CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

2054374Orig1s011

Trade Name:	OTEZLA
Generic or Proper Name:	apremilast
Sponsor:	Amgen Inc.
Approval Date:	December 20, 2021
Indication:	OTEZLA, an inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment of: • Adult patients with active psoriatic arthritis • Adult patients with 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

2054374Orig1s011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2054374Orig1s011

APPROVAL LETTER

NDA 205437/S-011

SUPPLEMENT APPROVAL

Amgen Inc.
Attention: Sarah Wilczynski, MS, RAC, PMP
Manager, Regulatory Affairs
One Amgen Drive
Mail Stop 27-2-D
Thousand Oaks, CA 91320-1799

Dear Ms. Wilczynski:

Please refer to your supplemental new drug application (sNDA) dated February 19, 2021, received February 19, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Otezla (apremilast) tablets.

This Prior Approval supplemental new drug application provides for changes to the Indication and Usage, and Clinical Studies sections of the labeling to include data for subjects with mild to moderate plaque psoriasis, and to allow for an expansion of the indication to include adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy. Additionally, a subsection entitled "Hypersensitivity" was added under the Warnings and Precautions section of the label.

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.

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.

We are waiving the pediatric study requirements for patients less than 6 years of age because the necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric studies for ages 6 to 17 years of age (inclusive), because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4207-1 A Phase 3, multicenter, open-label study to assess the safety of apremilast in approximately 50 pediatric subjects (6 through 17 years of age, inclusive) with mild-to-moderate plaque psoriasis

Final Protocol Submission: 01/2024
Study Completion: 12/2026

[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.

Final Report Submission: 09/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 070270, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

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 Dawn Williams, Safety Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information
  - Carton and Container Labeling

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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/

TATIANA OUSSOVA
12/20/2021 02:52:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2054374Orig1s011

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, Plaque Psoriasis (1.2)	12/2021
Warnings and Precautions, Hypersensitivity (5.1)	12/2021

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

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

- Adult patients with active psoriatic arthritis (1.1)
- Adult patients with 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 dosage 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 dosage 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 to any of the excipients in the formulation (4)

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

- Hypersensitivity: Cases of angioedema and anaphylaxis have been reported during post marketing surveillance. Avoid the use of OTEZLA in patients with known hypersensitivity to apremilast or to any of the excipients in the formulation. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue OTEZLA and institute appropriate therapy (5.1).
- Diarrhea, Nausea, and Vomiting: Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting (5.2)
- 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 (5.3)
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of OTEZLA (5.4)
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended because loss of efficacy may occur (5.5, 7.1)

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

- Psoriatic Arthritis: The most common adverse reactions (≥ 5%) are diarrhea, nausea, and headache (6.1)
- Plaque 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 Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) 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 dosage to 30 mg once daily is recommended (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2021

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 Plaque Psoriasis

OTEZLA is indicated for the treatment of adult patients with 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, Plaque 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 Hypersensitivity

Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported during post marketing surveillance. Avoid the use of OTEZLA in patients with known hypersensitivity to apremilast or to any of the excipients in the formulation. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue OTEZLA and institute appropriate therapy.

5.2 Diarrhea, Nausea, and Vomiting

There have been 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.

5.3 Depression

Treatment with OTEZLA is associated with an increased incidence 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. 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.

Plaque Psoriasis: During the 0 to 16-week placebo-controlled period of the 3 controlled clinical trials in subjects with moderate to severe plaque psoriasis, 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.

During the 0 to 16-week placebo-controlled period of the mild to moderate plaque psoriasis clinical trial, the incidence of subjects reporting depression was similar to what was observed in the moderate to severe plaque psoriasis trials.

Behçet's Disease: During the placebo-controlled period of the phase 3 trial, 1% (1/104) of subjects 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 discontinuation from the trial. No instances of suicidal ideation or behavior were reported during the placebo-controlled period of the phase 3 trial in subjects treated with OTEZLA (0/104) or treated with placebo (0/103).

5.4 Weight Decrease

During the placebo-controlled period of the trials 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 placebo-controlled period of the trials in moderate to severe plaque 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 placebo-controlled period of the mild to moderate plaque psoriasis clinical trial, weight decrease was similar to what was observed in the moderate to severe plaque psoriasis trials.

During the placebo-controlled period of the phase 3 trial 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) subjects 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)]*.

5.5 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:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Diarrhea, Nausea, and Vomiting *[see Warnings and Precautions (5.2)]*
- Depression *[see Warnings and Precautions (5.3)]*
- Weight Decrease *[see Warnings and Precautions (5.4)]*
- Drug Interactions *[see Warnings and Precautions (5.5)]*

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 (PsA-1, PsA-2, and PsA-3) of similar design in adult subjects with active psoriatic arthritis *[see Clinical Studies (14.1)]*. Across the 3 trials, there were 1493 subjects 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 subjects 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 subjects remained on their initial treatment. Subjects 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 subjects taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of subjects with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for subjects taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated subjects.

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

	Placebo		OTEZLA 30 mg BID[d]	
Adverse Reactions	**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 subject 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 subjects and percent.
[d] BID = twice daily.

Moderate to Severe Plaque 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 (see Table 3). 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 plaque 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)

Adverse Reactions	Placebo (N=506) n (%)	OTEZLA 30 mg BID[b] (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[a]	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)

[a] Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.
[b] BID = twice daily.

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

OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled trial (PSOR-3) in adults with moderate to severe plaque psoriasis of the scalp *[see Clinical Studies (14.2)]*. A total of 302 subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. The most commonly reported adverse reactions that occurred at a higher rate in the OTEZLA group than in the placebo group were: diarrhea (31% vs. 11%), nausea (22% vs. 6%), headache (12% vs. 5%), and vomiting (6% vs. 2%). The proportion of subjects who discontinued treatment because of any adverse reaction during the 16-week placebo-controlled period of the trial was 6% for subjects who received OTEZLA 30 mg twice daily and 3% for subjects who received placebo. Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs. 0%), nausea (1.5% vs. 1%), and vomiting (1.5% vs. 0 %) in the OTEZLA group compared to placebo.

Mild to Moderate Plaque Psoriasis Clinical Trial
OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled trial (PSOR-4) in adult subjects with mild to moderate plaque psoriasis *[see Clinical Studies (14.3)]*. A total of 595 subjects were randomized to receive OTEZLA 30 mg twice daily (297 subjects) or placebo twice daily (298 subjects) during the placebo-controlled phase of the trial. The trial also included an open-label extension phase during which all subjects received OTEZLA 30 mg twice daily. Overall, the safety profile observed in the OTEZLA group during the placebo-controlled phase was consistent with the safety profile previously established in adult subjects with moderate to severe plaque psoriasis.

Behçet's Disease Clinical Trials

OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled trial (BCT-002) in adult subjects with Behçet's Disease (BD) with active oral ulcers *[see Clinical Studies (14.4)]*. A total of 207 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)]*. After Week 12, all subjects received treatment with OTEZLA 30 mg twice daily. Subjects 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 (see Table 4). The proportion of subjects with BD who discontinued treatment due to any adverse reaction during the placebo-controlled period of the trial, was 2.9% for subjects treated with OTEZLA 30 mg twice daily and 4.9% for placebo-treated subjects.

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

Adverse Reactions	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.

Other adverse reactions reported in subjects on OTEZLA in psoriatic arthritis, plaque psoriasis, and Behçet's Disease clinical trials are:

- Gastrointestinal Disorders: Gastroesophageal reflux disease
- Immune System Disorders: Hypersensitivity
- Investigations: Weight decrease
- Metabolism and Nutrition Disorders: Decreased appetite*
- Nervous System Disorders: Migraine
- Respiratory, Thoracic, and Mediastinal Disorders: Cough
- Skin and Subcutaneous Tissue Disorders: Rash

*1 subject treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

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 (5.5) 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 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 post-natal 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 than 18 years of age have not been established.

8.5 Geriatric Use

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

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

Because patients 65 years of age or older may be at a higher risk of complications such as volume depletion or hypotension from severe diarrhea, nausea, or vomiting, monitor geriatric patients closely for such complications *[see Warning and Precautions (5.2)]*.

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 dosage adjustment is needed in patients with mild or moderate renal impairment, the dosage 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)]*.

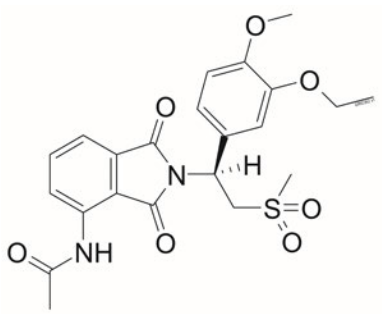
8.7 Hepatic Impairment

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

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

Patients with 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 trials 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 trials 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 (5.5) 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 (PsA-1 [NCT01172938], PsA-2 [NCT01212757], and PsA-3 [NCT01212770]) of similar design. A total of 1493 adult subjects with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized. Subjects enrolled in these trials 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 Trial PsA-3. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 trials, subjects 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)]*. Subjects 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 Trials PsA-1, PsA-2 and PsA-3. There was an additional stratification of body surface area (BSA) > 3% with psoriasis in Trial PsA-3. The subjects 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 subjects achieving American College of Rheumatology (ACR) 20 response at Week 16. Placebo-controlled efficacy data were collected and analyzed through Week 24. Subjects 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 subjects remained on their initial treatment. At Week 24, all remaining placebo subjects were re-randomized to either 20 mg twice daily or 30 mg twice daily.

Subjects with subtypes of PsA were enrolled across the 3 trials, 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. Subjects 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 subjects and prior treatment with biologic DMARDs was reported in 22.0% of subjects, which includes 9.0% who had failed prior biologic DMARD treatment.

Clinical Response in Subjects with Psoriatic Arthritis

The percent of subjects achieving ACR 20, 50 and 70 responses in Trials 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 subjects with an ACR 20 response at Week 16.

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

	PsA-1		**PsA-2**		**PsA-3**	
	Placebo ± DMARDs	**OTEZLA 30 mg twice daily ± DMARDs**	**Placebo ± DMARDs**	**OTEZLA 30 mg twice daily ± DMARDs**	**Placebo ± DMARDs**	**OTEZLA 30 mg twice daily ± DMARDs**
N[a]	**N=168**	**N=168**	**N=159**	**N=162**	**N=169**	**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 subjects.
[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 Trial PsA-1 (Table 6). Consistent results were observed in Trials PsA-2 and PsA-3.

Table 6: ACR Components Mean Change from Baseline at Week 16 in Trial 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 subjects; actual number of subjects evaluable for each endpoint may vary by timepoint.

Treatment with OTEZLA resulted in improvement in dactylitis and enthesitis in subjects 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 Trial 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 Trial PsA-1. Consistent results were observed in Trials PsA-2 and PsA-3.

14.2 Moderate to Severe Plaque Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled trials (PSOR-1 [NCT01194219] and PSOR-2 [NCT01232283]) 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 plaque psoriasis of the scalp were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.

Trial PSOR-1 enrolled 844 subjects and Trial PSOR-2 enrolled 413 subjects. In both trials, subjects were randomized 2:1 to OTEZLA 30 mg twice daily (BID) or placebo for 16 weeks. Both trials assessed the proportion of subjects who achieved PASI-75 at Week 16 and the proportion of subjects who achieved an sPGA score of clear (0) or almost clear (1) at Week 16. Across both trials, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.2% (median 21.0%), the mean baseline PASI score was 19.1 (median 16.8), and the proportion of subjects with an 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 Moderate to Severe Plaque Psoriasis

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

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

	Trial PSOR-1		Trial PSOR-2	
	Placebo	OTEZLA 30 mg BID	Placebo	OTEZLA 30 mg BID[d]
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 subjects.
[b] PASI = Psoriasis Area and Severity Index.
[c] sPGA = Static Physician Global Assessment.
[d] BID = twice daily.

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.

Plaque Psoriasis Involving the Scalp Area

A randomized, double-blind, placebo-controlled trial (PSOR-3 [NCT03123471]) was conducted in 303 adult subjects with moderate to severe plaque psoriasis of the scalp. Enrolled subjects had a Scalp Physician Global Assessment (ScPGA) score of ≥ 3, Scalp Surface Area (SSA) involvement of ≥ 20%, an inadequate response or intolerance to at least one topical therapy for plaque psoriasis of the scalp, and moderate to severe plaque psoriasis (BSA involvement of ≥ 10%, sPGA of ≥ 3 [moderate or severe disease], and PASI score ≥ 12).

