively big in the USA subgroup due to the small sample size in this subgroup. In general, the treatment effect was consistent across the different subgroups.

Figure 2: Study 002 Subgroup Analysis for Gender, Region, Age, and Race, for AUC for Number of Oral Ulcers from Day 1 to Day 85



Abbreviations: Shrink = Shrinkage
Source: FDA Statistical Reviewer

Integrated Review of Effectiveness

The evaluation of efficacy is based on one phase 2 study (Study 001), and a phase 3 study (Study 002). The two studies included patients between 18 and 65 years in age. Based on the Applicant's pre-specified analyses, results from each study were statistically significant in the overall population for the respective primary endpoint (Number of Oral Ulcers at Day 85 for Study 001, and AUC for Number of Oral Ulcers from Baseline Until Day 85 for Study 002). Sensitivity analyses for the primary efficacy endpoint in each study suggest that the respective primary analyses are statistically robust. AUC for Number of Oral Ulcers from Baseline Until Day 85 in Study 001 were also supportive of the claim for efficacy. However, a clinical interpretation of the AUC endpoint results revealed a treatment effect estimate that is modest. Specifically, the reduction of apremilast compared to placebo in the daily average number of oral ulcers during the 12-week placebo-controlled treatment phase was estimated to be 1.0 (95% CI: 0.6 to 1.4) in Study 001, and 1.1 (95% CI: 0.7 to 1.6) in Study 002. Given the modest treatment effect estimate in each study, secondary efficacy endpoints were evaluated for additional support for efficacy.

Results of analyses for secondary efficacy endpoints such as complete response, partial response, change from baseline in oral ulcer pain, change from baseline in Behçet's syndrome activity score, and change from baseline in Behçet's Disease current activity form provided support for efficacy. Particularly in Study 002 where multiplicity was controlled, the primary analyses for these endpoints were statistically significant. Sensitivity analyses for these analyses largely suggested that the primary analysis results were statistically robust to violations of some assumptions made in the primary analyses.

In Study 001, analysis results for AUC for Number of Oral Ulcers from Baseline Until Day 85 were largely consistent across the subgroups considered by the Agency's review team, except that the treatment effect estimate for the non-white subgroup was noticeably lower. However, given that this subgroup included only three patients, the ability to draw conclusions regarding this subgroup is very limited. Conversely, analysis results for the same endpoint were largely consistent across the subgroups considered by the Agency's review team, except that the treatment effect estimate for the US subgroup was noticeably lower. However, given that this subgroup included only 25 patients, the ability to draw conclusions regarding this subgroup is limited. For each study, shrinkage estimates for the subgroup treatment effects, based on a Bayesian hierarchical model, were relatively similar across all subgroups considered.

In summary, Studies 001 and 002 achieved statistically significant results for the respective primary efficacy endpoints and several secondary efficacy endpoints based on the prespecified primary analyses. Sensitivity analyses for these endpoints were largely supportive of the primary analysis results. As such, in the opinions of the primary clinical reviewer and the primary statistical reviewer, these data provide adequate support for efficacy for this product in the indicated population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of apremilast for adult patients with oral ulcers associated with Behçet's Disease relies on data from studies BCT-001 and BCT-002.

The warnings and precautions from the current apremilast USPI include: diarrhea, nausea, vomiting, depression, and weight decrease.

8.2.2. Review of the Safety Database

Overall Exposure

In Study BCT-001, during the placebo-controlled period, the mean duration of treatment was 10.65 weeks in the placebo group and 11.43 weeks in the APR 30 BID group. Eleven (19.6%) patients in the placebo group and four (7.3%) patients in the APR 30 BID group received less

than 10 weeks of study drug. Two patients in the APR 30 BID group required a dose reduction, and one patient required dose interruption. There were no dose reductions or interruptions in the placebo group. During the apremilast-exposure period, the mean duration of apremilast treatment was 12.10 weeks in the placebo/APR 30 BID group and 22.00 weeks in the APR 30 BID/APR 30 BID group. The majority of patients (85.5%) in the APR 30 BID/APR 30 BID group received ≥ 22 to < 26 weeks of treatment. All patients in the placebo/APR 30 BID group received ≥ 10 to < 14 weeks of apremilast. Two patients in the APR 30 BID/APR 30 BID group required a dose reduction, and one required dose interruption. There were no dose reductions or interruptions in the placebo/APR 30 BID group.

As noted in the original sNDA submission, in Study BCT-002 a total of 112 patients had been exposed to APR 30 BID for at least 48 weeks. In addition, 91 patients had been exposed to APR 30 BID for more than 52 weeks and 29 patients for at least 64 weeks. In the 4-month SUR, 146 patients were exposed to APR 30 BID for at least 48 weeks, 124 patients were exposed for at least 52 weeks, and 51 patients were exposed for at least 64 weeks.

Adequacy of the safety database:

The sample size is appropriate for the population and objectives of the study. The types of safety assessments conducted in studies BCT-001 and BCT-002 are also consistent with reasonable monitoring for the known AEs of apremilast and for this patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no specific concerns regarding data integrity and submission quality as they relate to the safety assessment.

Categorization of Adverse Events

In both study BCT-001 and study BCT-002, an AE was defined as any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study.

In study BCT-001, patients who experienced a flare of Behçet's Disease were to be recorded as adverse events. In study BCT-002, worsening of a patient's BD (any manifestation) was considered as worsening of disease under study, and should not have been captured as an AE, unless the event met the definition of an SAE.

In both studies, a SAE was defined as any AE which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or constitutes an important medical event. For each SAE, the investigator was to provide information on severity,

start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 for study BCT-001 and MedDRA Version 20.0 for study BCT-002.

The adverse events of special interest (AESI) for study BCT-001 included: gastrointestinal (GI) events, malignancies, infections, major adverse cardiovascular events (MACE), and suicidal ideation and behavior events based on PDE4 inhibitors.

The AESI for study BCT-002 included: serious diarrhea, defined as more than two watery/liquid stools in a day.

The AESI in the summary of clinical safety included: SMQs of: MACE, malignancies, opportunistic infections, suicide/self-injury, depression, upper respiratory tract infection, diarrhea, GI pain and abdominal pain, headache, cardiac failure, tachyarrhythmia, liver-related investigations, gallstone and gallbladder symptoms, acute renal failure, hypersensitivity, vasculitis, and GI hemorrhage.

The AESI in the summary of clinical safety four-month update included: AESIs using MedDRA SMQs, and SCQs that were assessed in the original sNDA were repeated in this four-month update including malignancies, opportunistic infections, MACE and potential MACE (including tachyarrhythmia), depression (excluding suicide and self-injury), suicide/self-injury, serious diarrhea, nausea and vomiting, hypersensitivity, GI hemorrhage, uveitis, vasculitis and vasculopathy, and weight change.

Routine Clinical Tests

Study BCT-001
Clinical laboratory evaluations included serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, lactate dehydrogenase, magnesium, complete blood count (RBC count, hemoglobin, WBC count and differential, absolute WBC counts, platelet count), fibrinogen, ESR, hs-CRP, and dipstick urinalysis (microscopic analysis [epithelial cells, RBC, WBC, and casts] was to be performed only if the first and repeated dipstick urinalyses were abnormal). These laboratory evaluations were done at screening and then days 1, 15, 43, 85 (end of treatment/ early termination from treatment phase) and then on days 99, 127, 169 and 197 in the extension and observational follow-up phases. In addition, shift tables were provided to show the number of patients with pretreatment versus post-treatment values that are categorized as low, normal, or high relative to the normal reference ranges.

Study BCT-002
Laboratory parameters measured during the study included tests of hematology, serum

chemistry, urinalysis, inflammatory protein biomarkers, leukocyte subsets (to explore the effects of apremilast on T lymphocytes that include, but are not limited to T regulatory cells, T helper 17 cells, and total T cells). Clinical laboratory information was tabulated and summarized by treatment group.

Laboratory data were to be summarized by visit descriptively. In addition, shift tables showing the number of patients with values low, normal, high compared to the normal ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, was provided. Regardless of severity grade, only laboratory abnormalities that fulfilled a seriousness criterion were to be documented as a serious adverse event.

In Both Study BCT-001 and BCT-002, an abnormal laboratory value was to be considered to be an AE if the abnormality resulted in discontinuation from the study, required treatment, modification/interruption of IP dose, or any other therapeutic intervention, or was judged to be of significant clinical importance. If a laboratory abnormality was one component of a diagnosis or syndrome, then only the diagnosis or syndrome was to be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality was to be recorded as the AE.

8.2.4. Safety Results

Deaths

There were no deaths in Study BCT-001 or BCT-002.

Serious Adverse Events

During the placebo-controlled period of Study BCT-001, serious TEAEs were reported in two (4%) patients in the APR 30 BID group (one patient experienced diplegia and one had worsening of hemorrhoids complicated with anal fissures) and three (5%) patients in the placebo group (two patients experienced serious Behçet's syndrome/flare and the third patient experienced serious pyrexia).

During the apremilast-exposure period of Study BCT-001, four additional serious TEAEs were reported (three patients with Behçet's syndrome/flare and one patient with influenza).

During the placebo-controlled period of Study BCT-002, serious TEAEs were reported in three patients (3%) in the APR 30 BID treatment group (one patient with Behçet's Disease, one with soft tissue injury, and one with migraine), and in four patients (4%) in the placebo treatment group (one acute febrile neutrophilic dermatosis, one with a fungal genital infection and erythema multiforme, one with mouth ulceration and skin lesion, and one with a genital infection and infectious diarrhea).

During the apremilast-exposure period of Study BCT-002, serious TEAEs were reported by 10% (10/104) of patients in the APR 30 BID/APR 30 BID treatment group and 7% (6/83) of patients in

the placebo/APR 30 BID group. All serious TEAEs during the apremilast exposure period were reported in no more than one patient per treatment group. The exposure-adjusted incidence rate (EAIR) per 100 patient-years for the APR 30 BID treatment group in the apremilast-exposure period and the placebo-controlled period was 10.4 and 13.2, respectively. In the four-month safety update, the EAIR per 100 patients-years was 9.8. The incidence of overall serious TEAEs did not increase with longer duration of apremilast exposure.

Dropouts and/or Discontinuations Due to Adverse Effects

There were fewer patients with SAEs and AEs leading to discontinuation in the apremilast groups during the placebo-controlled period: four (7%) in study BCT-001 and three (3%) in Study BCT-002 in the APR group versus five (9%) in study BCT-001 and five (5%) in study BCT-002 in the placebo groups.

During the apremilast-exposure period of Study BCT-001, TEAEs leading to drug withdrawal occurred in one patient (2%) in the PBO/APR group (Behçet's syndrome) and seven (13%) in the APR/ APR group (two patients each with diarrhea and nausea).

During the apremilast-exposure period in Study BCT-002, there were 11 patients (11%) in the APR 30 BID/APR 30 BID treatment group and two patients (2%) in the placebo/APR 30 BID treatment group who had a TEAE leading to drug withdrawal. Apart from nausea (reported in two patients in the APR 30 BID/APR 30 BID treatment group), all TEAEs leading to drug withdrawal were reported by one patient in either treatment group. The EAIR per 100 patient-years for the APR 30 BID total treatment group in the apremilast exposure period and the placebo-controlled period was 8.2 and 13.0, respectively, for TEAEs leading to drug withdrawal.

Significant Adverse Events

There were no significant AEs of serious diarrhea, malignancy or suicide/self-injury (Table 37).

Table 37: Significant Adverse Events during the placebo-controlled period (safety population)

	Study BCT-001		Study BCT-002	
Number of Subjects with:	Placebo N=56 n (%)	Apremilast N=55 n (%)	Placebo N=103 n (%)	Apremilast N=104 n (%)
Opportunistic Infections	7 (13)	3 (5)	1 (1)	2 (2)
Potential MACE	2 (4)	1 (2)	3 (3)	1 (1)
Hematemesis	0	1 (2)	0	0
Headache	25 (45)	26 (47)	11 (11)	15 (14)
Nausea	10 (18)	22 (40)	11 (11)	20 (19)
Diarrhea	2 (4)	12 (22)	21 (20)	43 (41)
Vomiting	1 (2)	9 (16)	2 (2)	9 (9)

In the apremilast-exposure period for study BCT-002, there were no suicidal ideation events, systemic vasculitis, uveitis, or serious diarrhea reported.

Rates of AEs stabilized (decreased), based on the four-month safety follow-up. The overall safety is consistent with the known safety profile of apremilast in psoriasis and psoriatic arthritis.

Treatment Emergent Adverse Events and Adverse Reactions

During Study BCT-001, there was a total of 50 (89%) TEAE in the PBO group and 49 (89%) in the APR group during the placebo-controlled period. The most frequently reported TEAEs (in ≥ 5% of subjects in any treatment group) in decreasing order of frequency in the APR treatment group were headache, nausea, Behçet's flare, abdominal pain, pain in extremity, and arthralgia. TEAEs (in ≥ 5% of subjects) only in the APR treatment group were diarrhea, vomiting, asthenia, decreased appetite, hypoesthesia, dyspepsia, dizziness, influenza, back pain and myalgia.

During Study BCT-002, there was a total of 74 (72%) TEAEs in the PBO group and 82 (79%) in the APR group during the placebo-controlled period. The most frequently reported TEAEs (in ≥ 5% of subjects in any treatment group) in decreasing order of frequency in the APR treatment group were diarrhea, nausea, headache, upper respiratory tract infection, abdominal pain upper, vomiting, back pain, viral upper respiratory tract infection, and arthralgia. During the apremilast-exposure period, the most frequently reported TEAEs (subject incidence ≥ 5% in any treatment group) were similar to those observed during the placebo-controlled period, with the addition of insomnia (8% in the PBO/APR group and 5% in the APR/APR group) and abdominal pain (6% in the PBO/APR group and 5% in the APR/APR group).