Subjects were randomized 2:1 to receive either OTEZLA 30 mg twice daily (n =201) or placebo twice daily (n = 102) for 16 weeks. The primary endpoint was the proportion of subjects who achieved an ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline at Week 16). Secondary endpoints included the proportion of subjects with Whole Body Itch Numeric Rating Scale

(NRS) response (defined as ≥ 4-point reduction from baseline) and the proportion of subjects with a Scalp Itch NRS response (defined as ≥ 4-point reduction from baseline).

Subjects had a mean age of 46.9 years, 61.7% were men and 75.6 % were white. At baseline, 76.9% of subjects had moderate plaque psoriasis of the scalp (ScPGA of 3), 23.1% had severe plaque psoriasis of the scalp (ScPGA of 4), 71.6% of subjects were biologic naïve, and 58.8% had failed 1 or 2 topical treatments. At baseline, the mean Whole Body Itch NRS score was 7.2 and the mean Scalp Itch NRS score was 6.7 with the scales ranging from 0 to 10. The mean baseline SSA involvement was 60.6% and the mean baseline BSA involvement was 19.8%.

The proportion of subjects who achieved an ScPGA response, Whole Body Itch NRS response, and Scalp Itch NRS response at Week 16 are presented in Table 8.

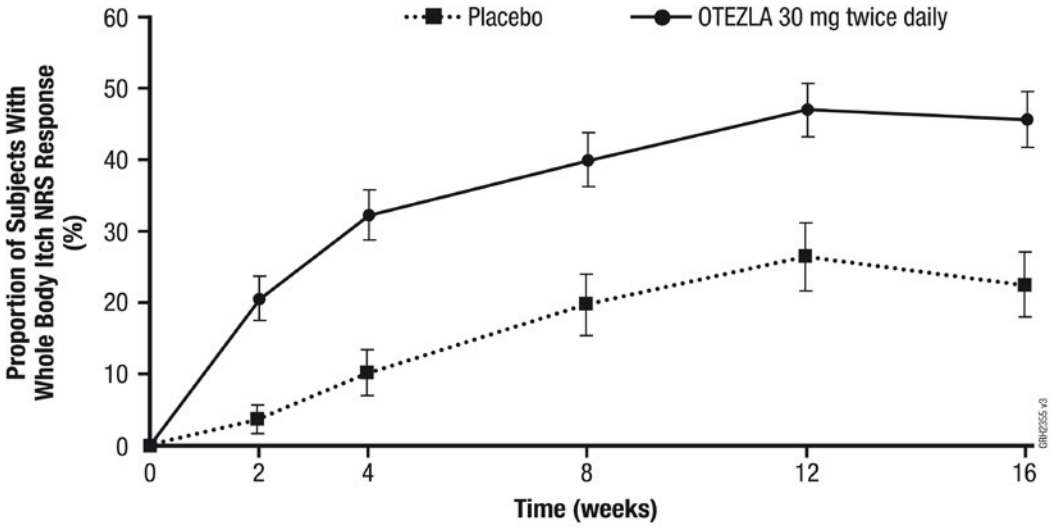
Figure 1 displays the proportion of subjects achieving Whole Body Itch NRS response at each visit, while Figure 2 displays the proportion of subjects achieving Scalp Itch NRS response at each visit.

Table 8: Efficacy Results at Week 16 in Adults with Plaque Psoriasis of the Scalp

	Trial PSOR-3		
	Placebo	**OTEZLA 30 mg twice daily**	**Treatment Difference[a,b] (95% CI[c])**
Number of subjects randomized	**N = 102**	**N = 201**	
ScPGA response[d]	13.7%	43.3%	29.6% (19.5%, 39.7%)
Number of subjects with baseline Whole Body Itch NRS Score ≥4	**N = 94**	**N = 185**	
Whole Body Itch NRS response	22.5%	45.5%	23.0% (11.5%, 34.6%)
Number of subjects with baseline Scalp Itch NRS Score ≥4	**N = 90**	**N = 175**	
Scalp Itch NRS response	21.1%	47.1%	26.2% (13.9%, 38.5%)

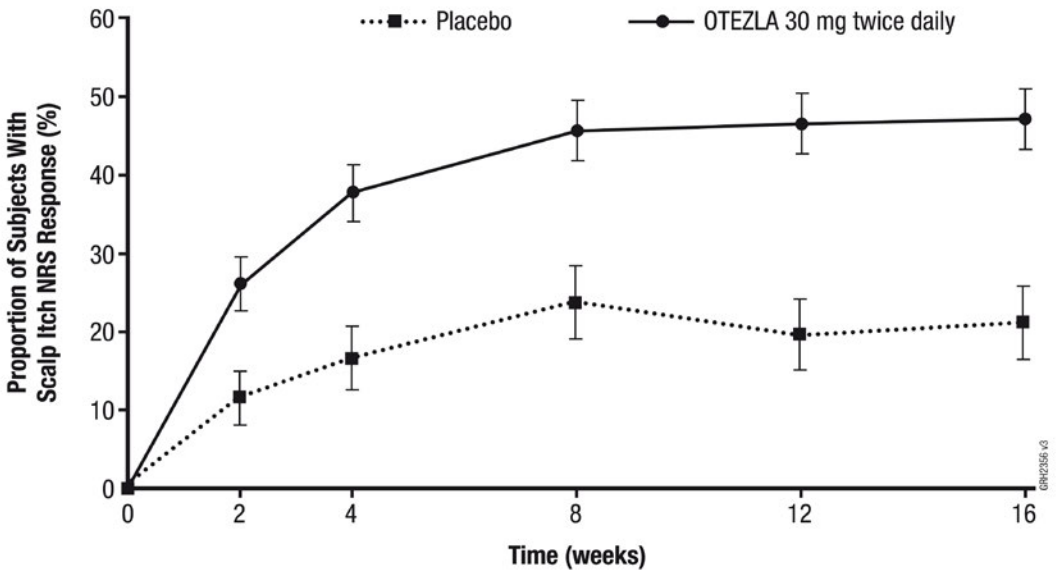
[a] OTEZLA – Placebo.
[b] Adjusted difference in proportions is the weighted average of the treatment differences across baseline ScPGA scores with the Cochran-Mantel-Haenszel weights.
[c] CI = confidence interval.
[d] ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.

Figure 1: Proportion (± SE) of Subjects Achieving Whole Body Itch NRS Response through Week 16



NRS = Numeric Rating Scale; SE = standard error

Figure 2: Proportion (± SE) of Subjects Achieving Scalp Itch NRS Response through Week 16



NRS = Numeric Rating Scale; SE = standard error

14.3 Mild to Moderate Plaque Psoriasis

A multicenter, randomized, double-blind, placebo-controlled trial (PSOR-4 [NCT03721172]) was conducted in 595 adult subjects with mild to moderate plaque psoriasis (BSA involvement of 2-15%, sPGA score of 2-3 [mild or moderate disease], and PASI score of 2–15). Enrolled subjects had an inadequate response or were intolerant to at least one topical therapy and had not received prior biologic therapy. Subjects were allowed to use unmedicated emollients for lesions on non-scalp areas of the body and non-medicated shampoos for lesions on the scalp.

Subjects were randomized 1:1 to receive either OTEZLA 30 mg twice daily (n = 297) or placebo twice daily (n = 298) for 16 weeks. At Week 16, the placebo group was switched to receive OTEZLA and the OTEZLA group remained on drug through Week 32. The primary endpoint was the proportion of subjects who achieved an sPGA response (defined as an sPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) at Week 16. Subjects with mild disease (sPGA = 2 at baseline) were required to be clear (sPGA = 0) to achieve an sPGA response. Other evaluated endpoints include the proportion of subjects with a Whole Body Itch NRS response (defined as a ≥ 4-point reduction from baseline) at Week 16 among subjects with a baseline Whole Body Itch NRS ≥ 4 and the proportion of subjects with an ScPGA response (defined as an ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) at Week 16 among subjects with a baseline ScPGA score ≥ 2.

Subjects ranged in age from 18 to 85 years, with an overall median age of 50 years. The mean baseline BSA involvement was 6.4%, the mean baseline PASI score was 6.5, and the proportions of subjects with an sPGA score of 2 (mild) and 3 (moderate) at baseline were 30.6% and 69.4%, respectively.

Clinical Response in Subjects with Mild to Moderate Plaque Psoriasis

The proportions of subjects who achieved an sPGA response, Whole Body Itch NRS response, and an ScPGA response at Week 16 are presented in Table 9.

Table 9: Efficacy Results at Week 16 in Adults with Mild to Moderate Plaque Psoriasis

	Trial PSOR-4		
	Placebo	**OTEZLA 30 mg twice daily**	**Treatment Difference[a,b] (95% CI[c])**
Number of Subjects Randomized	**N = 298**	**N = 297**	
sPGA Response[d]	4.1%	21.6%	17.5% (12.2%, 22.8%)
Number of Subjects with Baseline Whole Body Itch NRS Score ≥ 4	**N = 249**	**N = 253**	
Whole Body Itch NRS Response[e]	18.6%	43.2%	24.7% (16.5%, 32.8%)
Number of Subjects with Baseline ScPGA Score ≥ 2	**N = 199**	**N = 212**	
ScPGA Response[f]	16.6%	44.0%	27.4% (18.6%, 36.3%)

[a] OTEZLA – Placebo.

[b] Adjusted difference in proportions is the weighted average of the treatment differences across baseline sPGA scores with the Cochran-Mantel-Haenszel weights.

[c] CI = confidence interval.

[d] sPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.

[e] Whole Body Itch NRS score reduction of ≥ 4-points from baseline.

[f] ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline.

14.4 Oral Ulcers Associated with Behçet's Disease

A multicenter, randomized, placebo-controlled trial (BCT-002 [NCT02307513]) enrolled a total of 207 adult subjects with BD with active oral ulcers. Subjects were previously treated with at least one nonbiologic BD medication and were candidates for systemic therapy. Subjects met the International Study Group (ISG) Criteria for BD. Subjects 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.

Subjects 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 subjects received OTEZLA 30 mg twice daily.

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

Subjects ranged in age from 19 to 72 years, 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 10.

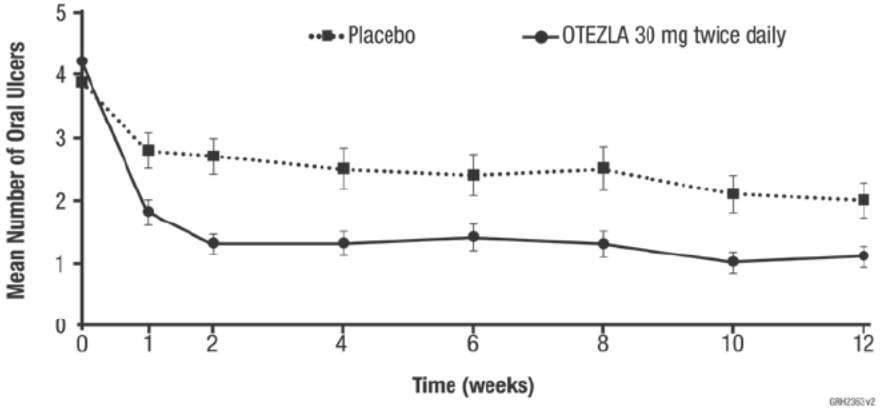
Table 10: Clinical Response of Oral Ulcers at Week 12 in the BCT-002 Trial (ITT[a] Population)

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] Subjects 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 3 displays the mean number of oral ulcers for each treatment group at each visit, while Figure 4 displays the mean oral ulcer pain on a visual analog scale for each treatment group at each visit.

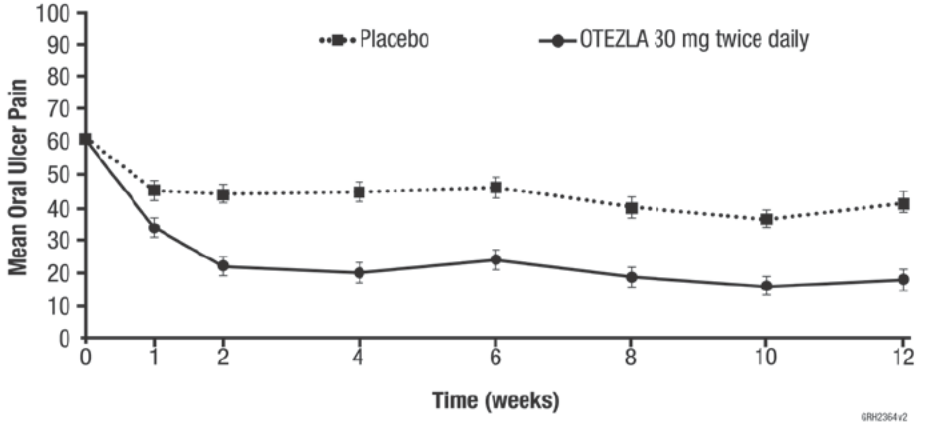
Figure 3: Mean (± SE) Number of Oral Ulcers by Time Point Through Week 12 (ITT Population)



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 4: 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	55513-137-60 59572-631-06
Bottles of 500	30 mg	55513-137-50
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	55513-137-28 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	55513-369-55 59572-632-55

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

17 PATIENT COUNSELING INFORMATION

- *Administration Instructions*
  Instruct patients to take OTEZLA only as prescribed.
  Advise patients that OTEZLA can be taken with or without food, and that the tablets should not be crushed, split, or chewed *[see Dosage and Administration (2.1)]*.

- *Hypersensitivity*
  Inform patients that hypersensitivity reactions can occur following administration of OTEZLA. Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1)]*.

- *Diarrhea, Nausea, and Vomiting*
  Advise patients of the potential complications of severe diarrhea, nausea, or vomiting and instruct them to contact their healthcare provider if they experience these adverse reactions, especially if the patient is 65 years of age or older *[see Warnings and Precautions (5.2)]*.

- *Depression*
  Inform patients that treatment with OTEZLA is associated with an increased incidence of depression. 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 *[see Warnings and Precautions (5.3)]*.

- *Weight Decrease*
  Instruct patients to have their weight monitored regularly and, if unexplained or clinically significant weight loss occurs, to contact their healthcare provider for evaluation of the weight loss *[see Warnings and Precautions (5.4)]*.

- *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.

AMGEN®

OTEZLA® (apremilast)

Manufactured for:
Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A

OTEZLA® is a registered trademark of Amgen Inc.

https://pat.amgen.com/otezla

<part number> v5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2054374Orig1s011

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	sNDA
Application Number(s)	NDA 205437, Efficacy Supplement-11
Priority or Standard	Standard
Submit Date(s)	2/19/2021
Received Date(s)	2/19/2021
PDUFA Goal Date	12/19/2021
Division/Office	Division of Dermatology and Dentistry, Office of Immunology and Inflammation
Review Completion Date	12/16/2021
Established/Proper Name	Apremilast
(Proposed) Trade Name	OTEZLA
Pharmacologic Class	Phosphodiesterase-4 Inhibitor
Code name	CC-10004
Applicant	Amgen, Inc.
Dosage form	10 mg, 20 mg, 30 mg Tablets
Applicant proposed Dosing Regimen	30 mg orally twice daily. To reduce risk of gastrointestinal symptoms, titrate to the recommended dose of 30 mg twice daily over 6 days (as per current USPI)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	200965009 |Plaque psoriasis (disorder)|
Recommended Dosing Regimen	30 mg twice daily. To reduce risk of gastrointestinal symptoms, titrate to the recommended dose of 30 mg twice daily over 6 days (as per current USPI)

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Dawn Williams, BSN
Clinical Reviewer	Hamid Tabatabai, MD
Clinical Team Leader	Dave Kettl, MD
Statistical Reviewer	Matthew Guerra, PhD
Statistical Team Leader	Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	Dave Kettl, MD
Office Director (or designated signatory authority)	Tatiana Oussova, MD, MPH

Additional Reviewers of Application

OPQ	Joel Hathaway
OPDP	Laurie Buonaccorsi
OSE/DMEPA	Madhuri Patel

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
Clinical Reviewer	Hamid Tabatabai	Office of Immunology and Inflammation /Division of Dermatology and Dentistry	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.2	**Select one:** _X_ Authored ___ Approved
	Signature:			
Clinical Team Leader	David Kettl	Office of Immunology and Inflammation /Division of Dermatology and Dentistry	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.2	**Select one:** ___ Authored _X_ Approved
	Signature:			
Division Director (Clinical)			Sections:	**Select one:** ___ Authored _X_ Approved
Statistical Reviewer	Matthew Guerra, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature:			
Statistical Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature:			

Glossary

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

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

1 Executive Summary

1.1. Product Introduction

OTEZLA (apremilast) is a Phosphodiesterase 4 (PDE-4) inhibitor approved by the FDA for the indications of treatment of the following:

- Adult patients with active psoriatic arthritis
- Adult 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

The applicant submitted Prior Approval Efficacy Supplement-11 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act to add the indication of (b) (4) (b) (4) to the OTEZLA label.

The applicant proposes a change from the approved indication from "for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy" to (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

Trial CC-10004-PSOR-022, supporting efficacy supplement-11, was conducted in adult subjects with mild to moderate plaque psoriasis (defined as affected 2% ≤ BSA ≤ 15%, sPGA= 2 or 3, and 2 ≤ PASI ≤15) who were eligible for systemic therapy or phototherapy, with no prior treatment with biologics therapies and an inadequate response to, or intolerance of at least 1 topical therapy for the treatment of plaque psoriasis. This trial had a 16-week placebo-controlled period followed by a16-week apremilast-extension period. All subjects received dose titration to 30 mg BID at the start of their treatment with apremilast.

The primary efficacy endpoint for this trial was the proportion of subjects achieving sPGA response (sPGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline) at Week 16. The secondary efficacy endpoints (pre-specified and controlled for multiplicity, for which the applicant seeks labeling claims) were the proportion of subjects achieving whole body itch NRS response (≥4-point improvement from baseline) at Week 16, and the proportion of subjects achieving ScPGA response (ScPGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline) at Week 16.

Substantial evidence of efficacy was demonstrated based on the analysis of the results from the primary efficacy endpoint. Analysis of the results from the secondary efficacy endpoints were supportive of efficacy.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk profile of apremilast for the treatment of mild to moderate plaque psoriasis is favorable, based on data from one adequate and well-controlled clinical trial (CC-10004-PSOR-022) in patients 18 years of age and older. This trial enrolled 595 adult subjects with mild to moderate plaque psoriasis.

- Efficacy: Apremilast was statistically superior to the placebo for the primary and the following secondary efficacy endpoints (pre-specified in the protocol and controlled for multiplicity), for the ITT population at Week 16:
  - i. For the primary efficacy endpoint of sPGA response (sPGA score = 0 or 1 with ≥ 2-grade reduction from baseline), the apremilast group achieved a response of 21.6%, compared to 4.1% for the placebo group ($p<0.001$), a treatment effect of approximately 17.5%.
  - ii. For the secondary efficacy endpoint of whole-body itch (≥ 4-points improvement from baseline), the apremilast group achieved a response of 43.2%, compared to 18.6% for the placebo group ($p<0.001$), a treatment effect of approximately 24.7%.
  - iii. For the secondary efficacy endpoint of ScPGA response (ScPGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline), the apremilast group achieved a response of 44.0%, compared to 16.6% for the placebo group ($p<0.001$), a treatment effect of approximately 27.4%.

- Safety: Analysis of the primary safety database for trial CC-10004-PSOR-022 did not identify any new safety signals, was qualitatively similar to safety data from clinical trials for apremilast (conducted for psoriasis, psoriatic arthritis, and oral ulcers in Behcet's disease), and was adequate to characterize the safety profile of apremilast for the treatment of mild to moderate psoriasis. Adverse Reactions reported through Week 16 in ≥ 5% of subjects treated with apremilast (and ≥1% more frequently than subjects receiving placebo) compared to subjects treated with placebo included diarrhea (16.4% vs. 5.1%), nausea (12.8% vs. 4.4%), headache (13.1% vs. 5.1%), and nasopharyngitis (7.4% vs. 2.7%).

The available results support expansion of the indication of "treatment of adult patients with moderate to severe plaque psoriasis" (b) (4) (b) (4) in the "Indications and Usage Section" of the label, and inclusion of the efficacy and safety data from trial CC-10004-PSOR-022 in Sections 14 and 6 of the OTEZLA label. Apremilast offers an alternative treatment option to a number of FDA-

approved products with an acceptable risk-benefit profile for [redacted]. None of the FDA-approved treatments provides a permanent cure or universal response, and all are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options for this subgroup of patients with plaque psoriasis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multi-system disorder, which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3%, of which an estimated 80 percent have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome[1].	Plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	Currently, there are no FDA-approved systemic products for the indication of "[redacted]". Available treatment options for patients with [redacted] include targeted phototherapy (e.g. excimer light therapy with UV-B	There are a number of FDA-approved products with an acceptable risk-benefit profile for [redacted]. None of these treatments provides a permanent cure or universal

[1] Menter A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008; 58:826-50.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	at a wavelength of 308 nm), off-label use of topical calcineurin inhibitors (TCI) tacrolimus or pimecrolimus (not FDA-approved for psoriasis); and the following FDA-approved topical treatments for psoriasis: • Multiple classes/strengths/formulations of topical corticosteroids (TCS) approved for the indication of "treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CSRD)" • Vitamin D analogues (e.g. calcipotriene) • Keratolytic/Retinoid (e.g. tazarotene) • Combination topical therapies [TCS/vitamin D analogue, TCS/retinoid]	response and all of these products are associated with one or more potential risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.
Benefit	The primary efficacy endpoint for sPGA response (sPGA score = 0 or 1 with ≥ 2-grade reduction from baseline) at Week 16 for ITT population, was achieved in 21.6% of subjects in apremilast group compared to 4.1% of subjects in placebo group in trial CC-10004-PSOR-022 (a treatment effect of approximately 17.5%). The secondary efficacy endpoints for Trial CC-10004-PSOR-022 included: • The proportion of subjects achieving whole-body itch NRS response (≥4-point improvement from baseline) at Week 16. • The proportion of subjects achieving ScPGA response (ScPGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline) at Week 16. For all secondary efficacy endpoints, apremilast was statistically superior to placebo for the ITT population at Week 16.	The data submitted by the applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trial CC-10004-PSOR-022 was adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a patient with mild to moderate plaque psoriasis treated with apremilast 30 mg BID is likely to achieve clear or almost clear skin by Week 16.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Diarrhea, nausea, vomiting, depression, and weight decrease are labeled risks of treatment in the OTEZLA label.	The safety profile of apremilast has been adequately characterized by the premarket and Postmarket safety data for psoriasis, psoriatic arthritis, and oral ulcers of Behcet's disease. Prescription labeling, patient labeling (including Medication Guide), and routine pharmacovigilance are adequate to manage the potential risks of the product.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Section 8.1 Whole Body Itch NRS, DLQI
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	Section 8.1 sPGA, BSA, PASI, ScPGA,
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	x	Patient-focused drug development or other stakeholder meeting summary reports		Patient-focused drug development meeting for psoriasis held by the FDA on 3/17/2016
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution[2]. Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines which trigger and perpetuate the inflammatory cascade[3].

In the U.S. and Canada, prevalence as high as 4.7% have been reported[2]. It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of patients with psoriasis[4].

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The average age of onset is earlier in women than in men[2].

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history and physical examination in most cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions[2].

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants

[2] Feldman, Steven R., MD. PhD; Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis; UpToDate.com; updated December 9, 2015

[3] Blauvelt, Andrew and Ehst, Benjamin D, Pathophysiology of Psoriasis; UpToDate.com; updated July 8,1 2015

[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May; 58 (5):826-50.

with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults[2].

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders[5].

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development (PFDD) Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social and emotional impact including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed need to enlarge the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the PFDD meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal.

2.2. Analysis of Current Treatment Options

The FDA-approved systemic products for the treatment of moderate-to-severe plaque psoriasis belong to multiple categories, including Antimetabolite/Immunosuppressant (e.g. methotrexate), Tumor Necrosis Factor Inhibitor (e.g. infliximab, adalimumab, etanercept, certolizumab), IL-12/IL-23 Inhibitor (e.g. ustekinumab), IL-17A Inhibitor (e.g. secukinumab, ixekizumab), IL-17A receptor antagonist (e.g. brodalumab), IL-23 Inhibitor (e.g. guselkumab, tildrakizumab, rizankizumab), T-Cell Inhibitor/ Immunosuppressant (e.g. cyclosporine), Retinoid (e.g. acitretin), PDE-4 Inhibitor (e.g. apremilast), and phototherapy.

[5] Korman, Neil; Comorbid Disease in Psoriasis; UpToDate.com; updated March 24, 2017.