Laboratory Findings

In Study BCT-001, marked abnormalities in hematology laboratory parameters at any time during treatment were infrequent during the placebo-controlled period and the apremilast-

exposure period. The most frequent abnormal values during the placebo-controlled period occurred for lymphocytes (< 1.0 GI/L) in 7% of placebo patients and 5% of APR 30 BID patients. This was similar in the apremilast-exposure period, 4% of PBO/APR patients and 13% of APR/APR patients.

In Study BCT-002**,** no clinically significant mean changes from baseline in laboratory values were noted in the placebo-controlled period and Apremilast-exposure period for hematology.

In both Studies BCT-001 and BCT-002, there were no clinically significant mean changes from baseline in laboratory values in the placebo-controlled period and apremilast-exposure period for serum chemistry.

In Study BCT-001, there were no cases of liver function test (LFT) elevations during the placebo-controlled period. No cases of LFT elevations met Hy's Law criteria during the apremilast-exposure period.

There are currently no labeled effects of apremilast on laboratory parameters.

Vital Signs

In Study BCT-001, mean and median changes from baseline in vital signs were small, with no consistent trend to increase or decrease over time.

In Study BCT-002, there were no clinically significant changes in mean vital sign measures, including diastolic and systolic blood pressure, pulse rate, temperature, and respiration rate, in any treatment groups at any time point during the placebo-controlled period and apremilast-exposure period.

Weight Change

In Study BCT-001, the majority of weight change was ≥ -5% to < 0% in both periods and groups: 30% of PBO patients and 37% of APR patients during PBO period, and 49% of PBO/APR patients and 36% of APR/APR patients during exposure period.

In Study BCT-002, the majority of weight change was > 0% to ≤ 5% in the PBO period: 46% of PBO patients and 39% of APR patients. During the Exposure period there was: ≥ -5 to < 0 weight % change in 40% of PBO/APR patients and > 0 to ≤ 5 weight % change in 39% of APR/APR patients.

Electrocardiograms (ECGs)/ QT

In Study BCT-001, twelve-lead ECGs were performed at Visits 1, 2, 9, and 16, after the patient had been in the supine position for three minutes. Three (5%) patients in the APR group had an increase from baseline > 30 but < 60 msec in QTc interval. 64% of patients in the placebo group and 62% of patients in the APR group had a change from baseline of > 5 but ≤ 30 msec in QTc

interval based on QT interval corrected for heart rate by Bazett's formula (similar percentages based on Fridericia's formula).

The ECG abnormalities during the placebo-controlled period were similar between the APR and placebo treatment groups. No patient experienced a QT interval > 500 msec or clinically significant QTc interval (male: ≥ 450; female: ≥ 470). No patient had a ≥ 60 msec increase from baseline in QTc interval. Abnormal ECG findings in the apremilast-exposure period were similar to those observed in apremilast treated patients in the placebo-controlled period.

In Study BCT-002, ECG was only done at the screening visit.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to Significant Adverse Events in section 8.2.4.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Not applicable.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information regarding human carcinogenicity is included in this supplement.

Human Reproduction and Pregnancy

Refer to PLLR information below in section 11.1.

Pediatrics and Assessment of Effects on Growth

Not applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new information regarding overdose, drug abuse potential, withdrawal and rebound is included in this supplement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There are no post-marketing data available for apremilast in oral ulcers associated with Behçet's Disease.

Expectations on Safety in the Postmarket Setting

The observed safety profile for apremilast in oral ulcers associated with Behçet's Disease is generally similar to the observed safety profile of apremilast in psoriatic arthritis and psoriasis. Therefore, the expected safety in Behçet's Disease is anticipated to be similar to the safety in psoriatic arthritis and psoriasis.

8.2.11. Integrated Assessment of Safety

Not applicable.

8.3. Statistical Issues

The main statistical issue identified during the review of this submission was the common use of the Last Observation Carried Forward (LOCF) imputation procedure, despite multiple pre-submission communications to the applicant regarding its inappropriateness. As noted previously in this review, such an imputation procedure may not be clinically or statistically appropriate. For each efficacy endpoint evaluated in this review where the primary analysis utilized the LOCF imputation procedure, a sensitivity analysis using multiple imputation did not call into question the robustness of the primary analysis results, except for change from baseline in the Behçet's Disease Current Activity Index Score component of the Behçet's Disease Current Activity Form.

Additionally, for each study, there were one or two subgroups with results for AUC for Number of Oral Ulcers from Baseline Until Day 85 that were inconsistent with those for the other subgroups. However, due to the number of subgroups being evaluated in each study, it is feasible that by chance there is at least one subgroup where the results were notably different than those for the remaining subgroups. For this reason, a shrinkage analysis was performed for each study using a Bayesian hierarchical model. The resulting shrinkage estimates suggest a consistency in the treatment effect among all of the subgroups, with respect to AUC for Number of Oral Ulcers from Baseline Until Day 85.

8.4. Conclusions and Recommendations

Studies 001 and 002 achieved statistical significance in the primary analyses for the primary efficacy endpoints. Sensitivity analyses suggest that these results are statistically robust. The treatment effect estimate is modest in each study for AUC for Number of Oral Ulcers from

Baseline Until Day 85. However, the secondary efficacy endpoint analysis results in the two studies are largely supportive of efficacy. In each study, there is one subgroup where the observed treatment effect is attenuated (non-white in Study 001 and US in Study 002). However, shrinkage analysis results suggest that the treatment effect is relatively consistent across the different subgroups.

Overall, safety observed in Studies BCT-001 and BCT-002 is consistent with the known safety profile of apremilast.

Due to the evidence of efficacy and no new safety signals as discussed above, it is the opinion of the primary clinical reviewer and the primary statistical reviewer that there is sufficient evidence to conclude that the benefits of apremilast outweigh the risks in adults with oral ulcers associated with Behçet's Disease. Therefore, we recommend that apremilast be approved for marketing in this population. We recommend that for continuous endpoints the product labeling include analysis results that properly reflect the statistical uncertainty in parameter estimation due to missing data, such as analyses that make use of a multiple imputation procedure.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee was deemed necessary for this supplemental NDA.

10 Pediatrics

Not applicable. On January 17, 2013, apremilast was given an Orphan Drug Designation for the indication: “treatment of Behçet's Disease”, of which oral ulcers are a manifestation.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information:

Indications and usage heading: Changed from (b) (4) to Oral Ulcers associated with Behçet's Disease to align with the indication.

In section 6.1: Revised to clarify that the noted adverse events leading to discontinuation were those reported during the placebo-controlled period.

In Table 4, arthralgia and viral upper respiratory tract infection were added since they both met the title criterion for being reported in ≥ 5% of subjects on OTEZLA and with at least 1% greater frequency than patients on placebo.

The labeling for Section 8: Pregnancy was converted to Pregnancy and Lactation Labeling Rule (PLLR) compliancy with supporting information on February 21, 2019 (SD-876). A nonclinical review of this conversion was completed on June 3, 2019. Changes to the clinical aspects were recommended by the Clinical Reviewers and DPMH consult team.

In section 14.3: (b) (4) was changed to BD with active oral ulcers (b) (4)

(b) (4)

The Division recommended that superscripts indicating a p-value less than 0.0001 be removed from the presentation of the data, and that 95% confidence intervals instead be included to provide more information to prescribers and patients.

For Figure 2 in the proposed labeling, the Division recommended that it has Mean Oral Ulcer Pain as a function of time through Week 12, instead of (b) (4) (b) (4). This change will result in the figure being more informative to prescribers and patients.
Also, when changing this figure to reflect Mean Oral Ulcer Pain instead of (b) (4) (b) (4) the Division recommended that the y-axis for this figure ranges from 0 to 100, to avoid representations of the observed data being misleading.

Finally, the Division recommended that both, this figure and Figure 1 in the product labeling, include the by-arm sample sizes through Week 12, as done in Figures 2 and 3 of the clinical study report of Study CC-10004-BCT-002.

(b) (4)

These changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional safety concerns that would warrant consideration of a REMS.

13 Postmarketing Requirements and Commitment

No Postmarketing Requirements and Commitments are warranted based on this supplemental NDA.

14 Division Director (or Designated Signatory) Comments

Celgene submitted supplement 007 to New Drug Applicantion (NDA) 205437 for apremilast oral tablets, to provide data from two clinical studies, BCT-001 and BCT-002, in support of a new indication, treatment of adult patients with oral ulcers associated with Behçet's Disease. The proposed dosing regimen is initial titration over (b) (4) days followed by 30 mg twice daily, the same as the dosing regimen for the approved indications of treatment of adult patients with active psoriatic arthritis, and of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
In support of the supplement, the applicant provided data from two two studies:

- Study BCT-001, a proof-of-concept, multicenter, randomized, placebo-controlled, double blind, parallel group study in 111 patients with Behçet's Disease with at least two oral ulcers at randomization. Oral or topical analgesics had to be discontinued for 24 hours prior to each study visit in order to avoid interference with the pain assessments. Chronic medications were to be dosed on a stable regimen. The primary endpoint was number of oral ulcers at Day 85.
- Study BCT-002, a confirmatory, multicenter, randomized, placebo-controlled study in 207 adult patients with active BD with active oral ulcers. Patients were previously treated with at least one nonbiologic BD medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for BD. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for BD was not allowed. Patients were randomized 1:1 to receive either apremilast 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks. After Week 12, all patients received apremilast 30 mg twice daily. The efficacy was assessed based on the number and pain of oral ulcers.

Both studies were conducted as planned.

The primary endpoint proposed to support the supplement was pre-specified as the area under the curve (AUC) for the number of oral ulcers from baseline through Week 12:

- In study BCT-001, the adjusted mean difference between apremilast and placebo was -87.5 (95% CI: -122.7 to -52.4).
- In Study BCT-002, the adjusted mean difference between apremilast and placebo was -89.5 (95% CI: -126.4 to -52.6). For better intepretability of this endpoint, the same data are presented in the product labeling as daily average number of oral ulcers during the 12-week placebo-controlled treatment phase: the adjusted mean difference between apremilast and placebo with respect to the 12-week average oral ulcer count is -1.1 (95% CI: -1.6 to -0.7), which is consistent with the results from Study BCT-001, where the difference was -1.0 (95% CI: -1.4 to -0.6) oral ulcers over 85 days. The results from sensitivity analyses were consistent with the primary analysis.

However, consistent with the FDA's concerns expressed at pre-submission communications with the applicant, this endpoint was considered difficult to interpret and possibly inappropriate to capture the waxing and waning nature of the disease. Thus, the FDA review team relied on other prospectively captured and pre-specified in the statistical analysis plan endpoints, such as improvements of pain, as well as the proportion of patients with no new ulcers, which are measures of direct patient benefit. Specifically:

- The adjusted mean difference of change from baseline in oral ulcer pain visual analog scale (VAS) between apremilast and placebo was -24.8 (95% CI: -32.8 to -16.8).
- The adjusted mean difference of the proportionf of subjects achieving oral ulcer complete response (oral ulcer-free) by Week 6, and who remain oral ulcer-free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phasebetween apremilast and placebo was 25.1% (95% CI: 15.5% to 34.6%).
- The adjusted mean difference in the proportion of subjects achieving oral ulcer complete response (oral ulcer-free) at Week 12 between apremilast and placebo was 30.6% (95% CI: 18.1% to 22.3%).

The safety of apremilast was consistent with the know safety profile of apremilast in the approved indications.

Based on these data, the primary clinical and statistical review teams concluded, and I agree that there is sufficient evidence to support that the benefits of apremilast outweigh the risks in adults with oral ulcers associated with Behçet's Disease.

Results from the confirmatory clinical study, BCT-002, are described in the product labeling. The labeling was also revised to comply with the Pregnancy and Lactation Labeling Rule.

The regulatory action for this supplement is Approval. No PMR/PMCs are warranted.

15 Appendices

15.1. References

1) J. C. Jennette, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. 08 October 2012.
2) http://www.behcets.com/site/c.8oIJJRPsGcISF/b.9196317/k.904C/Behcets_Disease.htm
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4) F. Davatchi et al. Behçet's disease: epidemiology, clinical manifestations, and diagnosis. 04 Feb 2016.
5) Z. Saleh. Update on the therapy of Behçet disease. Ther Adv Chronic Dis. 2014 May; 5(3): 112–134.
6) Hatemi G, Christensen R, Bang D, et al 2018 update of the EULAR recommendations for the management of Behçet's syndrome Annals of the Rheumatic Diseases 2018;77:808-818.
7) Otezla USPI

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study CC-10004-BCT-001 (BCT-001) and Study CC-10004-BCT-002 (BCT-002).

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 613		
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): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the Sponsor of covered study: 0		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

None.

15.4. Additional Clinical Outcome Assessment Analyses

Behçet's Syndrome Activity Score (BSAS):
The Behçet's Syndrome Activity Score (BSAS) contains 10 questions, including ones that assess the number of new oral and genital ulcers and skin lesions; assess gastrointestinal (GI), CNS, vascular, and ocular involvement; and evaluates the subject's current level of discomfort. The item scores are totaled to create a score ranging from 0 to 100. The BSAS is completed by the subject on a secure, validated hand-held device.

Behçet's Disease Quality of Life (BD QoL):
The BD QoL questionnaire was developed to measure the influence of BD on a patient's life. It consists of 30 self-completed items that measure disease related restrictions on the patient's activities and the patient's emotional response to these restrictions.