Currently, there are no FDA-approved systemic products for the indication of "(b) (4)(b) (4)". In clinical practice[6], treatment options for patients with (b) (4) include targeted phototherapy (e.g. excimer light therapy with UV-B at a wavelength of 308 nm), off-label use of topical calcineurin inhibitors (TCI) tacrolimus or pimecrolimus (TCIs are not FDA-approved for topical treatment of psoriasis); and the following FDA-approved topical treatments[6] as summarized in the following Table:

- Multiple classes/strengths/formulations of topical corticosteroids (TCS) approved for the indication of "treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CSRD)"
- Vitamin D analogues
- Keratolytic/Retinoid (tazarotene)
- Combination topical therapies [TCS/vitamin D analogue, and TCS/retinoid] as summarized in the following table:

Table 1: Summary of Topical Treatments for Plaque Psoriasis

Product Class	Example Product/ Year Approved	Relevant Indication [7]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Cortico-steroid	Olux E (clobetasol propionate) Foam/ 2007	CSRD (one trial was done in mild-to-moderate Plaque-type psoriasis)	Apply a thin layer twice daily. Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 g per week	In a randomized study of subjects 12 years of age and older with mild-to-moderate plaque psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with vehicle foam. 41 of 253 subjects (16%) treated with Olux-E Foam compared with 5 of 123 (4%) treated with vehicle foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with at least 2-grade improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness.	Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic pituitary-adrenal (HPA) axis suppression.
Synthetic vitamin D3 derivative	Dovonex (calcipotriene cream)/1996	Plaque psoriasis	Apply a thin layer twice daily	Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This	Reversible elevation of serum calcium has occurred.

[6] Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA*. 2020;323(19):1945–1960. doi:10.1001/jama.2020.4006

[7] Some corticosteroids are indicated for the "treatment (or relief) of inflammatory and pruritic manifestations of moderate-to-severe corticosteroid responsive dermatoses (CSRD)," which is inclusive of the psoriasis indication.

Product Class	Example Product/ Year Approved	Relevant Indication [7]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
				improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearing.	
Synthetic vitamin D3 derivative/ corticosteroid combination product	Taclonex (calcipotriene and betamethasone dipropionate) Ointment/2006	Plaque psoriasis in patients 12 years of age and older	Use once daily for up to 4 weeks	1603 subjects with mild-to very severe plaque psoriasis on trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Taclonex Ointment, calcipotriene hydrate 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively. Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks).	Hypercalcemia and hypercalciuria and HPA axis suppression have been observed. Patients age 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% body surface area is not recommended.
Retinoid	Tazorac (tazarotene) cream, 0.05%, 0.1%/ 2000	Plaque psoriasis	Apply a thin film once daily.	Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.05% and 0.1% vs. vehicle.	Retinoids may cause fetal harm when administered to a pregnant woman.
Retinoid / Cortico-steroid combination product	Duobrii (halobetasol propionate and tazarotene lotion, 0.01%/0.045%) / 2019	Plaque psoriasis	Apply a thin film once daily.	In 2 Phase 3 trials, 276 adult subjects with moderate to severe plaque psoriasis (baseline IGA=3, 4) were treated with Duobrii and 142 with vehicle lotion. Duobrii lotion achieved treatment success, compared to vehicle (Trial -301: 35.8% vs 7.0% and in Trial -302: 45.3% vs 12.5%); Treatment success was defined by an IGA score of clear (0) or almost clear (1) with at least 2-grade improvement from baseline at Week 8.	Risks from corticosteroids and Retinoids: Embryofetal risk in pregnant patients, Photosensitivity and risk of sunburn, Reversible HPA axis suppression and AEs from corticosteroids

Source: Modified from Table 1, NDA 207589/S-010 (Enstilar: calcipotriene and betamethasone dipropionate Foam), Multidisciplinary Review and Evaluation by Dr. Melinda McCord. [Duobrii example added by this reviewer].

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

OTEZLA (apremilast) was developed under IND 070270, submitted on 9/21/2013, and was approved by the Agency on 3/21/2014 for the treatment of adult subjects with active psoriatic arthritis (NDA 205437) and on 9/23/2014 for the treatment of subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (NDA 206088, administratively closed on 10/7/2014). In April 2020, sNDA 205437-008 Prior Approval Efficacy Supplement was approved to support the inclusion of psoriasis of the scalp efficacy claims in Section 14 (Clinical Studies) of the prescribing information for the treatment of subjects with moderate to severe plaque psoriasis of the scalp.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant developed apremilast for the treatment of moderate to severe plaque psoriasis under the 505(b)(1) regulatory pathway. The applicant conducted a clinical study (CC-10004-PSOR-022) to evaluate the efficacy and safety of apremilast in the treatment of subjects with mild to moderate plaque psoriasis, and to broaden the patient population included in the "INDICATION AND USAGE" section of the prescribing information for OTEZLA to include adult patients with plaque psoriasis who are candidates for systemic therapy or phototherapy. Milestone interactions with the applicant were the following:

Type C Guidance (WRO)- 4/25/2018:
Study design, including primary and secondary efficacy endpoints, target population, safety assessment and database, and pediatric studies plans were discussed.

Initial Pediatric Study Plan (iPSP)
An Agreed iPSP Agreement letter (2/8/2019) was conveyed to the applicant following a discussion at the pediatric review committee (PeRC) meeting (1/30/2019); and the PeRC's concurrence with the applicant's proposed Agreed iPSP, including the following plans:

i. Request partial waiver to conduct studies in pediatric subjects < 6 years of age, because studies are impossible or highly impracticable.
ii. Request for deferral to conduct studies in pediatric subjects between 6 to 17 years of age, until study data from clinical studies in adult subjects with mild to moderate plaque psoriasis (PSOR-022), and (b) (4) .

Pre-sNDA meeting (8/26/2020):

i. Safety data (and efficacy data for maintenance of response) to be submitted by disease severity (mild, moderate) and total population for the 32-week duration of study PSOR-022.

ii. The Clinical Overview for Study PSOR-022 was deemed acceptable as the required Clinical Summary for efficacy and safety. No SCS/SCE/ISS/ISE was required.
iii. Inclusion of narratives and case report forms for deaths, SAEs, and AELDs.
iv. Applicant's Proposed plan to submit datasets (CDISC, SDTM, ADaM) and SAS programs and supporting documents was acceptable.

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate.

The by-country (US and Canada) efficacy results for Study CC-10004-PSOR-022 for the primary efficacy endpoint were generated by the statistical reviewer for this sNDA (Matthew Guerra, PhD), see Table 12 in Section 8.1.7.2. Considering the marketing history of apremilast (initial approval 2014) and the results of by-country efficacy Table for this product, The Clinical and Statistical reviewers did not request a clinical study site inspection from the Office of Scientific Investigations.

4.2. Product Quality

No new information was submitted related to Product Quality in the submission.

4.3. Clinical Microbiology

Not applicable for this supplement.

4.4. Devices and Companion Diagnostic Issues

Not applicable for this supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical information was submitted for review in this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

No new clinical pharmacology information was submitted for review in this supplement.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The applicant conducted a single Phase 3 trial, CC-10004-PSOR-022 entitled "A Phase 3, multicenter, randomized, placebo-controlled, double blind study of the efficacy and safety of apremilast (CC-10004) in subjects with mild to moderate plaque psoriasis" to provide clinical data pertinent to the evaluation of the efficacy and safety of apremilast for (b) (4) (b) (4) .

Additionally, for the Agency awareness, the applicant submitted the results of a Phase 3b Study conducted in Japan (CC-10004-PSOR-023) entitled "A Phase 3b, Open-label, Single-arm Study of the Efficacy and Safety of Apremilast, in Subjects with Plaque Psoriasis that is not Adequately Controlled by Topical Therapy".

Table 2: Listing of Clinical Trials Relevant to sNDA 205437/Supplement 11

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
CC-10004-PSOR-022	NCT 037 211 72	Phase 3, multicenter, randomized, placebo-controlled, double-blind study with apremilast extension period	Placebo or apremilast 30 mg BID (after titration) for 16 weeks, followed by apremilast 30 mg BID for 16 weeks.	Primary: Proportion of subjects with sPGA score of clear (0) or almost clear (1) with ≥ 2-point reduction from baseline at Week 16 Secondary (Weeks 16, 32): Proportion of subjects with≥ 75% improvement in BSA from baseline Changes from baseline in BSA, PASI, DLQI Proportion of subjects with BSA<=3% (baseline BSA >3%) Proportion of subjects with ≥ 4-point reduction from baseline in the Whole-Body Itch NRS (baseline NRS≥ 4)	Placebo-controlled period (weeks 0-16) Apremilast extension period (weeks 16-32)	N=595 1:1	Adult subjects with mild to moderate plaque psoriasis defined as: • sPGA score= 2, 3 (mild or moderate) at baseline • BSA= 2 % to 15% • PASI= 2 to 15 • Inadequate response or intolerance of topical therapies • No prior exposure to biologics	61 sites: US (40), Canada (21)

7.2. Review Strategy

Data Sources

The applicant provided CSR and datasets (NDA 205437, SDN 1333 eCTD 0275) by electronic submission at the following network path: View submission in docuBridge

Data and Analysis Quality

In general, the data submitted by the applicant to support the efficacy and safety of apremilast for the treatment of mild to moderate plaque psoriasis in adult subjects appeared adequate and the data quality was found to be acceptable by the review team.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

Trial PSOR-022 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group, Phase 3 trial to evaluate the safety and efficacy of apremilast compared to placebo in subjects with mild to moderate plaque psoriasis. For enrollment, the protocol specified the following key inclusion criteria:

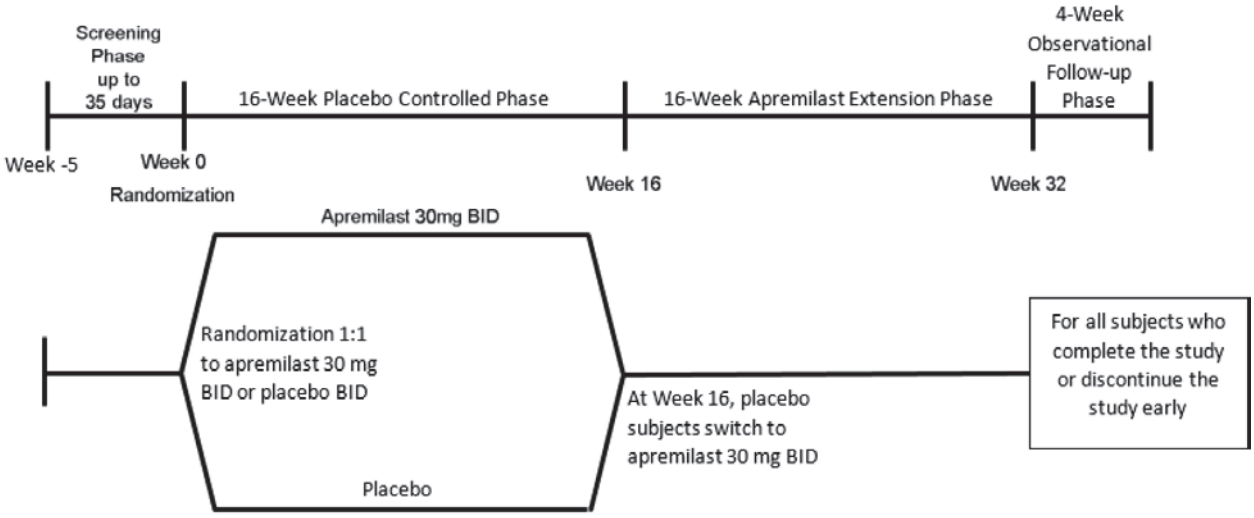
- Males or females, ≥18 years of age
- Diagnosis of plaque psoriasis for at least 6 months
- Mild to moderate plaque psoriasis at both screening and baseline defined as:
    - Static Physician Global Assessment (sPGA) score of 2 (mild) or 3 (moderate), see Table 3 for details on the sPGA
    - Body Surface Area (BSA) involvement of 2-15%
    - Psoriasis Area Severity Index (PASI) score 2-15
- Inadequately controlled with, or intolerant of at least one topical therapy (including topical corticosteroids, topical retinoids or vitamin D analog preparations, calcipotriene and betamethasone dipropionate ointment or foam, tacrolimus, pimecrolimus, or anthralin/dithranol) for the treatment of psoriasis at both screening and baseline

The trial was designed to enroll and randomize approximately 574 subjects from sites in North America (United Stated and Canada) in a 1:1 ratio to receive either apremilast tablets (N=287) or placebo tablets (N=287). The protocol specified stratifying the randomized by baseline sPGA score (2 [mild] and 3 [moderate]). In addition, the protocol specified that approximately 30% of subjects enrolled will have a sPGA score of 2 (mild) at baseline. Figure 1 presents the study design schematic for Trial PSOR-022. The trial consisted of the following four phases:

- Screening Phase (Weeks -5 to 0; up to 35 days)
- Placebo-controlled Phase (Weeks 0 to 16): subjects received apremilast tablets, 30 mg BID (approved dosage) or placebo tablets BID for 16 weeks. In addition, the approved dose titration scheduled was used for the first week.
- Apremilast Extension Phase (Weeks 16 to 32): placebo subjects switched to apremilast tablets, 30 mg BID and the approved dose titration scheduled was used for the first week. Dummy titration blister cards (dosing at 30 mg BID directly) was used for subjects initially randomized to receive apremilast 30 mg BID. All subjects were specified to maintain this dosing through Week 32.
- Observational Follow-up Phase (4 weeks): all subjects who completed the trial or discontinued the trial early were scheduled to a 4-week follow-up visit.

Subjects were scheduled to have the following site visits: screening (up to Day -35), baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 32, and 4 weeks after last dose.

Figure 1: Study Design Schematic for Trial PSOR-022



Source: page 25 of the protocol for Trial PSOR-022.

The protocol-specified primary efficacy endpoint was the proportion of subjects achieving a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16.

The protocol specified the following as secondary efficacy endpoints:

- Proportion of subjects who improved ≥ 75% in BSA from baseline at Week 16
- Change from baseline in affected BSA at Week 16
- Change from baseline in total PASI score at Week 16
- Proportion of subjects who achieved BSA ≤ 3% among subjects with baseline BSA > 3%
- Proportion of subjects with ≥ 4-point reduction (improvement) from baseline in whole body itch numeric rating scale (NRS) score at Week 16 among subjects with baseline whole body itch NRS ≥ 4
- Proportion of subjects with Scalp Physician Global Assessment (ScPGA) score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16 among subjects with baseline ScPGA score ≥ 2 (mild)
- Change from baseline in Dermatological Life Quality Index (DLQI) at Week 16

In an advice letter (dated October 19,2018), the Agency stated:

> "The DLQI does not appear to be fit-for-purpose in the context of this drug development program due to lack of item relevancy. The DLQI contains questions that measure broad concepts related to general skin conditions (e.g., going shopping, making your home messy) which may lack clinical relevance and be insensitive to treatment effect among mild to moderate psoriasis patients. Further, there are issues surrounding content validity, specifically the use of multi-barreled questions (questions measuring more than one concept; e.g., Questions 1-3, 5, 7, 8 and 10) which can be problematic from measurement standpoint…It is at your discretion to proceed with the use of this instrument. (b) (4) (b) (4) ."

Therefore, the results for DLQI are not presented in this review.

Table 3: Static Physician Global Assessment (sPGA)

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

Source: page 78 of the protocol for Trial PSOR-022.

Table 4: Scalp Physician Global Assessment (ScPGA)

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

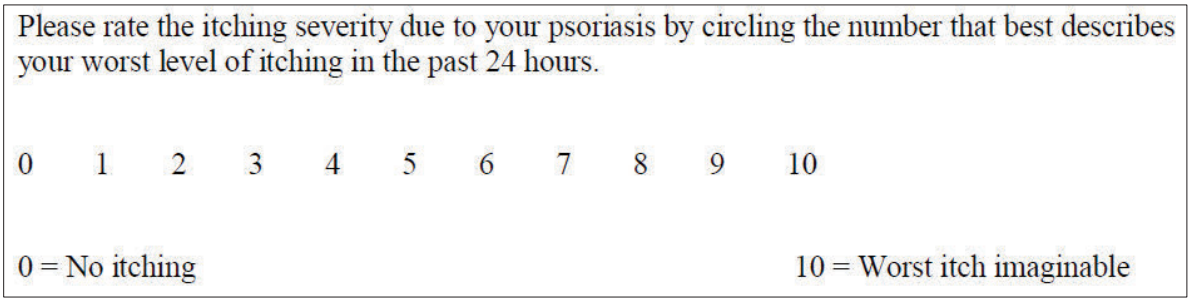
Source: page 80 of the protocol for Trial PSOR-022.

Figure 2: Psoriasis Area and Severity Index (PASI)

STEP A. Please write in the appropriate number for rows 1 - 3 using the scale below:				
0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe				
	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
1. Erythema				
2. Thickness				
3. Scaling				
4. TOTAL Each Column				
STEP B. Enter the number of hands the psoriasis covers on each body area				
	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
5. Number of Hands				
6. Area (% of total BSA)	10	30	20	40
STEP C. Calculate % of involvement:				
7. % of each region involved **[(Row 5 ÷ Row 6) x 100*]**				
8. TOTAL BSA (sum of # of hands from row 5)				
STEP D. Select Degree of Involvement using value in Row 7:				
0 = No involvement				
1 = <10%				
2 = 10 < 30%				
3 = 30 < 50%				
4 = 50 < 70%				
5 = 70 < 90%				
6 = 90 < 100%				
9. Degree of Involvement (0-6) of each region				
STEP E. Calculate PASI (Row 4 x Row 6 x Row 9) ÷ 100*				
10. PASI for each body region				
11. TOTAL PASI (sum of Row 10 subscores)				

Source: page 79 of the protocol for Trial PSOR-022.

Figure 3: Whole Body Itch Numeric Rating Scale (NRS)



Source: page 87 of the protocol for Trial PSOR-022.

8.1.2. Statistical Methodologies

The protocol-specified primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol specified conducting supportive analyses using the per-protocol (PP) population. The PP population was defined as all subjects included in the ITT population who receive at least one dose of study product, have both baseline and at least one post-treatment sPGA evaluation, and have no important protocol deviations which may affect analyses in the placebo-controlled phase.

The protocol specified analyzing the binary efficacy endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline sPGA score (i.e., the factor used to stratify the randomization). For the analysis of the continuous efficacy endpoints, the protocol specified using a mixed-effect model for repeated measure (MMRM) with treatment, visit, treatment-by-visit interaction, baseline sPGA score, and baseline value as factors in the model. The protocol specified using an unstructured covariance matrix to model the correlation among the repeated measures. In addition, the protocol specified conducting sensitivity analyses where these endpoints will be analyzed using analysis of covariance (ANCOVA) with treatment, baseline sPGA score and baseline value as factors in the model. For ANCOVA, missing data was specified to be imputed using the last observation carried forward (LOCF).

To control the Type I error rate for testing multiple secondary efficacy endpoints, the protocol specified using a sequential gatekeeping approach. For each secondary efficacy endpoint, the protocol specified that statistical significance will be claimed only if its two-sided p-value is below 0.05 and the tests for all previous secondary efficacy endpoints are significant at the two-sided 0.05 level. The secondary efficacy endpoints will be tested in the order listed in Section 8.1.1 and will only be tested if the primary efficacy endpoint is significant at the two-sided 0.05 level.

For the primary efficacy endpoint, the protocol-specified method for handling missing data was the multiple imputation (MI) approach, which was done in two steps. In the first step, the Markov Chain Monte Carlo (MCMC) method was used to impute non-monotone missing sPGA scores by treatment group and stratification factor (i.e., baseline sPGA score) to create 50

imputed datasets. The imputed scores were rounded to the nearest integer. The minimum and the maximum values for imputation was set to be 0 and 4, which correspond to the lowest and the highest sPGA scores. In the second step, the predictive mean matching method was used to impute the remaining missing values for the 50 datasets. For the predictive mean matching, the protocol specified using treatment group, stratification factor, and data visits from baseline to Week 16. The protocol specified using non-responder imputation and a tipping point analysis as sensitivity analyses for the handling of missing data.

The protocol specified imputing missing data for the binary secondary efficacy endpoints using a similar MI method as the primary efficacy endpoint. In addition, the protocol specified using non-responder imputation as a sensitivity analysis for the handling of missing data. For the continuous secondary efficacy endpoints, the primary method for handling missing data was not impute the missing data and analyze these endpoints using MMRM. As noted above, the protocol specified a sensitivity analysis where missing data is imputed using LOCF and then analyzed using ANCOVA.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial PSOR-022 enrolled and randomized a total of 595 subjects (297 to apremilast and 298 to placebo) from 61 centers in North America (United Stated and Canada). Table 5 presents the subject disposition for the placebo-controlled phase of the trial. The discontinuation rate was slightly higher in the placebo group compared to the apremilast group. The demographics and baseline disease characteristics were generally balanced across the two treatment groups and are presented in Table 6 and Table 7, respectively.

Table 5: Subject Disposition for Placebo-Controlled Phase (Weeks 0-16) – Trial PSOR-022 (ITT[1])

	Apremilast (N=297)	Placebo (N=298)	Total (N=595)
Discontinued	39 (13)	52 (17)	91 (15)
Withdrawal by subject	18 (6)	23 (8)	41 (7)
Lost to follow-up	13 (4)	15 (5)	28 (5)
Adverse event	7 (2)	7 (2)	14 (2)
Lack of efficacy	0	4 (1)	4 (1)
Other	0	3 (1)	3 (1)
Non-compliance with study drug	1 (<1)	0	1 (<1)

[1] Intent-to-treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt

Table 6: Demographics – Trial PSOR-022 (ITT[1])

	Apremilast (N=297)	Placebo (N=298)	Total (N=595)
Age (years)			
Mean (SD)	49.2 (14.7)	48.3 (14.5)	48.7 (14.5)
Median	51	49	50
Min, Max	18, 85	18, 85	18, 85
Categories, n (%)			

	Apremilast (N=297)	Placebo (N=298)	Total (N=595)
< 65	248 (84)	260 (87)	508 (85)
≥ 65	49 (16)	38 (13)	87 (15)
Sex, n (%)			
Male	174 (59)	151 (51)	325 (55)
Female	123 (41)	147 (49)	270 (45)
Race, n (%)			
White	254 (86)	257 (86)	511 (86)
Asian	15 (5)	18 (6)	33 (6)
Black	14 (5)	17 (6)	31 (5)
Other	14 (5)	6 (2)	20 (3)
Weight (kg)			
Mean (SD)	91.9 (22.6)	89.1 (22.7)	90.5 (22.7)
Median	89.5	86.1	87.5
Min, Max	40, 191	34, 184	34, 191

[1] Intent-to-treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt

Table 7: Baseline Disease Characteristics – Trial PSOR-022 (ITT[1])

	Apremilast (N=297)	Placebo (N=298)	Total (N=595)
sPGA Score, n (%)			
2 – Mild	91 (31)	91 (31)	182 (31)
3 – Moderate	206 (69)	207 (69)	413 (69)
PASI Score			
Mean (SD)	6.4 (2.9)	6.5 (2.9)	6.5 (2.9)
Median	6	6	6
Min, Max	2, 15	2, 15	2, 15
Categories, n (%)			
< 12	279 (94)	282 (95)	561 (94)
≥ 12	18 (6)	16 (5)	34 (6)
Percent BSA			
Mean (SD)	6.4 (3.6)	6.3 (3.3)	6.4 (3.4)
Median	5.5	5.5	5.5
Min, Max	2, 18	2, 21	2, 21
Categories, n (%)			
< 10	246 (83)	248 (83)	494 (83)
≥ 10	51 (17)	50 (17)	101 (17)
ScPGA Score, n (%)			
0 – Clear	71 (24)	88 (30)	159 (27)
1 – Almost Clear	14 (5)	11 (4)	25 (4)
2 – Mild	71 (24)	82 (28)	153 (26)
3 – Moderate	130 (44)	113 (38)	243 (41)
4 – Severe	11 (4)	4 (1)	15 (3)
Whole Body Itch NRS			
Mean (SD)	6.1 (2.4)	6.3 (2.6)	6.2 (2.5)
Median	6	7	7
Min, Max	0, 10	0, 10	0, 10
Categories, n (%)			
< 4	44 (15)	49 (16)	93 (16)
≥ 4	253 (85)	249 (84)	502 (84)

[1] Intent-to-treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADBL.xpt

8.1.4. Results of the Primary Efficacy Endpoint

Table 8 presents the results of the primary efficacy endpoint at Week 16 in the ITT population. Apremilast was statistically superior to placebo for the primary efficacy endpoint (p-value < 0.001). The results in the PP population (not shown) were similar to those obtained using the ITT population.