The scoring algorithm used to combine the different rating scale into a single score may weight the items disproportionally. It is unclear whether this scoring algorithm is appropriate or interpretable as no rationale or justification is provided.

(b) (4)

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/s/

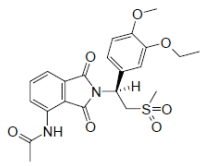
NIKOLAY P NIKOLOV
07/19/2019 10:26:27 AM
Signed under the authority, delegated by Dr. Sally Seymour, Division Director, DPARP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION BRANCH 1/DPMA1/OLDP/OPQ	2. NDA NUMBER **205-437**
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Celgene Corporation 86 Morris Avenue Summit, NJ 07901 Tel: (908) 673-9000, Fax: (908) 860-7515 e-mail: vrpatel@celgene.com **Name and Title of Applicant's Responsible Official** Vrunda Patel, Pharm.D., Senior Manager, Regulatory Affairs Tel: (908) 679-7892, Fax: (908) 860-7515 e-mail: vrpatel@celgene.com		4. AF NUMBER
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) **S-007; SE; SDN 801; SN 0079** Letter Date: 9/21/18 Stamp Date: 9/21/18 **Due Date: 7/21/19**
6. NAME OF DRUG Otezla	7. NONPROPRIETARY NAME Apremilast	
8. SUPPLEMENT PROVIDES FOR: an efficacy supplement for a new indication.		
9. PROPOSED INDICATION FOR USE Treatment of adult patients with oral ulcers associated with Behçet's disease	10. HOW DISPENSED RX x OTC	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Film-coated tablet	13. POTENCY 10 mg, 20 mg, 30 mg	
14. CHEMICAL NAME AND STRUCTURE **Apremilast:** N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro -1H-isoindol-4-yl]acetamide  Molecular formulae: $C_{22}H_{24}N_2O_7S$, Molecular weight: 460.5		15. RECORDS AND REPORTS CURRENT YES__NO REVIEWED YES__NO
16. COMMENTS: This efficacy supplement is approvable from CMC standpoint.		
17. CONCLUSIONS AND RECOMMENDATIONS This supplement is approvable from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED June 12, 2019

Background:

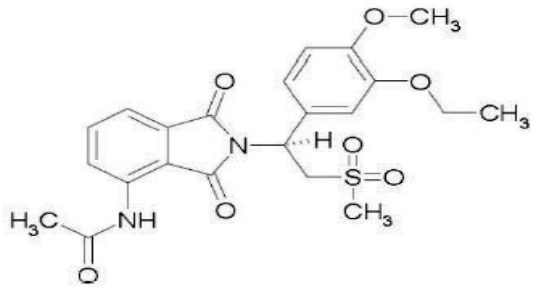
Celgene Corporation (Applicant) is submitting an efficacy supplement to NDA 205437 under Section 505(b) of the Federal Food, Drug and Cosmetic Act (the Act). The information submitted in this supplemental NDA (sNDA) supports the safety and efficacy of apremilast for the following indication:

> OTEZLA® (apremilast) is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease.

Review:

1.12.14 Environmental Analysis

Identification of the drug substance

Chemical name:	Acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-
Generic Name:	Apremilast
Identifier:	CC-10004
CAS Number:	608141-41-9
Molecular weight	460.5
Empirical formula:	$C_{22}H_{24}N_2O_7S$
Molecular/structural formula:	
Appearance:	White to pale yellow powder

CATEGORICAL EXCLUSION FROM PREPARATION OF AN ENVIRONMENTAL ASSESSMENT (EA)

Celgene Corporation claims a Categorical Exclusion from the requirement to prepare an Environmental Assessment for Apremilast in compliance with the categorical exclusion criteria 21 CFR Part 25.31, applicable

when the FD A's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will nonetheless be below 1 part per billion (ppb) (21 CFR Part 25.31 (b)). Further, Celgene Corporation claims that to the best of their knowledge no extraordinary circumstances exist that may significantly affect the quality of the human environment (21 CFR 25.21).

Evaluation: *Acceptable*
Categorical Exclusion from the requirement to prepare an Environmental Assessment is acceptable.

1.14 Labeling

1.14.1 Draft Labeling

1.14.1.1 Draft Carton and Container Labels

Evaluation: *Acceptable*

1.14.1.3 Proposed Redlined Labeling Text

Evaluation: *Acceptable*
There are no changes proposed for Section 3 (DOSAGE FORMS AND STRENGTHS), Section 11 (DESCRIPTION), and Section 16 (HOW SUPPLIED/STORAGE AND HANDLING).

CONCLUSION AND RECOMMENDATION

This efficacy supplement is approvable from CMC standpoint.

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/s/

CHONG HO KIM
06/12/2019 12:22:43 PM

RAMESH RAGHAVACHARI
06/12/2019 02:44:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW AND EVALUATION

Application number:	205437
Supporting document/s:	SD-801 (Supplement 7), and SD-876 (PLLR)
Applicant's letter date:	September 21, 2018, and February 21, 2019
CDER stamp date:	September 21, 2018, and February 21, 2019
Product:	Otezla (apremilast)
Indication:	Treatment of oral ulcers associated with Behçet's disease
Applicant:	Celgene Corp.
Review Division:	DPARP
Reviewer:	L.S. Leshin, DVM, PhD
Supervisor/Team Leader:	Carol Galvis, PhD
Division Director:	Sally Seymour, MD
Project Manager:	Ngoc-Linh Do

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205437 are owned by Celgene Corp. or are data for which Celgene Corp. has obtained a written right of reference.
Any information or data necessary for approval of NDA 205437 that Celgene Corp. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205437.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Supplement 7 is a submission to support a new indication for Otezla (apremilast), the treatment of oral ulcers associated with Behçet's disease. Orphan drug designation for the treatment of Behçet's disease was granted on January 17, 2013. Otezla was previously approved for psoriatic arthritis under NDA 205437, for plaque psoriasis under NDA 206088, and an extended release (XR) formulation under NDA 210745. After submission of this supplement, the applicant was notified on December 10, 2018 of the requirement to revise the label to comply with the June 30, 2019, Pregnancy and Lactation Labeling Rule (PLLR) label conversion. The applicant submitted a revised label with supporting information on February 21, 2019 (SD-876). The supporting nonclinical information was a summary of previously submitted studies that were reviewed for the approval of Otezla.

There were no new nonclinical pharmacology or toxicology studies submitted to support the indication (b) (4). There were no new nonclinical studies to support the PLLR labeling changes. New clinical information concerning pregnancy was submitted and is being reviewed by the clinical team and Pediatric and Maternal Health (DPMH, reviews forthcoming).

The following review includes the nonclinical sections of the proposed PLLR revisions. We defer to the clinical team for final language for the clinical sections.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies were reviewed for the previous approvals for psoriatic arthritis under NDA 205437 (approved March 21, 2014) and for plaque psoriasis under NDA 206088 (approved September 23, 2014). There were no new nonclinical studies to support Supplement 7 for the treatment of Behçet's disease.

1.3 Recommendations

1.3.1 Approvability

Defer to the Clinical team for approvability for the Behçet's disease indication. From the nonclinical standpoint, there are no outstanding issues.

1.3.2 Additional Nonclinical Recommendations

Refer to the recommended labeling changes in the next section.

1.3.3 Labeling

The sponsor's proposed labeling is presented below. The reviewer's recommendations are in blue font (strikethrough as eliminations and underlining as additions). The text of the nonclinical aspects of PLLR labeling was slightly revised to comply with the most recent labeling practice. Changes to eliminate subheadings are recommended to

comply with the CFR. Changes to the clinical aspects were recommended by the Clinical Reviewers and DPMH.

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary
Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Based on findings from animal reproduction studies, OTEZLA may increase the risk for fetal loss. ~~Adequate and well-controlled studies with OTEZLA have not been conducted in pregnant women.~~ (b) (4)

In animal embryo-fetal development studies, the administration of apremilast to pregnant cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. (b) (4) (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. (b) (4)

Data
Animal Data
~~Monkey embryo-fetal development:~~ In an embryo-fetal developmental study, pregnant cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation Days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during Weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an area under the curve [AUC] basis at doses ≥50 mg/kg/day). No abortifacient effects were observed at a dose approximately 1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

~~Mouse embryo-fetal development:~~ In an embryo-fetal development study in mice, apremilast was administered at doses of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study in mice, apremilast was administered at doses of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately 1.3-times the MRHD (10 mg/kg/day).

Apremilast distributed across the placenta into the fetal compartment in mice and monkeys.

In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥4.0-times the MRHD (on an AUC basis at doses ≥80 mg/kg/day). No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

8.2 Lactation

Risk Summary
There are no data on the presence of apremilast in human milk, the effects (b) (4) (b) (4) on the breastfed infant, or the effects of the drug on milk production.

However, apremilast was detected in the milk of lactating mice. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed child from OTEZLA or from the underlying maternal condition.

Data
Animal Data
In mice, following a single injection of 10 mg/kg to dams on postpartum day 13, apremilast concentrations in milk were approximately 1.5-times that of simultaneously collected blood samples.

Reviewer's comment: The reviewer recommends elimination of the animal data subheadings above to comply with CFR format, (21 CFR 201.56 and 201.57). Other minor edits are suggested according with current labeling practice.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

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.

Reviewer's comment: The Applicant proposes to eliminate naming the specific patient diseases (previous labeling statement: "The specific mechanism(s) by which apremilast exerts its therapeutic action ~~in psoriatic arthritis patients and psoriasis patients~~ is not well defined.") since a third one and possibly others may be added. This is acceptable to the nonclinical reviewer but defer to the clinical reviewer for a final decision.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8-times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).

Reviewer's comment: The Applicant did not propose changes to Section 13 of the label and the nonclinical reviewer agrees with the current labeling.

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/s/

LAWRENCE S LESHIN
06/03/2019 11:39:36 AM

CAROL M GALVIS
06/03/2019 12:00:05 PM
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s007

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2019143
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 205437
Sponsor/Applicant:	Celgene Corporation
Established Name/Trade Name:	Apremilast/Otezla
Indication:	Adult patients with oral ulcers associated with Behcet's disease
Meeting Type/Deliverable:	Recommendations to the Division
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Clinical Reviewer	Nadia Habal
Clinical Team Leader (TL)	Rachel Glaser
Review Division Project Manager:	Ngoc-Linh Do
COA Reviewer:	Wen-Hung Chen
COA TL:	Elektra Papadopoulos
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	April 30, 2019
Date COA Review Completed:	June 21, 2019

Please check all that apply: ☒Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to supplemental NDA 205437 for apremilast. The applicant has one completed phase 2 clinical trial and one on-going phase 3 trial for this drug development program, and has submitted an application for regulatory approval. The proposed indication is treatment for adult patients with oral ulcers associated with Behcet's disease (BD).

Supportive efficacy and safety data through Week 24 from the completed Phase 2 Study BCT-001 in subjects with BD are also included in this submission. Results from the ongoing study, BCT-002, supported by the Phase 2 study, BCT-001, provide the basis to support this supplemental NDA (sNDA) for oral ulcers associated with BD.

The applicant administered the following patient-reported outcome (PRO) measures in their ongoing randomized, double-blind, placebo-controlled Phase 3 study in patients with least 18 years of age with a BD diagnosis meeting the International Study Group (ISG) criteria for BD.

Table 1. COAs Included in Study BCT-002

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
Behçet's Syndrome Activity Score (BSAS)/(PRO)	BD Symptom Activity	Secondary	Appendix A
Behçet's Disease Quality of Life (BD QoL)/(PRO)	Quality of Life	Secondary	Appendix B

PRO= Patient-reported outcome

This submission included study protocol, study report body, and clinical overview. (b) (4) [redacted]

The review concludes that the evidence submitted by the applicant is insufficient to demonstrate that the BSAS and BD QoL are fit-for-purpose[2] to measure symptom activity and quality of life, respectively, in the context of use (see Table 2). (b) (4) [redacted]

(b) (4) [redacted]

The Behçet's Syndrome Activity Score (BSAS):

- Based on the face validity, BSAS appears to assess symptoms that are relevant and important to the patients. However, qualitative data (e.g., input from patients) is needed to support its content validity.
- BSAS uses a mixture of rating scales that includes yes/no response, and 3-point and 21-point rating scales. It is unclear whether the patients understand and interpret the items and response scales correctly as intended, and are able to choose responses that match their experiences.
- A specific scoring algorithm is used to combine the different rating scale into a single score. This algorithm weights the items disproportionally. It is unclear whether this scoring algorithm is appropriate or interpretable as no rationale or justification is provided.
- In addition, we are concerned that the 4-week recall may be too long for the patients to clearly remember the number of new ulcers or acnes appeared over the past 4 weeks.

Behçet's Disease Quality of Life (BD QoL):

- The BD QoL contains 30 items that assess four domains including: relationships, emotions, limitations in day to day activities, and self-image. Quality of life is a complex,

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.
[2] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

multi-domain concept that can be challenging to measure. Because QoL measures concepts that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect, we recommend the applicant selects and separately analyzes the most important patient-reported symptoms and functional impacts (i.e., activities of daily living) that are responsive to treatment.

- It is not clear whether all of the items included in BD QoL are relevant and important to the patients with BD. It is necessary for the applicant to provide evidence of its content validity to demonstrate that the domains are most relevant to the disease with the focus on the domains that are most likely to benefit from treatment.
- We also have concern with the dichotomous scale used in BD QoL. Various aspects of quality of life generally change gradually following the improvement in disease symptoms. As such, a true/not true dichotomous response scale is not likely to capture the granularity of the change that the patients may experience, especially within 12 weeks. This dichotomous response scale may force the patients to choose the all-or-none response that does not fully reflect the changes that they have experiences.
- Finally, the recall period, "at the moment," may not be well-defined. The understanding and interpretation of "at the moment" may vary greatly among individuals.