Table 8: Results for the Primary Efficacy Endpoint – Trial PSOR-022 (ITT[1])

	Apremilast (N=297)	Placebo (N=298)
sPGA Response[2] at Week 16		
Proportion[3]	21.6%	4.1%
Unadjusted Difference (95% CI)	17.5% (12.1%, 22.8%)	
Adjusted Difference (95% CI)[4]	17.5% (12.2%, 22.8%)	
P-Value[4]	<0.001	

[1] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[2] Response was defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[3] The value displayed is the average of the 50 imputed datasets.
[4] Adjusted difference in proportions is the weighted average of the treatment differences across the baseline sPGA strata with the CMH weights, and the 2-sided 95% CI is based on the stratified Newcombe method. P-value is based on the CMH test stratified by baseline sPGA score.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADQSPGAI.xpt

Table 9 presents the number of subjects with missing data for the primary efficacy endpoint at Week 16 along with the results of this endpoint for the two prespecified methods for handling missing data (i.e., MI [primary] and NRI [sensitivity]). The proportion of subjects with missing data was slightly higher in the placebo group compared to the apremilast group. The treatment effect (i.e., difference) was slightly smaller when the missing data was imputed using NRI. The protocol also specified conducting a tipping point analysis as a sensitivity analysis for the handling of missing data. The results tipped (i.e., p-value no longer < 0.05) when all 36 subjects in the apremilast group with missing sPGA scores at Week 16 were assumed to be non-responders and 29 out of the 49 subjects (59%) in the placebo group with missing sPGA score at Week 16 were assumed to be responders. Given that the placebo rate in subjects with complete data is approximately 4%, the plausibility that 59% of the subjects in the placebo group with missing sPGA scores at Week 16 would have been responders is extremely low.

Table 9: Results for the Primary Efficacy Endpoint at Week 16 with Different Approaches for Handling Missing Data – Trial PSOR-022 (ITT[1])

	Apremilast (N=297)	Placebo (N=298)	Difference (95% CI)[2]
Subjects with Missing Data	36 (12.1%)	49 (16.4%)	--
MI (primary)[3]	21.6%	4.1%	17.5% (12.2%, 22.8%)
NRI[4]	19.2%	3.7%	15.5% (10.5%, 20.7%)

[1] Intent-to-treat (ITT) population: all randomized subjects.
[2] Adjusted difference in proportions is the weighted average of the treatment differences across the baseline sPGA strata with the CMH weights, and the 2-sided 95% CI is based on the stratified Newcombe method.
[3] Missing data was imputed using multiple imputation (MI). Response rate is the average over the 50 imputed datasets.
[4] Missing data was imputed using non-responder imputation (NRI).
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADQSPGAI.xpt, ADQSPGA.xpt

8.1.5. Results of the Secondary Efficacy Endpoints

Table 10 presents the results for the secondary efficacy endpoints. For all of the secondary efficacy endpoints, apremilast was statistically superior to placebo (p-values < 0.001). As discussed in Section 8.1.1, the results for the secondary efficacy endpoint based on the DLQI are not presented in this review.

Table 10: Results for the Secondary Efficacy Endpoints – Trial PSOR-022

	Apremilast (N=297)	Placebo (N=298)
BSA-75 at Week 16		
Proportion[5]	33.0%	7.4%
Unadjusted Difference (95% CI)	25.6% (19.2%, 32.1%)	
Adjusted Difference (95% CI)[6]	25.6% (19.1%, 32.1%)	
P-Value[6]	<0.001	
Absolute Change in Percent BSA at Week 16		
N[1]	261	249
Mean[5]	-3.49	-0.06
LS Mean[7]	-3.45	-0.07
Difference (95% CI)[7]	-3.38 (-4.04, -2.73)	
P-Value	<0.001	
Absolute Change in PASI at Week 16		
N[1]	261	249
Mean	-3.54	-0.56
LS Mean	-3.47	-0.54
Difference (95% CI)	-2.93 (-3.47, -2.39)	
P-Value	<0.001	
BSA ≤ 3% at Week 16		
N[2]	245	255
Proportion[5]	61.0%	22.9%
Unadjusted Difference (95% CI)	38.1% (29.7%, 46.4%)	
Adjusted Difference (95% CI)[6]	38.0% (29.7%, 46.3%)	
P-Value[6]	<0.001	
Whole Body Itch Response[8] at Week 16		
N[3]	253	249
Proportion[5]	43.2%	18.6%
Unadjusted Difference (95% CI)	24.7% (16.5%, 32.8%)	
Adjusted Difference (95% CI)[6]	24.7% (16.5%, 32.8%)	
P-Value[6]	<0.001	
ScPGA Response[9] at Week 16		
N[4]	212	199
Proportion[5]	44.0%	16.6%
Unadjusted Difference (95% CI)	27.4% (18.5%, 36.3%)	
Adjusted Difference (95% CI)[6]	27.4% (18.6%, 36.3%)	
P-Value[6]	<0.001	

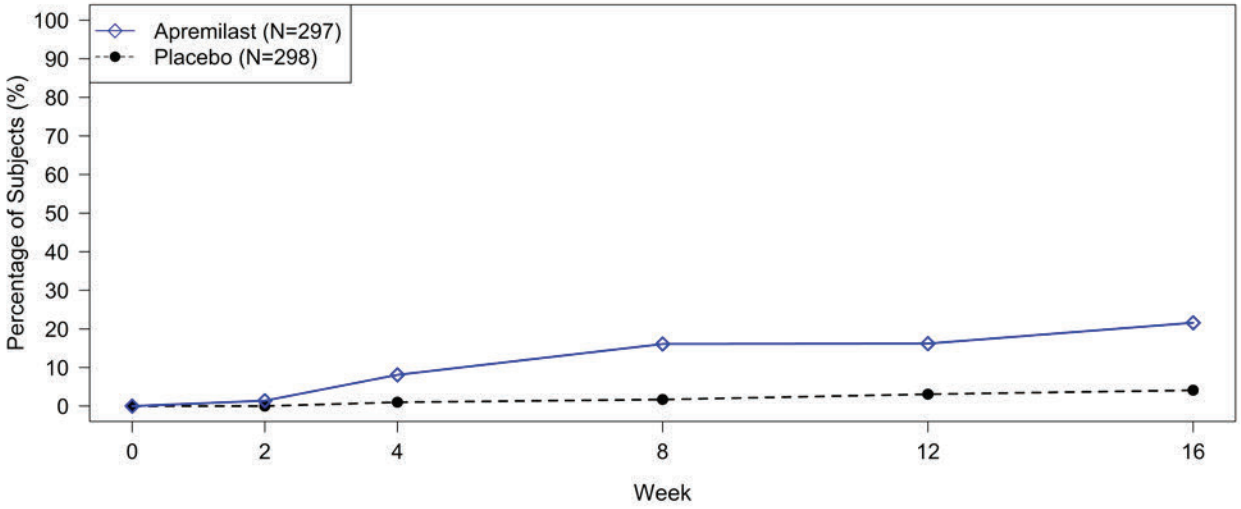
[1] All randomized subjects with baseline and at least one post-baseline assessment.
[2] All randomized subjects with baseline BSA score > 3 %. Missing data was imputed using multiple imputation (MI).
[3] All randomized subjects with baseline Whole Body Itch NRS score ≥ 4. Missing data was imputed using multiple imputation (MI).
[4] All randomized subjects with baseline ScPGA score ≥ 2 (mild). Missing data was imputed using multiple imputation (MI).
[5] The value displayed is the average of the 50 imputed datasets.
[6] Adjusted difference in proportions is the weighted average of the treatment differences across the baseline sPGA strata with the CMH weights, and the 2-sided 95% CI is based on the stratified Newcombe method. P-value is based on the CMH test stratified by baseline sPGA score.

[7] LS Mean, difference, and 95% CI are based on MMRM with treatment group, visit, treatment-by-visit interaction, and baseline sPGA score as fixed effects, and baseline value as a covariate.
[8] Response was defined as a ≥4-point improvement from baseline on the Whole Body Itch NRS.
[9] Response was defined as a ScPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADQSBSAI.xpt, ADQSNRSI.xpt, ADQSCPGI.xpt

8.1.6. Efficacy Over Time

During the placebo-controlled period (i.e., Weeks 0 to 16), subjects were evaluated for sPGA at Weeks 0, 2, 4, 8, 12, and 16. Figure 4 presents the results for sPGA response during the placebo-controlled phase in Trial PSOR-022.

Figure 4: Results for sPGA Response[1] During the Placebo-Controlled Phase (Weeks 0-16) – Trial PSOR-022 (ITT[2])



[1] Response was defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
Source: Statistical Reviewer's Analysis; ADQSPGAI.xpt

8.1.7. Findings in Special/Subgroup Populations

8.1.7.1. Baseline Disease Severity

Table 11 presents the results for the primary efficacy endpoint at Week 16 by baseline sPGA score (2 [mild] vs. 3 [moderate]), baseline PASI score (<12 vs. ≥12), and baseline BSA (<10% vs. ≥10%). In addition, the table also presents the results by whether the subjects met the key inclusion criteria that has been used to define moderate to severe plaque psoriasis (i.e., sPGA ≥ 3 (moderate), PASI ≥ 12, and BSA ≥ 10%).

For baseline sPGA score, the treatment effect was much larger in the subjects with sPGA score of 3 (moderate) compared to subjects with sPGA score of 2 (mild). It should be noted that subjects with a sPGA score of 2 (mild) at baseline are required to achieve a sPGA score of 0 (clear) in order to be a responder for the primary efficacy endpoint; however, subjects with a

sPGA score of 3 (moderate) at baseline can be a responder for the primary efficacy endpoint if they achieve a sPGA score of 0 (clear) or 1 (almost clear). The treatment effect was similar for subjects with a baseline PASI score < 12 compared to those with a baseline PASI score ≥ 12. For baseline BSA, the treatment effect was slightly higher in subjects with a BSA ≥ 10% compared to those with a BSA < 10%. The treatment effect was similar between those who met the moderate to severe plaque psoriasis criteria to those that did not; however, it should be noted that only 28 subjects met the moderate to severe plaque psoriasis criteria. Therefore, it would be difficult to make reliable conclusions regarding this subgroup comparison.

Table 11: Results for the Primary Efficacy Endpoint at Week 16 by Baseline Disease Severity – Trial PSOR-022 (ITT[1])

Subgroups (n[A], n[P])	Apremilast (N=297)	Placebo (N=298)	Difference (95% CI)
sPGA Score			
2 – Mild (91, 91)	6.9%	1.6%	5.3% (-0.9%, 11.5%)
3 – Moderate (206, 207)	28.1%	5.2%	22.9% (15.8%, 30.0%)
PASI Score			
< 12 (279, 282)	21.4%	4.0%	17.5% (12.0%, 22.9%)
≥ 12 (18, 16)	24.1%	6.5%	17.9% (-5.7%, 41.5%)
BSA			
< 10% (246, 248)	21.0%	4.1%	17.0% (11.1%, 22.8%)
≥ 10% (51, 50)	24.3%	4.2%	20.1% (6.9%, 33.3%)
Moderate to Severe Plaque Psoriasis Criteria[2]			
Yes (14, 14)	23.9%	7.1%	16.7% (-10.2%, 43.6%)
No (283, 284)	21.5%	3.9%	17.5% (12.1%, 23.0%)
Overall	21.6%	4.1%	17.5% (12.1%, 22.8%)

[1] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[2] Subjects that meet all of the following: sPGA ≥ 3 (moderate), PASI ≥ 12, and BSA ≥ 10%.
Source: Statistical Reviewer's Analysis; ADBL.xpt, ADQSPGAI.xpt

8.1.7.2. Age, Sex, Race, and Country

Table 12 presents the results for the primary efficacy endpoint at Week 16 by age (<65 vs. ≥65), sex, race (White vs. Non-white), and country (United States vs. Canada). There were no substantial differences in efficacy across these subgroups. The treatment effect was higher in females compared to males. In addition, the treatment effect was higher in Canada compared to the United States.