Please refer to Section B for detailed comments and additional advice to the sponsor.

B. SUGGESTED COMMENTS TO APPLICANT

No COA-related questions were submitted by the applicant. In completion of our COA Review, we have the following comments:

FDA Comments:

(b) (4)

At this time, we have insufficient information to comment fully on the both Patient-reported outcome (PRO) measures in the absence of information. We have the following recommendations:

- You have not provided evidence of content validity and measure properties to support that these two instruments are well-defined, reliable, and fit-for-purpose for use as study endpoints in the stated context of use.

- On the surface, BSAS appears to assess symptoms that are relevant and important to the patients. However, BSAS uses a mixture of rating scale that include yes/no response, and 3-point and 21-point rating scales. We recommend that you submit qualitative data (e.g., patient cognitive interviews) to demonstrate that the patients understand and interpret the items and response scales correctly as intended, and are able to choose responses that match their experiences. In addition, a scoring algorithm is developed to combine the different rating scale into a single score. This algorithm weighted the items disproportionally. We recommend that you provide rationale or justification to support that this scoring algorithm is appropriate and interpretable. Finally, we are concerned that

the 4-week recall may be too long for the patients to clearly remember the number of new ulcers or acnes appeared during the past 4 weeks.

- The BD QoL contains 30 items that assess four domains including relationships, emotions, limitations in day to day activities, and self-image. Quality of life is a complex, multi-domain concept that can be challenging to measure. Claiming a statistical and meaningful improvement in QoL implies (1) that all QoL domains that are important to the clinical trial's population related to how they feel or function; (2) that a general improvement was demonstrated; and (3) that no decrement was demonstrated in any domain. Because HRQL measures concepts that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect, we recommend you select and separately analyze the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment. A such, it is not clear whether the items included are relevant and important to the patients with BD. It is necessary that you to provide evidence of its content validity to demonstrate that it focuses on the most relevant domains to the disease and those are most likely to benefit from treatment.

- We also have concern with the dichotomous scale used in BD QoL. Various aspects of quality of life generally change gradually following the improvement in disease symptoms. As such, a true/not true dichotomous response scale is not likely to capture the granularity of the change that the patients may experience, especially within 12 weeks. This dichotomous response scale may force the patients to choose the all-or-none response that does not fully reflect their change. If you have evidence to support that the dichotomous scale is appropriate for this context of use, please provide evidence for our review. Finally, the recall period, "at the moment," does not appear to be well-defined or consistently interpret across patients

- 

- (b) (4)

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:
Apremilast was approved by the US Food and Drug Administration (FDA) on 21 Mar 2014 for the treatment of adult patients with active PsA (New Drug Application [NDA] 205437) and on 23 Sep 2014 for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (NDA 206088; administratively closed).

Regulatory guidance and advice from the US FDA relating to the clinical development program in BD are summarized in Table 2 (pp. 17-20) in the Clinical Overview Document (dated Sep. 21, 2018) included in this sNDA submission.

There are currently no approved drugs for the treatment of BD or any manifestation of BD in the US.

Disease Background:
Behçet's disease is a chronic multisystem variable vessel vasculitis characterized by oral ulcers, the hallmark of the disease, and genital ulcers, skin lesions, uveitis, arthritis, vascular, CNS, and GI involvement. Oral ulcers are usually the first and most frequent manifestation of BD. Patients report pain and have difficulty with activities of daily living such as eating and drinking, and speaking, which impedes communicating and social interactions with others and their QoL. The disease is characterized by a relapsing-remitting course, with symptoms of varying severity across almost all organ systems.

Investigational Product:
Otezla® (apremilast; CC-10004) is an oral small-molecule inhibitor of phosphodiesterase type 4 (PDE4) that works intracellularly to modulate a network of proinflammatory and anti-inflammatory mediators.

Other materials reviewed:
CC-10004-BCT-001 - Protocol Amendment 2
CC-10004-BCT-001 - Study Report Body – Amendment
CC-10004-BCT-001 – Synopsis
CC-10004-BCT-002 - Protocol Amendment 1
CC-10004-BCT-002 - Study Report Body
CC-10004-BCT-002 – Synopsis
Clinical Efficacy for Behçet's Disease - 21 Sep 2018
Clinical Overview - 21 Sep 2018

2 FIT-FOR-PURPOSE SUMMARY

Table 2 summarizes the fit-for-purpose assessment.

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established[3]	Supported by:	Location of Supporting Materials
Behçet's Syndrome Activity Score (BSAS)	☐ Yes ☒ Potentially - insufficient evidence available; additional information is needed ☐ No	☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	Not provided
Behçet's Disease Quality of Life (BD QoL)	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☐ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	Not provided

3 CONTEXT OF USE

3.1 Clinical Trial Population

The target population for Study BCT-002 are adult patients with a Diagnosed with BD meeting the International Study Group criteria. Key criteria for inclusion are as the followings:

- Male or female ≥ 18 years of age.
- Diagnosed with BD meeting the International Study Group criteria.

[3] See Sections 5 and 6 of this COA review for more detailed information.

- Oral ulcers that occurred at least 3 times in the previous 12-month period, including oral ulcers at the Screening Visit.
- Subjects must have had at least 2 oral ulcers at the Screening Visit. Subjects must have had 1 of the following:
    - At least 2 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurred at least 14 days after Visit 1; OR
    - At least 3 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurred at any time between 1 day and 42 days after Visit 1.

A complete list of the inclusion and exclusion criteria is summarized in CC-10004-BCT-002 - Protocol Amendment 1.

3.2 Clinical Trial Design

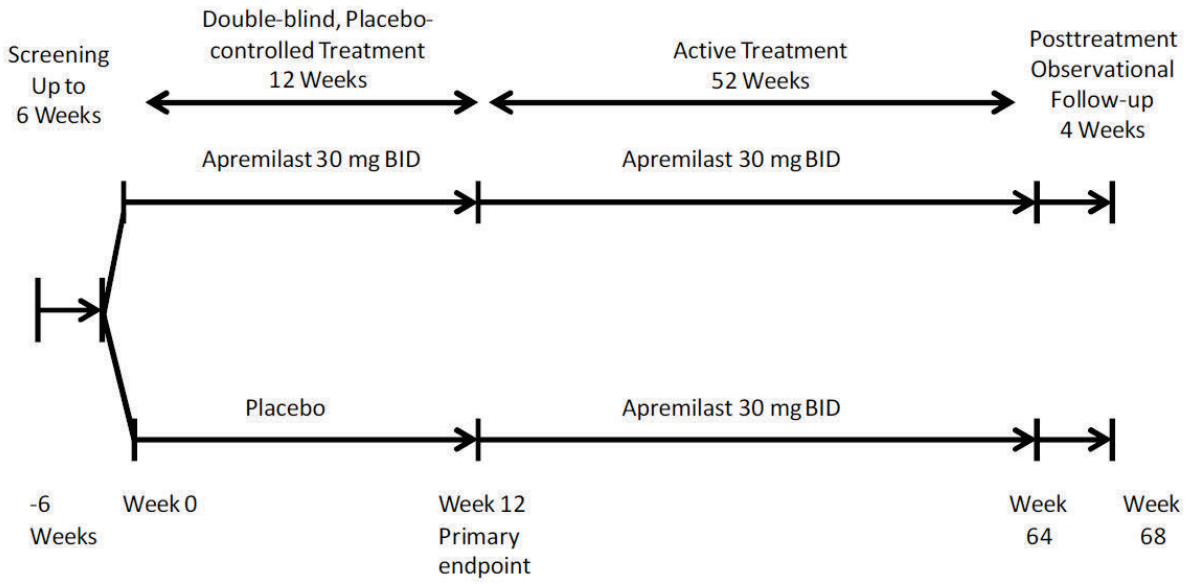
Table 3 describes the clinical trial design of Study BCT-002.

Table 3. Clinical Trial Design for Study BCT-002

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority	74 weeks	Yes

Figure 1 shows the overall study design. Refer to the CC-10004-BCT-002 - Protocol Amendment 1 for more details on the clinical trial design.

Figure 1. Overall study design for Study BCT-002



Reviewer's comment(s):

Study BCT-001, a completed phase 2 study, provides up to 24 weeks of efficacy data on apremilast (12-week placebo-controlled treatment phase and 12-week active treatment extension phase, both completed).

Study BCT-002, an on-going phase 3 study, provides up to 28 weeks of efficacy data on apremilast (12-week placebo-controlled treatment phase [completed] and the first 16 weeks of the 52-week active treatment phase [ongoing]).

Study BCT-002 consists of 4 phases: a 6-week screening phase, a 12-week double-blind placebo-controlled treatment phase, a 52-week active treatment phase, and a 4-week posttreatment observational follow-up phase.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study BCT-002.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Study BCT-002

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary (COA and/or biomarker)	Ulcers counts (ClinRO)	Total number of oral ulcers	Area under the curve for the number of oral ulcers from baseline through Week 12/Day 85 (AUCW0-12)	☐ Daily ☒ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary	Ulcers counts (ClinRO)	Ulcer free response	Complete response rate for oral ulcers at Week 12, defined as the proportion of subjects who were oral ulcer-free.	☐ Daily ☒ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	BSAS (PRO)	BD Symptom activity	Change from Baseline BSAS score at Week 12	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: at Baseline and Week 12 ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	BD QoL (PRO)	Quality of Life	Change from baseline in the BD QoL score at Week 12	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: at Baseline and Week 12 ☐ Assessment at cross-over or early discontinuation

ClinRO= Clinician-reported outcome; **PRO=** Patient-reported outcome

Reviewer's comment(s):

- ***There are four more secondary endpoints higher in the endpoint hierarchy than BSAS and BD QoL. They are:***

- ***Change from baseline in the pain of oral ulcers as measured by VAS at Week 12***
- ***Complete response rate for genital ulcers at Week 12 for subjects who had genital ulcers at Baseline***
- ***Change from baseline in the pain of genital ulcers, as measured by VAS at Week 12 in subjects who had genital ulcers at baseline***
- ***Change from baseline in disease activity as measured by Behçet's Disease Current Activity scores (BD Current Activity Form) at Week 12***

(b) (4)

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

Table 5. Concepts of Interest for COAs Included in Study BCT-002

COA name	Concept(s)
Behçet's Syndrome Activity Score (BSAS)/(PRO)	BD Symptom Activity
Behçet's Disease Quality of Life (BD QoL)/(PRO)	Quality of Life

The conceptual frameworks for BSAS and BD QoL are shown in Tables 6 and 7, respectively.

Table 6. Conceptual Framework for BSAS

Item	Domain (if applicable)	General Concept
Ex: Item 1. How much have ulcers in your mouth bothered you over the last 4 weeks	BD Symptom Activity	Severity and activity BD ulcers
Ex: Item 2. How many (new or old) ulcer did you have in your mouth over the last 4 weeks		

Table 7. Conceptual Framework for BD QoL

Item	Domain (if applicable)	General Concept
Ex: My life revolves around hospital visits	Limitation to daily activities	Quality of life
Ex: Nothing interests me	Emotions	
Ex: I do not like being touched	Social	
Ex: I feel terrible about the way I look	Self-imagine	

Reviewer's comment(s):

The conceptual framework regarding BSAS is not clear. The items mostly asked about the degree of bothersome of ulcers and numbers of ulcers in different locations. However, it also includes other BD symptoms, such as GI symptoms, vision problems, etc. The mixtures of response scales also make it difficult to identify how the items form the conceptual framework.

5 CLINICAL OUTCOME ASSESSMENT(S)

Behçet's Syndrome Activity Score (BSAS):

The Behçet's Syndrome Activity Score (BSAS) contains 10 questions, including ones that assess the number of new oral and genital ulcers and skin lesions; assess gastrointestinal (GI), CNS, vascular, and ocular involvement; and evaluates the subject's current level of discomfort. The item scores are totaled to create a score ranging from 0 to 100. The BSAS is completed by the subject on a secure, validated hand-held device.

Behçet's Disease Quality of Life (BD QoL):

The BD QoL questionnaire was developed to measure the influence of BD on a patient's life. It consists of 30 self-completed items that measure disease related restrictions on the patient's activities and the patient's emotional response to these restrictions.

Reviewer's comment(s):

- ***Based on the face validity, BSAS appears to assess symptoms that are relevant and important to the patients. However, qualitative data (e.g., input from patients) is needed to support its content validity.***

- ***BSAS uses a mixture of rating scales that includes yes/no response, and 3-point and 21-point rating scales. It is unclear whether the patients understand and interpret the items and response scales correctly as intended, and are able to choose responses that match their experiences.***
- ***In addition, we are concerned that the 4-week recall may be too long for the patients to clearly remember the number of new ulcers or acnes appeared over the past 4 weeks.***

- ***It is not clear whether all of the items included in BD QoL are relevant and important to the patients with BD. It is necessary for the applicant to provide evidence of its content validity to demonstrate that the domains are most relevant to the disease with the focus on the domains that are most likely to benefit from treatment.***
- ***We also have concern with the dichotomous scale used in BD QoL. Various aspects of quality of life generally change gradually following the improvement in disease symptoms. As such, a true/not true dichotomous response scale is not likely to capture the granularity of the change that the patients may experience, especially within 12 weeks.***
- ***The recall period, "at the moment," may not be well-defined. The understanding and interpretation of "at the moment" may vary greatly among individuals.***

6 SCORING ALGORITHM

Behçet's Syndrome Activity Score (BSAS):

Questions 1, 3, and 5 are scored 0-10
Questions 2, 4, and 6, are scored as 0, 5, or 10 depending on which of the 3 responses is checked
Questions 7, 8, and 10 are score as 0 or 10.