Table 12: Results for the Primary Efficacy Endpoint at Week 16 by Age, Sex, Race, and Country – Trial PSOR-022 (ITT[1])

Subgroups (n[A], n[P])	Apremilast (N=297)	Placebo (N=298)	Difference (95% CI)
Age (years)			
< 65 (248, 260)	21.7%	3.9%	17.8% (11.9%, 23.6%)
≥ 65 (49, 38)	21.1%	5.3%	15.7% (2.2%, 29.3%)
Sex			
Male (174, 151)	19.2%	4.9%	14.2% (7.3%, 21.1%)
Female (123, 147)	25.0%	3.2%	22.2% (13.4%, 30.2%)

Race			
White (254, 257)	21.5%	4.2%	17.3% (11.5%, 23.1%)
Non-White (43, 41)	22.1%	3.4%	18.7% (4.5%, 32.9%)
Country			
United States (164, 169)	20.4%	5.1%	15.3% (8.0%, 22.6%)
Canada (133, 129)	23.1%	2.7%	20.3% (12.4%, 28.2%)
Overall	21.6%	4.1%	17.5% (12.1%, 22.8%)

[1] Intent-to-treat (ITT) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[2] Subjects that meet all of the following: sPGA ≥ 3 (moderate), PASI ≥ 12, and BSA ≥ 10%.
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADQSPGAI.xpt

8.1.8. Comparison with Previous Phase 3 Trials

For the pivotal Phase 3 trials used to approve apremilast tablets for the treatment of moderate to severe plaque psoriasis (i.e., Trials PSOR-008 and PSOR-009), the protocols specified the following key inclusion criteria for enrollment regarding baseline disease severity: sPGA score ≥ 3 (moderate), PASI score ≥ 12, and BSA involvement ≥ 10%. Table 13 compares the baseline disease characteristics of the current trial (i.e., Trial PSOR-022) to those of the previous Phase 3 trials. In addition, the table presents the baseline PASI scores and percent BSA by baseline sPGA scores. It should be noted that the baseline PASI scores and percent BSA for subjects with a baseline sPGA score of 3 (moderate) in the previous Phase 3 trials were on average more than two times larger than those for subjects with a baseline sPGA score of 3 (moderate) in the current trial. Therefore, it appears that "moderate" disease in the current trial is less than "moderate" disease in the previous Phase 3 trials.

Table 13: Comparison of Baseline Disease Characteristics

	Trial PSOR-022[1]			Previous Phase 3 Trials (PSOR-008 and PSOR-009)[2]			
		Baseline sPGA Score			Baseline sPGA Score		
	Overall (N=595)	2 – Mild (N=182)	3 – Moderate (N=413)	Overall (N=1255)	2 – Mild (N=2)	3 – Moderate (N=879)	4 – Severe (N=374)
sPGA Score, n (%)							
2 – Mild	182 (31)			2 (<1)			
3 – Moderate	413 (69)			879 (70)			
4 – Severe	-			374 (30)			
PASI Score							
Mean	6.5	4.7	7.3	19.1	12.5	17.0	23.9
Median	6.0	4.4	7.0	16.8	12.5	15.6	20.8
Min, Max	1.5, 14.8	1.5, 11.8	2, 14.8	11.2, 60	12.2, 12.8	11.2, 51.1	12, 60
Percent BSA							
Mean	6.4	5.0	7.0	25.2	24.0	23.0	30.4
Median	5.5	4.0	6.0	21.0	24.0	19.0	26.0
Min, Max	2, 21	2, 15	2, 21	9, 86	13, 35	9, 86	10, 86

[1] Intent-to-treat (ITT) population: all randomized subjects.
[2] Full Analysis Set (FAS): all randomized subjects, excluding subjects that were randomized in error (i.e., there was one subject randomized in error to placebo).
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADBL.xpt [NDA 205437 S-11 and NDA 206088]

Table 14 and Table 15 presents the results for sPGA response at Week 16 for Trials PSOR-008 and PSOR-009, respectively. The tables present the results for the overall population as well as by baseline sPGA score. The results for the overall population in these two trials are similar to those in Trial PSOR-022, see Table 8 for the overall results in Trial PSOR-022.

Table 14: Results for sPGA Response[1] at Week 16 – Trial PSOR-008 (FAS[2])

	Apremilast (N=562)	Placebo (N=282)	Difference (95% CI)
Overall	21.7%	3.9%	17.8% (13.7%, 21.9%)
Baseline sPGA Score			
2 – Mild (0, 1)	-	0%	-
3 – Moderate (401, 192)	23.4%	5.2%	18.2% (13.0%, 23.4%)
4 – Severe (161, 89)	17.4%	1.1%	16.3% (10.0%, 22.5%)

[1] Response was defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Full Analysis Set (FAS): all randomized subjects, excluding subjects that were randomized in error. There were no subjects randomized in error for this trial. Missing data was imputed using last observation carried forward (LOCF).
Source: Statistical Reviewer's Analysis; ADBL.xpt, ADQSSP.xpt [NDA 206088]

Table 15: Results for sPGA Response[1] at Week 16 – Trial PSOR-009 (FAS[2])

	Apremilast (N=274)	Placebo (N=137)	Difference (95% CI)
Overall	20.4%	4.4%	16.1% (10.2%, 21.9%)
Baseline sPGA Score			
2 – Mild (1, 0)	0%	-	-
3 – Moderate (198, 88)	23.7%	5.7%	18.1% (10.4%, 25.7%)
4 – Severe (75, 49)	12.0%	2.0%	10.0% (1.6%, 18.3%)

[1] Response was defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[2] Full Analysis Set (FAS): all randomized subjects, excluding subjects that were randomized in error. There was one subjects randomized in error to placebo. Missing data was imputed using last observation carried forward (LOCF).
Source: Statistical Reviewer's Analysis; ADBL.xpt, ADQSSP.xpt [NDA 206088]

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of apremilast for adult subjects with mild to moderate psoriasis relied on safety data from trial CC-10004-PSOR-022.

The safety analysis set included 595 subjects randomized (1:1) to treatment with apremilast 30 mg BID (n=297) (with a 5-day initial dose titration) or placebo (n=298). Of the 258 subjects in the apremilast group and 246 subjects in the placebo group who completed the 16-week placebo-controlled (PC) period, all but 1 subject (in the apremilast group) continued on to treatment with apremilast 30 mg BID in the apremilast-extension period (Weeks 16-32).

Subjects treated with placebo during the PC period received apremilast dose titration at Week 16. As randomized at baseline visit (Week 0), 221 subjects (74.4%) in the apremilast group and 216 subjects (72.5%) in the placebo group completed the study.

The safety population included all randomized subjects who used the study drug at least once. Investigators conducted safety assessments at screening, baseline, Weeks 2, 4, 8, 12, and 16 visits during the PC period; at Weeks 20, 24, and 32 visits during apremilast-extension period; and at Week 36 (observational follow-up visit).

The WARNINGS AND PRECAUTIONS SECTION of the current OTEZLA label includes diarrhea, nausea, vomiting, depression, and weight decrease.
To determine the safety profile of apremilast for the treatment of mild to moderate psoriasis, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs, severe TEAEs, serious adverse events (SAEs), TEAEs leading to discontinuation (AELD), physical examinations, clinical laboratory measurements (chemistry, hematology, urinalysis, and serum or urine pregnancy tests for female subjects of child-bearing potential), vital signs (including weight), and psychiatric assessment (by C-SSRS). No Adverse Events of Special Interest (AESIs) were prespecified in the protocol.

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to apremilast in terms of frequency, duration and target population was adequate for the evaluation of safety. A total of 544 subjects were exposed to apremilast 30 mg BID and 180 subjects received treatment with apremilast 30 mg BID for 32 weeks.

During the PC period (weeks 0-16), the mean duration of exposure to apremilast and placebo were 15 (SD 3.6) weeks and 14.8 (SD 3.7) weeks respectively. One hundred and eighty (180) of 298 subjects (60.4%) in apremilast group and 188 of 296 subjects (63.5%) in the placebo group completed the PC period at Week 16.

During apremilast-exposure period (weeks 0--32), the mean duration of exposure to apremilast for subjects in the apremilast/apremilast group was 28.2 (SD 8.8) weeks and for subjects in the placebo/apremilast group was 15.5 (SD 3.1) weeks respectively.

The Demographic Characteristics of the study population at baseline were well-balanced across treatment groups and representative of the target population. Refer to Section 8.1.3 of this review for greater detail for Subject Disposition.

Adequacy of the safety database:

The safety database presented by the applicant is adequate to characterize the safety profile of apremilast for the treatment of mild to moderate plaque psoriasis in adult subjects. Safety assessments were reasonable and consistent with known adverse events for apremilast in the target population:

- The size of safety database is adequate.
- The total subject exposure to apremilast during the PC period (weeks 0-16) provides adequate data for the evaluation of safety.
- The demographics of the study population are sufficiently representative of the target population as presented in the following table:

Table 16: Baseline Demographic Characteristics, Trial CC-10004-PSOR-022 (ITT Population)

Characteristic	Placebo (n=298)	Apremilast (n=297)	Total (N=595)
Age			
Mean (SD)	48.3	49.2	48.7
Median	49.0	51.0	50.0
Minimum to maximum	18, 85	18, 85	18, 85
Sex, n(%)			
Male	151 (50.7)	174 (58.6)	325 (54.6)
Female	147 (49.3)	123 (41.4)	270 (45.4)
Race, n(%)			
American Indian or Alaska native	1 (0.3)	7 (2.4)	8 (1.3)
Asian	18 (6.0)	15 (5.1)	33 (5.5)
Black or African American	17 (5.7)	14 (4.7)	31 (5.2)
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.7)	3 (0.5)
White	257 (86.2)	254 (85.5)	511 (85.9)
unknown/unreported	4 (1.3)	5 (1.7)	9 (1.5)
Ethnicity, n(%)			
Hispanic or Latino	33 (11.1)	31 (10.4)	64 (10.8)
Not Hispanic or Latino	260 (87.2)	264 (88.9)	524 (88.1)
Unknown/unreported	5 (1.7)	2 (0.7)	7 (1.2)
Weight (kg)			

Mean (SD)	89.1 (22.7)	91.9 (22.6)	90.5 (22.7)
Median	86.1	89.5	87.5
Minimum to maximum	34.0, 184.2	40.4, 191.0	34.0, 191.0
BMI (kg/m^2)			
Mean (SD)	30.9 (7.0)	31.2 (7.2)	31.1 (7.1)
Median	30.4	30.2	30.3
Minimum to maximum	14.2, 54.7	15.8, 64.4	14.2, 64.4

Source: adapted from sNDA 205437-S11, CSR: CC-10004-PSOR-022, Section 9.3, Table 9-4 (Page 57).
Abbreviations: SD=standard deviation, BMI= Body Mass Index

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of apremilast for treatment of mild to moderate psoriasis. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time the informed consent was signed. Treatment Emergent Adverse Events (TEAEs) were AEs that occurred after the first administration of the study drug (TEAE start date no later than 28 days after the last dose of study drug). AEs were documented at each study visit as observed by the investigators or reported by subjects. If the treatment-emergent status of an AE was unclear due to a missing or incomplete start date, it was considered treatment-emergent unless shown otherwise by data.

The investigators categorized AEs by system-organ-class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for phase 3 trial CC-10004-PSOR-022, and there was good correlation between the verbatim and preferred terms used. No new safety signals emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs. Subjects were followed by the Investigators to resolution of the AE (return to normal/baseline or stabilization) for up to 4 weeks after last dose of study drug [Observational follow-up visit].

Serious Adverse Events (SAEs) were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators as mild, moderate, or severe.
Causality of AEs was assessed by investigators as "Suspected" or " Not Suspected"(related or unrelated) based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology.

Adverse Events of Special Interest (AESIs) were not prespecified in the Protocol. However, the applicant reported the frequency of TEAEs associated with the (identified or potential) key risks of apremilast, including Depression, Suicidal Ideation and Behaviors (SIB), Serious Infections, Hypersensitivity, and Weight decrease.

The applicant's assessment of adverse events conducted for the study CC-10004-PSOR-022 appears reasonable and appropriate. The applicant reported accurate definitions of treatment emergent adverse events, serious adverse events, and severity of adverse events.

Routine Clinical Tests

The applicant performed clinical laboratory evaluations (chemistry, hematology, and urinalysis) at screening, baseline, Week 8, Week 16, Week 24, and Week 32 visits. Serum pregnancy tests were performed at screening and Week 32/EOT visits, and urine pregnancy tests at baseline visit and at Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 visits.

An abnormal laboratory value was considered to be an AE if it required treatment, modification or interruption of dose, judged to be of significant clinical importance (for example, a new disease process/organ toxicity, or an exacerbation of an existing condition), or led to subject discontinuation from the study.

8.2.4. Safety Results

Deaths

No deaths were reported in Trial CC-10004-PSOR-022.

Serious Adverse Events

During the PC period, the following SAEs were reported for 5 subjects [1 subject (0.3%) in apremilast group, and 4 (1.4%) subjects in placebo group], with no SAE reported in more than 1 subject:

i. **Myocardial ischemia** (SAE, AELD) and **Angina pectoris** (SAE)
Subject ID: (b) (6) (apremilast group)
A 67 year old white male with history of hypothyroidism, hypersensitivity (environmental allergies), hypertension, and osteoarthritis, current alcohol (not tobacco) use.