Behçet's Disease Quality of Life (BD QoL):

Sum of the items that are checked as being 'true'

Reviewer's comment(s):

The scoring algorithm used to combine the different rating scale into a single score may weight the items disproportionally. It is unclear whether this scoring algorithm is appropriate or interpretable as no rationale or justification is provided.

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

☒ Copy of instrument
☐ Literature review and/or publications
☐ Documentation of expert input
☐ Qualitative study protocols and interview guides for focus group or patient interviews

☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
☐ Synopsis of qualitative findings
☐ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
☐ Quantitative summary report with evidence to support item retention and scoring
☐ Transcripts (if available)

Tables 8 amd 9 documents the adequacy of the content of the BSAS and BD QoL, respectively.

Table 8. Review of Content Validity for BSAS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☐ Literature ☒ Clinical input e.g. discussion with clinical reviewer	
Content validity	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☐ Target sample for qualitative research is appropriate. ☐ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	*Information not provided*

Table 9. Review of Content Validity for BD QoL

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☐ Literature ☒ Clinical input e.g. discussion with clinical reviewer	
Content validity	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☐ Target sample for qualitative research is appropriate. ☐ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	*Information not provided*

Reviewer's comment(s):

The sNDA submission does not include any information regarding the content validity of either BSAS or BD QoL.

8 OTHER MEASUREMENT PROPERTIES

Other measurement properties (reliability, construct validity and ability to detect change) are not reviewed until the COA's content validity has been established.

To date, no information regarding the measurement properties of either instrument has been submitted.

Reviewer's comment(s):

The sNDA submission does not include any information regarding the measurement properties of either BSAS or BD QoL.

9 INTERPRETATION OF SCORES

To date, the information regarding interpretation of the scores has not been submitted.

D. APPENDICES

Appendix A: Behçet's Syndrome Activity Score (BSAS)

Behçet's Syndrome Activity Scale (BSAS)

Your name:_____ **Date of Birth:** _____ **Today's Date:**_____

Your: **SEX:** ☐ Female ☐ Male **ETHNIC** ☐ Asian ☐ Hispanic ☐ Other _____ **GROUP:** ☐ Black ☐ White

1. How much have **ulcers in your mouth** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

2. How many **ulcers (new or old)** did you have in your **mouth** over the last 4 weeks?
   - 0 ☐
   - 1-3 ☐
   - More than 3 ☐

3. How much has **ulcers in genital area** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

4. How many **ulcers (new or old)** did you have in your **genital area** over the last 4 weeks?
   - 0 ☐
   - 1-3 ☐
   - More than 3 ☐

5. How much has **acne or acne like skin lesions (new or old)** bothered you over the last 4 weeks? Please indicate below

NO SKIN LESIONS ○○○○○○○○○○○○○○○○○○○○ **SKIN LESIONS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

6. How many **acne or acne like skin lesions (new or old)** did you have over the last 4 weeks?
   - 0 ☐
   - 1-5 ☐
   - More than 5 ☐

7. Have you had **abdominal pain and diarrhea** lasting most of the day for most days of the week over the last 4 weeks?
   ☐**No** ☐ **Yes**

8. Did you have **painful or red eyes and/or blurred or reduced vision** over the last 4 weeks?
   ☐**No** ☐ **Yes**

9. Did you have any **swelling/discoloration of your lower extremities, or a blood clot** over the last 4 weeks?
   ☐**No** ☐ **Yes**

10. In terms of your **Behcet's activity, (oral ulcers, genital ulcers, skin problems, joint pains, eye, neurologic problems),** how active would you say your condition has been over the last 4 weeks?

NOT ACTIVE AT ALL ○○○○○○○○○○○○○○○○○○○○ **EXTREMELY ACTIVE**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

Scoring:

Questions 1, 3, 5, and 10 are scored 0-10

Questions 2, 4, 6, are scored 0, 5 or 10 depending on which of the 3 are checked

Questions 7, 8, 9 are scored 0 or 10

For a total score of 100

Fig. 1. Behçet's Syndrome Activity Score (BSAS).

Appendix B: Behçet's Disease Quality of Life (BD QoL)

Please read each statement carefully and decide whether it applies to you *at the moment*

		True	Not True
1	My life revolves around hospital visits	☐	☐
2	Nothing interests me	☐	☐
3	It's too much effort to go out and see people	☐	☐
4	Walking is painful	☐	☐
5	It takes me longer to do things	☐	☐
6	I cannot stand for long	☐	☐
7	My condition interferes with my life	☐	☐

Please remember to read each statement thinking about your Behçet's Disease. Please choose the response that applies best to you at the moment.

		True	Not True
8	It is difficult to get out of bed	☐	☐
9	I feel terrible about the way I look	☐	☐
10	Talking is stressful	☐	☐
11	I feel dependent on others	☐	☐
12	I feel older than my years	☐	☐
13	It limits the places I can go	☐	☐
14	I find it difficult to take care of the people I am close to	☐	☐
15	I cannot rely on how I will be tomorrow	☐	☐

Please read each statement carefully and decide whether it applies to you *at the moment*

		True	Not True
16	My condition is drastically affecting my life	☐	☐
17	I often get frustrated	☐	☐
18	I feel like a prisoner in my own home	☐	☐
19	My condition affects important decisions in my life	☐	☐
20	I do not like being touched	☐	☐
21	I cannot speak properly	☐	☐
22	It puts a strain on my personal relationships	☐	☐

Please remember to read each statement thinking about your Behçet's Disease. Please choose the response that applies best to you at the moment.

		True	Not True
23	I feel useless	☐	☐
24	I worry that I hold others back	☐	☐
25	People close to me have lost out because of my condition	☐	☐
26	I feel unable to cope with my condition	☐	☐
27	I have lost contact with people	☐	☐
28	I worry about the effects on others	☐	☐
29	Everything is getting to me today	☐	☐
30	I feel lonely	☐	☐

Thank you for taking the trouble to fill in this questionnaire

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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/

WEN-HUNG CHEN
06/21/2019 09:08:40 PM

ELEKTRA J PAPADOPOULOS
07/06/2019 03:26:25 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 3, 2019

To: Ngoc-Linh Do, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm. D., Team Leader, OPDP

Subject: OPDP Labeling Comments for OTEZLA (apremilast) tablets, for oral use

NDA: 205437 / Supplement 007

In response to DPARP's consult request dated November 15, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for OTEZLA (apremilast) tablets, for oral use (Otezla). This supplement (S007) provides for the addition of the oral ulcers associated with Behcet's Disease indication to the labeling.

PI: OPDP has reviewed the attached proposed PI received by electronic mail from DPARP (Linh Do) on May 22, 2019, and we do not have any comments.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPARP (Linh Do) on May 21, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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

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/s/

ADEWALE A ADELEYE
06/03/2019 01:17:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 13, 2019 **Date consulted:** February 28, 2019

From: Carrie Ceresa, Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Pulmonary, Allergy and Rheumatology Products

Drug: OTEZLA (apremilast)

NDA: 205437

Applicant: Celegene Corporation

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Indications:

- *Approved*
  - Adult patients with active psoriatic arthritis
  - Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- *Proposed*
  - Adult patients with oral ulcers associated with Behçet's Disease

Materials Reviewed:

- September 21, 2019, Efficacy Supplement for NDA 205437, OTEZLA (apremilast)
- February 28, 2019, Consult form for NDA 205437, DARRTS Reference ID 4397412

- November 14, 2014, OTEZLA (apremilast), NDA 205437, IND 101761, Pregnancy Registry Protocol Review, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, DARRTS Reference ID 3656954
- December 6, 2013, OTEZLA (apremilast), NDA 205437, IND 101761, Labeling recommendations, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, DARRTS Reference ID 3416449

Consult Request: "Please review the applicant's proposed PLLR conversion of the label."

INTRODUCTION AND BACKGROUND

On September 21, 2018, Celgene Corporation submitted an Efficacy Supplement for Otezla (apremilast) tablets to expand the indication to include the treatment of adult patients with oral ulcers associated with Behçet's disease and to comply with the requirements of the Pregnancy and Lactation Labeling Rule (PLLR). The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 28, 2019, to assist with the PLLR subsections of labeling. This review also includes a summary of the April 13, 2018, interim report for the Apremilast Pregnancy Outcome Exposure Registry: An Autoimmune Disease in Pregnancy Project.

Otezla (apremilast) was originally approved on March 21, 2014 for the treatment of adult patients with active psoriatic arthritis and the indication was expanded on September 23, 2014 to include the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) which affects the activity of inflammatory cells that are present in psoriasis. Apremilast causes an elevation of cyclic adenosine monophosphate (cAMP) through its inhibition of PDE4. Cyclic adenosine monophosphate functions as a suppressor of the immune functions of phagocytes through the generation of inflammatory mediators. However, the mechanism by which apremilast exerts action in psoriatic arthritis patients and psoriasis patients is not well defined.[1] Apremilast has the following drug characteristics:[2]

- Molecular weight: 460.5 Daltons
- Human plasma protein binding is approximately 68%
- Volume of distribution: 87L
- Terminal elimination half-life of 6-9 hours
- Most common adverse reactions are diarrhea, nausea, headache and upper respiratory tract infection
- Warnings and precautions include diarrhea, nausea, vomiting, depression, weight decrease and drug interactions with strong cytochrome P450 enzyme inducers

Current State of the Labeling

The current package insert is in the Physician Labeling Rule (PLR) format but not the PLLR format.

- There is not a warning and precautions for embryofetotoxicity.

[1] December 6, 2013, Otezla (apremilast), NDA 205437, IND 101761, Labeling recommendations, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, DARRTS Reference ID 3416449

[2] June 6, 2017. FDA approved package insert. Otezla NDA 205437. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=205437

- There is not a contraindication for pregnancy or lactation.
- The current label does not contain any clinical data with regard to pregnancy and lactation but does contain nonclinical data.
- There are no existing pregnancy testing/contraception recommendations.
- There are no known drug-drug interactions with hormonal contraceptives.

PREGNANCY

Disease/Condition and Pregnancy

Psoriatic arthritis

- Psoriatic arthritis is a form of arthritis that causes joint pain, stiffness and swelling and is usually coupled by a red, silvery scaled rash on the skin.[1]
- Treatment options are focused on controlling the symptoms and preventing further damage to joints.[1]
- During pregnancy, symptoms are unpredictable as some women experience an improvement in symptoms while some women report worsening of symptoms.[1]

Plaque psoriasis

- Plaque psoriasis is the most common form of psoriasis. Plaque psoriasis manifests as scaly, silver rash in patches on the skin, often appearing on the scalp, knees, lower back or elbows.[3]
- According to the National Psoriasis Foundation, pregnancy and breastfeeding are generally safe for people with psoriatic disease. Many women often report disease flare shortly after giving birth.[3]
- Treatment with moisturizers, emollients and phototherapy are typically first line therapy; however, biologics and oral treatments may also be appropriate.[1,3]

Behçet's disease

- Behçet's disease is a rare autoimmune disorder of unknown cause that can affect multiple areas of the body such as the genitourinary, cardiovascular, pulmonary and skeletal.[4]
- There are only a small number of reported cases of pregnancy and Behçet's disease in the literature that suggest no increase in obstetric complications and adverse neonatal outcomes compared to patients without Behçet's disease.[5]
- The disease is present worldwide but highest prevalence is in the Middle East.[6]
- According to the American Behçet's Disease Association, because the disease affects different parts of the body, patients will likely be treated by a variety of specialists.[7] Treatment for oral ulcers includes a number of treatment options according to published

[3] Pregnancy and Breastfeeding. National Psoriasis Foundation. https://www.psoriasis.org/pregnancy. Accessed 11 April 2019.
[4] Gokcen O et al. Behcet's disease and pregnancy: what to expect? Journal of Obstetrics and Gynaecology. 2019. 38 (2):185-188.
[5] Iskender C et al. Behcet's disease and pregnancy: a retrospective analysis of course of disease and pregnancy outcome. J Obstet Gynecol Res. 2014. 40(6):1598-602.
[6] Saleh Z and T Arayssi. Update on the therapy of Behcet's disease. Ther Adv Chronic Dis. 2014. 5(3):112-134.
[7] Treatment. American Behcet's Disease Association. https://www.behcets.com/basics-of-behcets/treatment/. Accessed 15 April 2019.

literature including triamcinolone acetonide, colchicine, mycophenolate mofetil, thalidomide, dapsone, steroid gels and pentoxifylline.[6]

REVIEW

Nonclinical Experience

In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0-times the MRHD. The reader is referred to the Pharmacology/Toxicology review by Lawrence Leshin, Ph.D. in DARRTS.

Apremilast Pregnancy Registry Interim Report

The 2017 apremilast pregnancy exposure registry interim report was completed on April 14, 2018. The purpose of the registry is to monitor planned and unplanned pregnancies exposed to apremilast and to evaluate the possible teratogenic effects of apremilast relative to specified pregnancy outcomes and to evaluate potential effects of prenatal apremilast exposure on infant health status through one year of life. For a full review of the apremilast pregnancy registry protocol the reader is referred to the November 14, 2014, DPMH review.[8]

Overview of Study Design

The study is being conducted by the Organization of Teratology Information Specialists (OTIS), a network of tetragon information centers serving pregnant women and health care providers throughout North America. The primary objective of the study is to evaluate whether there is any increased risk of major birth defects, specifically a pattern of anomalies in apremilast-exposed pregnancies compared to the primary comparison group of disease-matched unexposed pregnancies. The secondary objectives of the registry are to determine if there is an increase in the risk of spontaneous abortion, stillbirth or preterm delivery in apremilast-exposed pregnancies compared to disease-match unexposed pregnancies, and among live born infants, to determine if there is an increase in the risk of a specific pattern of minor anomalies, reduced birth size, postnatal growth deficiency up to one year of age, and serious or opportunistic infections or malignancies up through one year of age compared to the primary comparison group. The tertiary objective of the registry is to compare the rate of major birth defects in the apremilast-exposed pregnancies to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program (Centers for Disease Control and Prevention, 1998).

Results

The study began enrolling subjects on October 31, 2014. As of October 2, 2017, two subjects have been enrolled in the apremilast-exposure group (one has completed pregnancy), 34 women have been enrolled in the diseased-unexposed group (29 have completed pregnancies), 27 women have been enrolled in the non-diseased unexposed group (all 27 have completed

[8] November 14, 2014, Otezla (apremilast), NDA 205437, IND 101761, Pregnancy Registry Protocol Review, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, DARRTS Reference ID 3656954.

pregnancies). One woman has been enrolled in the apremilast-exposed case series which enrolls women who did not meet the prospective cohort study design.

Demographics and Baseline Characteristics
Subjects were most commonly reported to be non-Hispanic and non-Latino ethnicity, white race and to have at least some undergraduate college education. BMI was reported for most subjects to be within the normal range of 18.5 to 24.9. The majority of subjects reported no previous spontaneous abortions at the time of enrollment. The majority of subjects reside in the United States whereas only 15 reside in Canada. Forty-three subjects reported some alcohol use post-conception (amount and timing unknown) and 12 subjects reported tobacco use in pregnancy post-conception (amount and timing unknown).

Lost to follow-up
To date, three women have been lost-to-follow up, one (1/24, 4.2%) in the psoriasis diseased unexposed group, one (1/29, 3.4%) in the disease unexposed group and one (1/27, 3.7%) in the non-diseased unexposed group.

Pregnancy Outcomes
Table 1. Pregnancy Outcomes in Women Enrolled in the Study (Corresponds to Appendix 6a, Table 10, Page 28, applicant's submission, PSUR)[9]

	Apremilast Exposed Psoriasis (N=1) n/N'(%)	Apremilast Exposed Psoriatic Arthritis (N=0) n/N'(%)	Apremilast Exposed Total (N=1) n/N'(%)	Psoriasis Diseased Unexposed (N=24) n/N'(%)	Psoriatic Arthritis Diseased Unexposed (N=5) n/N'(%)	Diseased Unexposed Total (N=29) n/N'(%)	Non-Diseased Unexposed (N=27) n/N'(%)
Live birth	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	21/24 (87.5)	5/5 (100.0)	26/29 (89.7)	22/27 (81.5)
Twin	0/1 (0.0)	----	0/1 (0.0)	0/21 (0.0)	0/5 (0.0)	0/26 (0.0)	0/22 (0.0)
Twin with like sex	----	----	----	----	----	----	----
Sex (Male)	----	----	----	----	----	----	----
Twin with non- like sex	----	----	----	----	----	----	----

[9] September 21, 2019, Efficacy Supplement for NDA 205437, Otezla (apremilast).

	Apremilast Exposed Psoriasis (N=1) n/N'(%)	Apremilast Exposed Psoriatic Arthritis (N=0) n/N'(%)	Apremilast Exposed Total (N=1) n/N'(%)	Psoriasis Diseased Unexposed (N=24) n/N'(%)	Psoriatic Arthritis Diseased Unexposed (N=5) n/N'(%)	Diseased Unexposed Total (N=29) n/N'(%)	Non-Diseased Unexposed (N=27) n/N'(%)
Twin with only one surviving	----	----	----	----	----	----	----
Sex (Male)	----	----	----	----	----	----	----
Singleton	1/1 (100.0)	----	1/1 (100.0)	21/21 (100.0)	5/5 (100.0)	26/26 (100.0)	22/22 (100.0)
Sex (Male)	1/1 (100.0)	----	1/1 (100.0)	8/21 (38.1)	3/5 (60.0)	11/26 (42.3)	11/22 (50.0)
Caesarian	1/1 (100.0)	----	1/1 (100.0)	11/21 (52.4)	2/5 (40.0)	13/26 (50.0)	7/22 (31.8)
Spontaneous Abortion	0/1 (0.0)	0/0 (0.0)	0/1	2/24	0/5	2/29	4/27
Spontaneous Abortion-Twins	----	----	----	0/2 (0.0)	----	0/2 (0.0)	0/4 (0.0)
Stillbirth	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)	0/24 (0.0)	0/5 (0.0)	0/29 (0.0)	0/27 (0.0)
Termination	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)	0/24 (0.0)	0/5 (0.0)	0/29 (0.0)	0/27 (0.0)
Social	----	----	----	----	----	----	----
Medical	----	----	----	----	----	----	----
Lost to Follow-up	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)	1/24 (4.2)	0/5 (0.0)	1/29 (3.4)	1/27 (3.7)
No contact	----	----	----	1/1 (100.0)	----	1/1 (100.0)	1/1 (100.0)
Withdrew	----	----	----	0/1 (0.0)	----	0/1 (0.0)	0/1 (0.0)

N: Number of subjects with pregnancy outcome
n/N' (%) is either out of total N or % of the N' subcategories under the live birth, termination or lost to follow-up rows.

- One malformation reported: patent foramen ovale (PFO) still present at 2 months of age (live-born infant born at 38.6 weeks gestation) in the psoriasis disease unexposed group
- One functional defect reported: pulmonary hypertension due to severe anoxia; intracranial hemorrhage due to anoxia in a live-born infant at 42.9 weeks gestation in the psoriasis diseased unexposed group.

Reviewer comment:
At this time, there is are insufficient data in the registry to analyze and draw conclusions regarding a drug-associated risk of major birth defects, miscarriage or adverse pregnancy or fetal outcomes. The Registry Advisory Committee has recommended continuation of the registry and DPMH agrees with this assessment. The registry is scheduled to continue until 2028.

Review of Pharmacovigilance Database
The applicant conducted a search of their safety database through March 20, 2018. The reader is referred to the applicant's submission for specific MedDRA search parameters. The search revealed 154 cases (132 post-marketing sources and 22 clinical trials) of potential fetal exposure to apremilast during pregnancy. The data includes prospective (n=125) and retrospective (n=7) apremilast pregnancy cases. In addition, the applicant also provided data on 69 cases received during the Periodic Safety Update Report (PSUR) March 21, 2017 through March 20, 2018, reporting period (55 from post-marketing and two from clinical studies). These data are summarized in Appendix A, Tables 1 and 2)

Prospective Post-Marketing Pregnancy Cases (n=125)
Table 2. Cumulative Prospective Post-Marketing Cases by Timing of Exposure to Apremilast in Pregnancy and Pregnancy Outcome (Corresponds to Appendix 3I, Table 1, Page 2, applicant's submission, PSUR)[9]

Pregnancy Outcome	**Timing of Exposure in Pregnancy (N = 125)**				
	Before Conception	**1st Trimester**	**After 1st Trimester**	**Unknown**	**Total**
Therapeutic abortion	0	1	0	1	2
Elective termination (foetal defects)	0	1	0	0	1
Elective termination (no foetal defects or unknown)	1	3	0	1	5
Live birth without congenital anomaly	1	2	2	1	6
Ongoing	5	3	0	8	16
Spontaneous abortion	0	6	0	5	11
Unknown	10	22	1	51	84
Grand Total	**17**	**38**	**3**	**67**	**125**

- The first trimester elective termination noted in the table above occurred after the patient discovered the fetus was diagnosed with an unknown chromosomal abnormality.
- There was one instance of elective termination due to an ectopic pregnancy.

Retrospective Post-Marketing Pregnancy Cases (n=7)

Table 3. Cumulative Retrospective Post-Marketing Cases by Timing of Exposure to Apremilast in Pregnancy and Pregnancy Outcome (Corresponds to Appendix 3I, Table 2, Page 3, applicant's submission)[9]

Pregnancy Outcome	**Timing of Exposure in Pregnancy (N = 7)**				
	Before Conception	**1st Trimester**	**After 1st Trimester**	**Unknown**	**Total**
Therapeutic abortion	0	0	0	0	0
Elective termination (foetal defects)	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	0
Live birth without congenital anomaly	0	1	1	2	4
Ongoing	0	0	0	0	0
Spontaneous abortion	1	2	0	0	3
Unknown	0	0	0	0	0
Grand Total	**1**	**3**	**1**	**2**	**7**

- 3 spontaneous abortions, no fetal defects, ectopic pregnancies or congenital anomalies

Prospective Clinical Study Cases (n=22)

Table 4. Cumulative Prospective Clinical Study Cases by Timing of Exposure in Pregnancy and Pregnancy Outcome (Corresponds to Appendix 3I, Table 3 Page 3, applicant's submission)[9]

Pregnancy Outcome	**Timing of Exposure in Pregnancy (N = 22)**		
	Before Conception	**First Trimester**	**Grand Total**
Elective termination (no foetal defects or unknown)	2	6	8
Therapeutic abortion	0	1	1
Live birth without congenital anomaly	1	6	7
Spontaneous abortion	0	1	1
Unknown	0	4	4
Ongoing	1	0	1
Grand Total	**4**	**18**	**22**

Review of Literature

The applicant and DPMH conducted a review of published literature with regard to apremilast exposure during pregnancy and no data were found. DPMH's search of published literature included PubMed and Embase regarding apremilast exposure during pregnancy using the following search terms, "apremilast and fetal malformations," "apremilast and spontaneous abortion and miscarriage," "apremilast and embryo-fetotoxicity. In addition to the applicant's review of literature, no additional relevant data were found for review. No additional information was found for review in Micromedex or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

Reviewer comment:
The applicant provided an adequate review of the literature to address the PLLR requirements with regard to apremilast exposure during pregnancy. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

Apremilast was detected in the milk of lactating mice. In a lacteal excretion study evaluating the oral administration of apremilast to lactating CD-1 mice, approximately 13 days postpartum (single dose of 10mg/kg by oral gavage in a volume of 10mL/kg), the mean apremilast plasma concentration at 1 and 6 hours post dose were 984 and 138 ng/mL and concentrations in milk were 1441 and 186 ng/mL, respectively. The mean milk to plasma ratio ranged from 1.46 to 1.62. The reader is referred to the Pharmacology/Toxicology review by Lawrence Leshin, Ph.D., DARRTS.

Review of Literature

The applicant and DPMH conducted a review of published literature with regards to apremilast and breast milk, and no data were found. Also, there are no additional data found in LactMed, *Medication and Mothers Milk,* or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

Reviewer comment:
The applicant conducted a review of the literature to address the PLLR requirements with regard to apremilast and breastfeeding, and no data were found.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8-times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early post implantation losses. There was no effect of apremilast at doses approximately 1.0-time the MRHD (10 mg/kg/day). The reader is referred to the Pharmacology/Toxicology review by Lawrence Leshin, Ph.D., DARRTS.

Review of Literature

The applicant and DPMH conducted a review of the literature that revealed no clinical data regarding apremilast exposure and effects on fertility.

Reviewer comment:
The applicant conducted a review of the literature to address the PLLR requirements with regards to apremilast and females and males of reproductive potential, and no data were found.

DISCUSSION AND CONCLUSIONS

Pregnancy

Although there is no published literature on apremilast exposure during pregnancy, the applicant submitted data from their pharmacovigilance database which consists of 154 exposures; however, the majority of outcomes are unknown. There was only one reported congenital anomaly, and after review of the data DPMH concluded that the data are insufficient to draw conclusions about any drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In addition, DPMH also reviewed the April 13, 2018, interim report for the Apremilast Pregnancy Outcome Exposure Registry: An Autoimmune Disease in Pregnancy Project. Although the registry has enrolled 92 subjects, only two women have been enrolled in the apremilast exposed group and only one of those women had completed their pregnancy by the date of the submission. The applicant's pharmacovigilance program is insufficient as almost 70% of the data collected do not contain outcomes, and therefore, it is not possible to make an assessment of the effects of apremilast exposure during pregnancy.

Lactation

Apremilast is present in the milk of lactating mice. There are no available human data with regards to breastfeeding and apremilast exposure. Because no risks have been identified that would preclude breastfeeding the standard risk/benefit statement is recommended:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed infant from OTEZLA or from the underlying maternal condition.

Females and Males of Reproductive Potential

In animal studies with apremilast, there were no effects observed on male fertility. In female mice, at doses ≥1.8-times the MRHD (≥20 mg/kg/day , estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early post implantation losses. Based on an April 24, 2019 e-mail communication between DPMH and the DPARP Pharmacology/Toxicology Team, the DPARP noted that although the estrous cycles was prolonged in mice, fertility was not affected. There are no available data on the effects of apremilast on human fertility. Therefore, there is no information to relay in subsection 8.3. The information about post-implantation loss will be described in subsection 8.1.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary
Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Based on findings from animal reproduction studies, OTEZLA may increase the risk for fetal loss. In animal embryo-fetal development studies, the administration of apremilast to pregnant cynomolgus monkeys during organogenesis resulted in dose-related increases in embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In pregnant mice, during organogenesis there were no apremilast induced malformations up to exposures 4.0-times the MRHD *(see Data)*. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In an embryo-fetal developmental study, pregnant cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation Days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during Weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an area under the curve [AUC] basis at doses ≥50 mg/kg/day). No abortifacient effects were observed at a dose approximately 1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

In an embryo-fetal development study in mice, apremilast was administered at doses of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study in mice, apremilast was administered at doses of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in post implantation loss at doses corresponding to a systemic exposure of

2.3-times the MRHD and greater (≥20 mg/kg/day . At doses of ≥ 20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately 1.3-times the MRHD (10 mg/kg/day).

Apremilast distributed across the placenta into the fetal compartment in mice and monkeys.

In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥4.0-times the MRHD (on an AUC basis at doses ≥80 mg/kg/day . No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of apremilast in human milk, the effects on the breastfed infant, or the effects on milk production. However, apremilast was detected in the milk of lactating mice. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed infant from OTEZLA or from the underlying maternal condition.

Data

In mice, following a single injection of 10 mg/kg to dams on postpartum day 13, apremilast concentrations in milk were approximately 1.5-times that of simultaneously collected blood samples.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Inform patients that there is a pregnancy registry for pregnant women who have taken OTEZLA during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll *[see Use in Specific Populations (8.1)]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy.

Appendix A

Table 1. Prospective Post-marketing Pregnancy Cases reporting during the PSUR Reporting Interval (March 21, 2017 through March 20, 2018) – corresponds to the applicant PSUR submsision, appendix 3I, Table 4, page 5-28)[1]

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-2016020209	Prior Interval/ Follow-up in PSUR Period	Spontaneous	36	30 mg daily	(b) (6)	Live birth without congenital anomaly	Unk	A pregnancy report was received on (b) (6) The patient stopped taking apremilast because she was pregnant. No details of the pregnancy or delivery were reported, but it was reported that the baby was healthy and normal. No additional information was provided by the prescriber.
USA-2016096932	Prior Interval/ Follow-up in PSUR Period	Spontaneous	31	30 mg BID		Live birth without congenital anomaly	After 1st trimester	A pregnancy report was received on (b) (6). The patient was pregnant and was still taking apremilast. Follow-up information on (b) (6) indicated that the patient had a baby. The gender of the baby and status of baby was not provided. No complications/adverse events were reported. Patient took apremilast during the pregnancy. No additional information was provided by the prescriber.
USA-2016014551	Prior Interval/ Follow-	Spontaneous	25	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). Patient was 8 weeks pregnant (at the time of reporting).
USA-2016046373	Prior Interval/ Follow-up in PSUR Period	Spontaneous	29	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). No additional information has been provided. Additional information was received on (b) (6) from the physician's office, it was noted that the patient was lost to follow up.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
AUS-2016075280	Prior Interval/ Follow-up in PSUR Period	Non-interventional study	30	30 mg BID	[redacted]	Live birth without congenital anomaly	1st trimester	A pregnancy report was received on [redacted]. The patient took apremilast while pregnant. A follow up was received on [redacted]. The date of the patient's last menstrual period was [redacted]. Estimated delivery date was reported as [redacted]. Ultrasounds taken on [redacted] and [redacted] were both normal. On [redacted] apremilast was discontinued. Additional information was received on [redacted] which indicated the mother delivered a healthy baby and there were no complications during pregnancy or delivery.
USA-2016074381	Prior Interval/ Follow-up in PSUR Period	Spontaneous	38	30 mg BID		Spontaneous abortion	1st trimester	A pregnancy report was received on [redacted]. Patient was four weeks into her pregnancy on [redacted]. At the patient's office visit on [redacted], the patient was reported as 30 weeks gestation. The patient delivered a still born baby at 33 weeks [redacted]). The cause of the still birth was unknown.
USA-2016023641	Prior Interval/ Follow-up in PSUR Period	Spontaneous	30	30 mg BID		Unk	Before conception	A pregnancy report was received on [redacted] No additional information has been provided. The prescriber reported that the patient was last seen in the office on [redacted]. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-2016125575	Prior Interval/ Follow-up in PSUR Period	Spontaneous	41	30 mg BID	(b) (6)	Live birth without congenital anomaly	After 1st trimester	A pregnancy report was received on (b) (6). The patient began taking apremilast on (b) (6). The prescriber reported that the patient had a normal delivery in Mid (b) (6) and was currently breastfeeding. The patient did not experience any adverse events during the pregnancy. Apremilast was discontinued on (b) (6) (b) (6).
USA-2016128528	Prior Interval/ Follow-up in PSUR Period	Pt Support	44	30 mg BID		Live birth without congenital anomaly	Before conception	A pregnancy report was received on (b) (6). It was reported that, patient's last menstrual period was on (b) (6). Patient completed term (gestation age at delivery was 39 weeks) without complications and had normal delivery on (b) (6) There were no complications during pregnancy/labor/delivery, no postpartum maternal complications. Pregnancy outcome was live normal infant with no fetal distress, no intrauterine growth retardation, no neonatal complications, and no other birth defects. Outcome of pregnancy was normal female who weighed 7.01 lbs and 19 inches at the time of birth. Apgar score was unknown.
AUT-20170808360	Initial case/ PSUR Period	Spontaneous	45	Unk		Unk	Unk	A pregnancy report was received on (b) (6). Relevant medical history and concomitant medications were not provided. On (b) (6), the patient had a positive pregnancy test while on apremilast. The action taken in response to the pregnancy was reported as withdrawn. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
AUT-20170901081	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Unk	Unk	A pregnancy report was received on (b) (6). Relevant medical history and concomitant medications were not provided. On an unknown date, the patient stopped apremilast due to pregnancy. No additional information was provided.
CAN-20170404843	Initial case/ PSUR Period	Spontaneous	31	30 mg BID	(b) (6)	Unk	1st trimester	A pregnancy report was received on (b) (6). The patient reported that she had discontinued Apremilast in (b) (6) due the pregnancy. Follow up could not be conducted since the consent to follow up with the prescriber was not provided.
CAN-20171107011	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Ongoing	1st trimester	A pregnancy report was received on (b) (6). It was reported that the patient became pregnant while on apremilast therapy. At the time of the report, the patient was 7 weeks pregnant. Apremilast therapy was stopped at 5 weeks. No further information was provided.
CAN-20171208605	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Ongoing	Before conception	A pregnancy report was received on (b) (6). The patient was receiving apremilast for over a year for an unspecified indication. The patient was 7 weeks pregnant at time of the report. Treatment with apremilast was stopped
CHE-20170806160	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Unk	Unk	A pregnancy report was received on (b) (6). Apremilast treatment start date and stop dates were not provided. The outcome of the pregnancy was unknown. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
CHE-20171100957	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Ongoing	Unk	A pregnancy report was received on (b) (6). On an unknown date, while under apremilast therapy, the patient became pregnant. The method of pregnancy confirmation was not specified. Date of LMP, weeks of amenorrhea were not provided.
DEU-20170310519	Initial case/ PSUR Period	Registry	28	Unk	(b) (6)	Elective termination (no fetal defects or unk)	Before conception	A pregnancy report was received on (b) (6). Concomitant medication included subcutaneous secukinumab 300 (unit and frequency not provided) from (b) (6) to (b) (6). The patient became pregnant (gravidity 7 plus 3 gestation week). Conception date was calculated as around (b) (6) (b) (6) ten days after apremilast was discontinued. Last menstrual period was unknown. On (b) (6) (b) (6), the patient had an elective abortion due to an unwanted pregnancy. The investigator confirmed that the abortion was intentional. This patient was enrolled in a PSOR registry study (PSOR-015, Long-Term Benefits and Safety of Systemic Psoriasis Therapy). No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
DEU-20170400295	Initial case/ PSUR Period	Spontaneous	34	30 mg BID	(b) (6)	Unk	1st trimester	A pregnancy report was received on (b) (6). While on apremilast the patient became pregnant, the onset date of pregnancy was reported as (b) (6) Apremilast was discontinued on the same day. As of (b) (6), she was 16 weeks pregnant and had elected to carry pregnancy to term with the expected delivery date on (b) (6). Patient received apremilast for 9 months. No additional information was provided.
ESP-20171209967	Initial case/ PSUR Period	Spontaneous	28	Unk		Ongoing	1st trimester	A pregnancy report was received on (b) (6). The patient used a barrier condom as a contraceptive method. Concomitant medications were not provided. While on treatment, the patient performed a home urine pregnancy test that was positive. Given the result of pregnancy test, the patient discontinued apremilast treatment on her own (date unknown). The patient's last menstruation period and gestation period are unknown
FRA-2017039079	Initial case/ PSUR Period	Spontaneous	adult	Unk		Elective termination (no foetal defects or unk)	Unk	A pregnancy report was received on (b) (6). The patient reported that she received on apremilast. The patient considered that the pregnancy was not compatible with apremilast and elected to terminate the pregnancy. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
FRA-20170901707	Initial case/ PSUR Period	Spontaneous	19	Unk	(b) (6) - Unk	Elective termination (no foetal defects or unk)	1st trimester	A pregnancy report was received on (b) (6). Concomitant medication included levonorgestrel/ ethinyl estradiol (Optilova) as contraception. Although the patient was taking contraceptives (Optilova) she became pregnant. She underwent elective abortion in (b) (6). No additional information was provided.
FRA-20170607191	Initial case/ PSUR Period	Spontaneous	28	Unk	(b) (6) (b) (6) - Unk	Unk	1st trimester	A pregnancy report was received on (b) (6). Relevant medical history included prior pregnancy without complications. While taking apremilast, the patient became pregnant. Pregnancy was confirmed on (b) (6) via a urinary pregnancy test. The patient thinks she was not pregnant at the time of apremilast initiation. The reporter stated, the patient is 2 to 4 weeks pregnant. The manufacturer calculated the estimated date of delivery (EDD) as (b) (6). Patient discontinued the medication. No additional information was provided.
FRA-20171106383	Initial case/ PSUR Period	Spontaneous	32	30 mg BID	(b) (6) - Unk	Ongoing	1st trimester	A pregnancy report was received on (b) (6). The patient had previously had 6-7 children and did not try to become pregnant. She used contraception (not specified). On (b) (6), the patient learned she was pregnant. At the time of the report, the patient was 5-weeks pregnant. A beta HCG test was performed but the result was not provided. Apremilast was discontinued.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
FRA-20180102054	Initial case/ PSUR Period	Spontaneous	Unk	30 mg BID	Unk	Ongoing	Unk	A pregnancy report was received on (b) (6). The patient received oral apremilast 30 mg twice a day from an unknown date for 6 days followed by 30 mg twice a day for 15 days. The physician saw the patient in early (b) (6). Ultrasound examination performed on an unknown date was normal. The patient was willing to continue her pregnancy.
GBR-20170503545	Initial case/ PSUR Period	Spontaneous	Unk	Unk	Unk	Unk	1st trimester	A pregnancy report was received on (b) (6). The patient became pregnant after 3 weeks of treatment with apremilast. Apremilast was discontinued. The pregnancy is ongoing, and no complications have been reported. No additional information was provided.
GBR-20170601495	Initial case/ PSUR Period	Spontaneous	32	Unk	(b) (6)	Unk	1st trimester	A pregnancy report was received on (b) (6). On (b) (6) the patient had a positive home urine pregnancy test. At the time of the report the patient was 6 weeks pregnant. The patient has decided to carry the pregnancy to term. Action taken with Apremilast was not provided; last administration was on (b) (6).
GBR-20170902245	Initial case/ PSUR Period	Spontaneous	34	30 mg BID		Ongoing	Before conception	A pregnancy report was received on (b) (6). On a separate unspecified date, it was reported that the patient was to stop receiving apremilast as she had become pregnant

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
GBR-20170905742	Initial case/ PSUR Period	Spontaneous	29	Unk	(b) (6)	Unk	1st trimester	A pregnancy report was received on (b) (6). Relevant medical history and concomitant medications were not provided. The reporter stated that on (b) (6) the patient had home pregnancy urine test. The patient was reported to be 6 weeks pregnant while on apremilast, but the date of the last menstrual period was reported as unknown. The patient had not decided yet whether she would carry or terminate pregnancy. No other information was provided.
GBR-20170907541	Initial case/ PSUR Period	Spontaneous	30	Unk		Ongoing	Before conception	A pregnancy report was received on (b) (6) On (b) (6), the patient was 14 weeks pregnant. The expected delivery date was (b) (6)
USA-20170311118	Initial case/ PSUR Period	Spontaneous	24	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6) The patient wanted to speak with a nurse about taking apremilast while pregnant. It is unknown if the patient has taken apremilast.
USA-20170311209	Initial case/ PSUR Period	Spontaneous	40	Unk		Unk	Before conception	A pregnancy report was received on (b) (6). It was reported that the patient was 23 weeks pregnant while taking apremilast therapy. Apremilast therapy was permanently discontinued. No additional information was provided.
USA-20170400162	Initial case/ PSUR Period	Spontaneous	40	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). It was reported that the patient was pregnant and stopped taking apremilast. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-20170400888	Initial case/ PSUR Period	Spontaneous	24	30 mg BID	(b) (6)	Unk	Unk	A pregnancy report was received on (b) (6). Apremilast was permanently discontinued in response to the pregnancy. The last menstrual period was on (b) (6). Up to the date of this report, no adverse events were reported. The estimated delivery date is (b) (6). No additional information was provided. On follow- up the prescriber reported that this patient was not on apremilast therapy.
USA-20170402960	Initial case/ PSUR Period	Spontaneous	33	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). It was reported that the patient discontinued She apremilast due to the pregnancy. No additional information was provided
USA-20170409029	Initial case/ PSUR Period	Support Plus	33	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). The patient reported pregnancy after starting apremilast. No additional information was provided.
USA-20170504217	Initial case/ PSUR Period	Spontaneous	32	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). The patient initiated apremilast on (b) (6). The pregnancy is ongoing. Action taken with apremilast was unknown. No additional information was provided.
USA-20170507555	Initial case/ PSUR Period	Spontaneous	35	30 mg BID		Elective termination (no foetal defects or unk)	1st trimester	A pregnancy report was received on (b) (6). At the time of the diagnosis, she was 5 weeks and 5 days pregnant. No additional information was provided regarding the pregnancy. Action taken with apremilast was unknown. The patient's pregnancy was terminated on an unspecified date. It is unknown the reason for elective termination. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-20170600312	Initial case/ PSUR Period	Spontaneous	21	5 mg BID	(b) (6)	Unk	Unk	A pregnancy report was received on (b) (6). It was reported that the patient was 3 months pregnant on (b) (6), additionally it was reported that the prescriber advised the patient to stop apremilast.
USA-20170507620	Initial case/ PSUR Period	Spontaneous	Unk	Unk		Unk	Unk	A pregnancy report was received on (b) (6) from a health care professional regarding a patient (age unspecified) who became pregnant while receiving apremilast. Relevant medical history and concomitant medications were not provided. Action taken with apremilast was unknown. Outcome of the pregnancy was not provided. No additional information was provided.
USA-20170600390	Initial case/ PSUR Period	Spontaneous	17	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6) regarding a 17-year-old female patient who received apremilast 30 mg oral twice daily from (b) (6) to (b) (6), for the treatment of psoriasis. On (b) (6) (b) (6) a home pregnancy test was taken and on (b) (6) serum quantitative test at office confirmed the pregnancy. No additional information was provided.
USA-20170603669	Initial case/ PSUR Period	Spontaneous	35	30 mg BID		Unk	Before conception	A pregnancy report was received on (b) (6). The pregnancy was confirmed on (b) (6). Apremilast was temporarily interrupted on an unspecified date. The pregnancy was reported as ongoing. No additional information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-20170609453	Initial case/ PSUR Period	Apremilast Support Plus	30	30 mg BID	(b) (6)	Unk	Unk	A pregnancy report was received on (b) (6) for a 30-year-old female patient who received apremilast 30 mg orally twice daily for the treatment of psoriasis from (b) (6) to (b) (6). Apremilast was permanently discontinued. Relevant medical history and concomitant medications were not provided. No additional information was provided.
USA-20170705342	Initial case/ PSUR Period	Apremilast Support Plus	22	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6) regarding a 22-year-old female patient who became pregnant in (b) (6). The pregnancy was ongoing at the time of the report. No action was taken with apremilast. No additional information was provided.
USA-20170800684	Initial case/ PSUR Period	Spontaneous	24	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). Patient initiated apremilast on (b) (6). It is unknown when the pregnancy occurred. It is unknown if apremilast was discontinued. No additional information was provided.
USA-20170804703	Initial case/ PSUR Period	Spontaneous	24	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). The patient initiated apremilast on (b) (6) for the treatment of psoriasis vulgaris. No relevant medical history was provided. The last menstrual period date was unk. No concomitant medications were provided. Patient discontinued apremilast. Outcome of the pregnancy was unknown. No other information was provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-20170901852	Initial case/ PSUR Period	Spontaneous	29	30 mg BID	(b) (6)	Unk	Unk	A pregnancy report was received on (b) (6). Relevant medical history was not provided. Concomitant medications included "Prenatal" and levothyroxine. On an unspecified date, the patient was pregnant. Action taken with Apremilast was unknown.
USA-20170904914	Initial case/ PSUR Period	Spontaneous	37	30 mg BID		Unk	Unk	A pregnancy report was received on (b) (6). Relevant medical history and concomitant medications were not provided. The patient became pregnant on an unspecified date while receiving apremilast. Apremilast was permanently discontinued. No additional information was provided.
USA-20170907532	Initial case/ PSUR Period	Spontaneous	33	Unk		Unk	Unk	A pregnancy report was received on (b) (6). It was reported that the patient was pregnant. The prescriber discontinued apremilast therapy until delivery.
USA-20170908253	Initial case/ PSUR Period	Spontaneous	32	30 mg BID		Unk	1st trimester	A pregnancy report was received on (b) (6). The patient became pregnant and was in her first trimester when she received apremilast. Action taken with apremilast therapy because of the events was unknown. The outcome of the events was unknown.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-20171003337	Initial case/ PSUR Period	Spontaneous	31	Starter Pack	(b) (6)	Ongoing	Unk	A pregnancy report was received on (b) (6). It was reported by a pharmacist that the patient was pregnant, and that the prescriber temporarily interrupted apremilast therapy until delivery. The prescriber's office reported that the patient was only seen once by the physician on (b) (6), and was given an apremilast starter pack with a prescription. There was no documentation on whether the patient started apremilast, as well as no documentation on the pregnancy (physician was not aware and was not notified about pregnancy).
USA-20171100409	Initial case/ PSUR Period	Spontaneous	36	30 mg BID		Unk	1st trimester	A pregnancy report was received on (b) (6). On (b) (6), the patient discontinued therapy with apremilast as the patient was pregnant approximately on (b) (6). The patient's expected date of delivery was not provided.
USA-20180103033	Initial case/ PSUR Period	Spontaneous	34	30 mg BID		Ongoing	Before conception	A pregnancy report was received on (b) (6). The patient became pregnant while on apremilast. Apremilast was temporarily discontinued. No further information provided.
USA-20180200282	Initial case/ PSUR Period	Spontaneous	32	30 mg BID		Ongoing	Unk	A pregnancy report was received on (b) (6). The patient discovered she was pregnant in (b) (6) and (b) (6) and stopped the apremilast.
CAN-20180207451	Initial case/ PSUR Period	Spontaneous	22	Unk		Ongoing	Before conception	A pregnancy report was received on (b) (6). The patient was pregnant and would have been on apremilast at the time she conceived and for the first few weeks of pregnancy. The first day of her last period was (b) (6). At the time of reporting, she was about 6-7 weeks pregnant

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
GRC-20180305446	Initial case/ PSUR Period	Spontaneous	25	30 mg BID	(b) (6)	Ongoing	Before conception	A pregnancy report was received on (b) (6). The patient had previously one full term pregnancy, no miscarriages and no ectopic or tubal pregnancies. The patient did not have any previous elective or therapeutic abortions. The patient had a positive pregnancy test on (b) (6). The last menstrual period was (b) (6). The patient's partner used condoms as contraception. The pregnancy was ongoing without complications. Expected delivery date is (b) (6).
USA-20180208667	Initial case/ PSUR Period	Spontaneous	Unk	Unk		Ongoing	Unk	A pregnancy report was received on (b) (6). It was reported that the patient was pregnant while on apremilast therapy. No additional details regarding pregnancy were reported.
USA-20180300112	Initial case/ PSUR Period	Spontaneous	23	30 mg BID		Ongoing	Unk	A pregnancy report was received on (b) (6). It was reported that the patient was childbearing. No additional information was provided regarding patient's pregnancy. Action taken with apremilast because of the childbearing was not provided.

MCN	Initial / FU	Source	Age (years)	Dose	Tx Dates	Pregnancy Outcome	Timing of Exposure in Pregnancy	Comments
USA-2016020273	Prior Interval/ Follow-up in PSUR Period	Spontaneous	34	30 mg BID	(b) (6)	Spontaneous abortion	1st trimester	A pregnancy report was received on (b) (6) Relevant medical history included Crohn's disease and infertility. The patient was informed that she was 11weeks pregnant. The patient had a history of low progesterone level, and she was prescribed progesterone to maintain her pregnancy hormones. Further obstetric ultrasound showed negative fetal heartbeat. Her provider did not believe that the spontaneous abortion was caused by apremilast, but rather that "it had something to do with a birth defect reportedly caused by two sperm implanting her egg cell". No additional information has been received.

Table 2. Retrospective Post-Marketing Pregnancy Cases reporting during the PSUR Reporting Interval (March 21, 2017 through March 20, 2018) – corresponds to the applicant PSUR submsision, appendix 3I, Table 5, page 5-28)[1]

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
USA-20170505421 Initial case/ PSUR Period USA	Spontaneous	32	30 mg BID	(b) (6)	Spontaneous abortion	1st trimester	A pregnancy report was received on (b) (6). The patient took apremilast for approximately one week and found out she was 5 weeks pregnant. Apremilast was discontinued. She had a miscarriage approximately one week later. There were no pathological or genetic reports. It is unknown whether the patient had a history of miscarriage. No additional information was provided.

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
USA-20170806053 Initial case/ PSUR Period USA	Spontaneous	40	30 mg BID	[redacted]	Live birth without congenital anomaly	After 1st trimester	A pregnancy report was received on [redacted]. The patient was treated with apremilast from [redacted] to [redacted]. On [redacted] at a gestational age of 38.29 weeks, she delivered a baby. The Apgar at 1 min and 5 min were 4 and 6 respectively. The birth weight was 2409.71 grams, and body length was 48.26 cm. Baby was diagnosed with presumed sepsis and suspected PPHN (persistent pulmonary hypertension). No complications during pregnancy were reported. No additional information was provided.
USA-20170402319 Initial case/ PSUR Period USA	Spontaneous	Unk	Unk	Unk	Live birth without congenital anomaly	1st trimester	A pregnancy report was received on [redacted]. The patient was on apremilast and realized she was pregnant 7 weeks into the pregnancy. Apremilast was discontinued. A healthy baby was delivered three weeks earlier than the due date. No additional information was provided.
CAN-20170906869 Initial case/ PSUR Period Canada	Spontaneous	Unk	Unk	Unk	Twins Live birth without congenital anomaly	Unk	A pregnancy report was received on [redacted]. It was reported that the patient was pregnant on an unknown date. She gave birth to twins. Both the twins are healthy. No complications at delivery were reported. It was not clear the duration of the pregnancy. Action taken with Apremilast therapy in response to patient's pregnancy was not provided.

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
CAN-20180 10831 8 Initial case/ PSUR Period Canada	Spontaneous	32	30 mg BI D	(b) (6)	Spontaneous abortion	1st trimester	A pregnancy report was received on (b) (6). The patient reported that she found out she was pregnant in mid-(b) (6). Immediately, she stopped taking apremilast. She was not on birth control at the time as she was told that she was infertile due to blockage of both fallopian tubes. On (b) (6), about eight weeks into her pregnancy, the patient suffered a miscarriage.
USA-20180307020 Initial case/ PSUR Period	Spontaneous	41	30 mg BI D		Spontaneous abortion	Before conception	A pregnancy report was received on (b) (6). The patient stated that she stopped medications 5 months ago due to pregnancy; however, the patient lost the pregnancy.

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
USA-20171202435 Initial case/ PSUR Period USA	Spontaneous	29	Unk	Unk	Live birth without congenital anomaly	Unk	A pregnancy report was received on (b) (6). The patient did not have any relevant medical history. The dates of apremilast use was not provided. Concomitant medication included adalimumab 40 mg subcutaneous for 14 days from (b) (6) to (b) (6) and (b) (6) (ongoing). In (b) (6) the patient was confirmed pregnant via ultrasound. The fetus was exposed to maternal use of Humira (in utero) during preconception and first trimester. In (b) (6) maternal use of adalimumab was discontinued. On (b) (6) (b) (6), at an unknown gestational age, the baby was born via vaginal delivery. No maternal medical problems or complications during delivery or postpartum period were reported. Neonatal birth weight was 6 lbs and 12 ounces, length was 20.5 inches, sex was male, Apgar scale at one minute was unknown and at 5 minutes was unknown. No neonatal complications, congenital anomalies or birth defects were reported.

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
POL-2017010275 Prior Interval/ Follow-up PSUR Period Poland	PSA-004-427-1030	32	APR 20 mg BID	(b) (6)	Unk	1st trimester	A pregnancy report was received on (b) (6). The patient was 16 weeks pregnant at the time of the report; expected delivery date of (b) (6). Methods of birth control included condom and an oral contraceptive. Ultrasonography and amniocentesis showed no complications to date. The dates of the positive pregnancy test ((b) (6)) and last menstruation ((b) (6)) were reported by the patient. Study drug was permanently discontinued on (b) (6) in response to the event. No additional information was provided.
EST-20170401442 Initial case/ PSUR Period Estonia	PSA-005-875-5001	35	APR 30 mg BID		Unk	1st trimester	A pregnancy report was received on (b) (6). The subject had a positive home pregnancy test on (b) (6) (b) (6). An ultrasound on (b) (6) did not show any complications. At the time of this report the subject was 15 weeks pregnant. She elected to carry the pregnancy to term with an expected delivery date of (b) (6). No additional information was provided.

MCN Time Period Country of Origin	Case Source	Age	Tx	Tx dates	Pregnancy outcome	Timing of exposure in pregnancy	Comments
FRA-20180104010 Initial case/ PSUR Period France	UC-001-214-1006	26	Blinded Active Treatment Phase	(b) (6)	Ongoing	Before conception	A pregnancy report was received on (b) (6). The patient had no prior pregnancy or had any terminations. Method of birth control included condom and diaphragm. Concomitant medication included mesalamine. The patient had a negative screening of pregnancy test on (b) (6) and last menstrual period was on (b) (6). On (b) (6), the patient was found to be 5-6 weeks pregnant after a positive home urine test. Patient decided to carry pregnancy to term. No further details provided.
USA-2015116279 Prior Interval/ Follow-up PSUR	PSOR-012-7051015	35	APR 30 mg BID		Elective termination (no foetal defects or unk)	1st trimester	A pregnancy report was received on (b) (6). The subject underwent elective termination of pregnancy with no complications. No additional information was provided.

BID = twice daily; EDD = estimated date of delivery; LMP = last menstrual period; PPHN = persistent pulmonary hypertension; Tx = therapy; Unk = unknown.

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/s/

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