On Day 36, subject was reported to experience a SAE of ischemic heart disease (myocardial ischemia), was evaluated at the emergency department, hospitalized, and underwent cardiac catherization with insertion of 2 coronary stents (study drug discontinued). On Day 41, subject had a second cardiac catherization with insertion of 2 additional stents. On Day 42, the SAE was considered resolved and subject was discharged from hospital.

On Day 54, subject was reported to experience a SAE of cardiac chest pain (angina pectoris) and was reevaluated at the emergency department, underwent a repeat cardiac catheterization (no coronary occlusion was reported). On Day 56, subject was discharged from hospital with no further episodes of pain reported, and the SAE of angina pectoris was considered resolved.

On Day 100, subject discontinued the study due to ischemic heart disease.
The investigator and the sponsor considered these SAEs to be not related to study Medication.

ii. Congestive heart failure/Pneumonia (SAEs)
Subject ID: (b) (6) (Placebo group)
A 73-year-old white male with history of type 2 diabetes mellitus, hypertension, gastroesophageal reflux disease, cardiac pacemaker insertion/cardiac failure, hypokalemia, hypercholesterolemia, alcohol use and former tobacco use.
Subject was treated with placebo for 125 days and apremilast for 100 days.

On Day 105 (Day –20 on active treatment), subject was reported to experience a mild TEAE of worsening of congestive heart failure (cardiac failure congestive).

On Day 106, subject was hospitalized for a moderately severe SAE of worsening of congestive heart failure (cardiac failure congestive) and study medication was interrupted .

On Day 110, subject was discharged from the hospital and readmitted for the same indication and discharged from hospital on Day 114.

On Day 112, while hospitalized, the subject experienced a moderate severity SAE of pneumonia.

On Day 114, The SAE of worsening of congestive heart failure was considered to be resolving and the SAE of pneumonia was ongoing.

The investigator and sponsor considered the SAE of cardiac failure congestive as not related to study medication; and the SAE of pneumonia as suspected to be related to study medication.

iii. Migraine without aura (SAE, AELD)
Subject ID: (b) (6) (Placebo group)
A 39-year-old white female with history of dysmenorrhea, cholecystitis, cholecystectomy, intestinal diverticulum, left ventricular hypertrophy, Arnold-Chiari malformation, headache, gastroesophageal reflux disease, ulcerative colitis, morbid obesity, a history of alcohol use (no history of tobacco use).

On Day 28, study medication was discontinued.

On Day 54, subject experienced a severe TEAE of worsening migraine headache (migraine) and received no treatment.

On Day 56, subject experienced a severe SAE of migraine without aura and without status migrainosus, not intractable (migraine without aura) and left-sided weakness and was hospitalized. A head CT-angiography showed multifocal areas of luminal irregularity and stenosis of major intracranial arteries (suspected occlusion of the anterior division at the right middle cerebral artery (MCA) bifurcation) concerning for underlying vasculitis, but no acute intracranial process. Subject received tissue plasminogen activator (TPA: alteplase) for a suspected stroke in the setting of previous migraines, suggestive of reversible cerebral vasoconstriction syndrome. A brain magnetic resonance imaging was negative for acute stroke or acute hemorrhage. A lumbar puncture was negative.

On Day 59, subject was discharged from hospital with the SAE considered to be not resolved/ongoing, and subject remained active in the study.
On Day 60, the SAE of migraine without aura improved to an ongoing/unresolved AE of moderate severity.

On Day 99, subject was lost to follow-up.
The investigator and sponsor considered the SAE as not suspected to be related to the study medication.

iv. Pneumococcal pneumonia (SAE, AELD)
Subject ID: (b) (6) (Placebo group)
A 61-year-old black female with medical history of hypertension, menopause,

alcohol use and current tobacco use.

On Day 69, subject was reported to experience a SAE of pneumococcal pneumonia (right perihilar lower lobe infiltrate on chest X-ray), was hospitalized, and treated with antibiotics and corticosteroids (study drug was discontinued) and discharged on Day 72.

On Day 74, the SAE of pneumococcal pneumonia improved to a nonserious AE of moderate severity and considered resolved on Day 90.

On Day 118, the subject discontinued from the study due to other reasons and did not experience any other AEs during this period of the study. The investigator and sponsor considered this SAE to be not related to study medication.

v. Ectopic pregnancy (SAE, AELD)
Subject ID: (b) (6) (Placebo group)
A 21-year-old white female with history of food allergy (bananas), alcohol use and no tobacco use.

On Day 61, subject was reported to experience a severe SAE of ectopic pregnancy, was treated with salpingectomy with the SAE considered resolved.

On Day 57, study medication was withdrawn permanently and subject was discontinued from study.

The investigator considered this SAE to be not related to study medication.
The sponsor considered causality assessment for the SAE as not applicable because the subject was in the placebo group.

By baseline sPGA subgroups (mild=2, moderate=3), SAEs were reported for:
Placebo group: 0 subjects in the mild and 4 (2%) subjects in the moderate subgroup.
Apremilast group: 0 subjects in the mild and 1 (0.5%) subjects in the moderate subgroup.

During the apremilast-exposure period (weeks 0-32 for any apremilast-treated subject), the following SAEs were reported in 12/544 (2.2%) subjects (including 1 subject during PC period): Pneumonia (3), cellulitis (1), prostate cancer (1), Myocardial ischaemia/Angina pectoris (1), Cardiac failure (1), Myocardial infarction (1), Abdominal pain (1), Intestinal perforation (1), Oral disorder (1), Pancreatitis acute (1), Osteoarthritis (1), and Post procedural complication (1).

During Trial PSOR-022, no SAEs of diarrhea, nausea, vomiting, depression, or suicidal ideation was reported in any treatment group.

Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo-controlled period, TEAEs leading to drug interruption were reported in 5 (1.7%) subjects in the placebo group, compared to 16 (5.4%) subjects in the apremilast group. The following TEAEs leading to drug discontinuations (AELDs) were reported in 7 (2.4%) subjects in the placebo group, compared to 13 (4.4%) subjects in the apremilast group:

- Placebo group: AELDs included diarrhea (2), nausea (2), abdominal pain (1), face edema (1), headache (1), cough (1), pharyngeal edema (1), pruritus (1), psoriasis (1), and ectopic pregnancy (1).
- Apremilast group: AELDs included diarrhea (4), nausea (2), abdominal pain (1), Crohn's disease (1), gastritis (1), vomiting (1), fatigue (2), Depression (1), Suicidal ideation (1), Gastroenteritis (1), headache (1), Myocardial ischaemia (1), Myalgia (1), and Eczema (1).

Most frequent AELDs were reported in the SOC of Gastrointestinal disorders for 7 (2.3%) subjects in the apremilast group, compared to 3 (1%) subjects in the placebo group . Diarrhea was the most frequently reported AELD for 4 (1.3%) subjects in the apremilast group, compared to 2 (0.7%) subjects in placebo group.

By baseline sPGA subgroups (mild = 2, moderate = 3), AELDs were reported for:
Placebo group: 3 (3.3%) subjects in the mild and 4 (2%) subjects in the moderate subgroup.
Apremilast group: 4 (4.4%) in the mild and 9 (4.3%) subjects in the moderate subgroup.

Significant Adverse Events

No Adverse Events of Special Interest (AESI) were prespecified for Trial PSOR-022.

Severe TEAEs
During the placebo-controlled period, the following severe TEAEs were reported in 8 (2.7%) subjects (depressed mood (1), diarrhea (1) , gastritis (1) , headache (1), menorrhagia (1) , migraine (1) , myocardial ischemia (1) , nerve compression (1), and pruritus (1)) in the apremilast group and 2 (0.7%) subjects (ectopic pregnancy (1), migraine without aura (1)) in the placebo group.

Treatment Emergent Adverse Events and Adverse Reactions

During the placebo-controlled period, TEAEs were reported at a higher frequency in subjects in the apremilast group (65.4%) compared to the placebo group (47%). Drug-related TEAEs (Adverse Reactions: ARs) were also reported at a higher frequency in subjects in the apremilast group (36.9%) compared to the placebo group (12.2%). In general, the proportion of subjects with SAEs, severe TEAEs, and TEAEs leading to drug interruption or drug withdrawal were similar between the apremilast and the placebo groups.

TEAEs By baseline sPGA subgroups (mild = 2, moderate = 3)

In general, TEAEs by baseline sPGA subgroups were more frequently reported for subjects treated with apremilast, compared to subjects treated with placebo (consistent with the overall treatment group). However; severe TEAEs, SAEs, and AELDs by baseline sPGA subgroups were generally reported with similar frequencies for subjects treated with apremilast, compared to subjects treated with placebo, as summarized in the following table:

Table 17: Summary of Subject Incidence of Adverse Events by Baseline sPGA Score in the Placebo-controlled Period (Weeks 0 to 16) (Safety Analysis Set)

Trial PSOR-022	**Placebo group**		**Apremilast group**		**Placebo total group**	**Apremilast total group**
Number of subjects in Subgroup	**sPGA= 2 (mild)** (N= 91), n(%)	**sPGA= 3 (moderate)** (N= 205), n(%)	**sPGA= 2 (mild)** (N= 91), n(%)	**sPGA= 3 (moderate)** (N= 207), n(%)	**sPGA= 2, 3** (N= 296), n(%)	**sPGA= 2, 3** (N= 298), n(%)
Any TEAE	40 (44.0%)	99 (48.3%)	60 (65.9%)	135 (65.2%)	139 (47.0%)	195 (65.4%)
Severe TEAE	0	2 (1.0%)	3 (3.3%)	5 (2.4%)	2 (0.7%)	8 (2.7%)
SAE	0	4 (2.0%)	0	1 (0.5%)	4 (1.4%)	1 (0.3%)
AELD	3 (3.3%)	4 (2.0%)	4 (4.4%)	9 (4.3%)	7 (2.4%)	12 (4.0%)

Source: Clinical Overview (M 2.5), Modified from Tables 11, 12. Consistent with Clinical Reviewer's JMP analysis.

TEAEs by System Organ Class (SOC) and Preferred Term (PT):

TEAEs (reported in ≥ 5% of subjects in any treatment group) for the apremilast group, compared to the placebo group, included diarrhea (16.4% vs. 5.1%), headache (13.1% vs. 5.1%), nausea (12.8% vs. 4.4%), nasopharyngitis (7.4% vs. 2.7%), and upper respiratory tract infection (5.7% vs. 5.1%) respectively, as summarized in the following table:

Table 18: TEAEs by baseline sPGA category (mild or moderate) and by SOC/PT- Reported in ≥ 2% of Subjects in the placebo or apremilast total groups in the Placebo-controlled Period (Weeks 0 to 16) (Safety Analysis Set)

Trial PSOR-022	**Placebo group**		**Apremilast group**		**Placebo total group**	**Apremilast total group**
SOC / PT	**sPGA= 2 (mild)** (N= 91) , n(%)	**sPGA= 3 (moderate)** (N= 205), n(%)	**sPGA= 2 (mild)** (N= 91), n(%)	**sPGA= 3 (moderate)** (N= 207), n(%)	**sPGA= 2, 3** (N= 296), n(%)	**sPGA= 2, 3** (N= 298), n(%)
Gastrointestinal disorders	9 (9.9)	31 (15.1)	34 (37.4)	66 (31.9)	40 (13.5)	100 (33.6)
Diarrhoea	3 (3.3)	12 (5.9)	15 (16.5)	34 (16.4)	15 (5.1)	49 (16.4)
Nausea	5 (5.5)	8 (3.9)	16 (17.6)	22 (10.6)	13 (4.4)	38 (12.8)
Vomiting	0	2 (1.0)	3 (3.3)	8 (3.9)	2 (0.7)	11 (3.7)
Gastroesophageal reflux disease	0	1 (0.5)	3 (3.3)	4 (1.9)	1 (0.3)	7 (2.3)

Infections and infestations	18 (19.8)	33 (16.1)	24 (26.4)	59 (28.5)	51 (17.2)	83 (27.9)
Nasopharyngitis	1 (1.1)	7 (3.4)	5 (5.5)	17 (8.2)	8 (2.7)	22 (7.4)
Upper respiratory tract infection	9 (9.9)	6 (2.9)	8 (8.8)	9 (4.3)	15 (5.1)	17 (5.7)
Nervous system disorders	5 (5.5)	15 (7.3)	16 (17.6)	29 (14.0)	20 (6.8)	45 (15.1)
Headache	5 (5.5)	10 (4.9)	14 (15.4)	25 (12.1)	15 (5.1)	39 (13.1)
Skin and subcutaneous tissue disorders	4 (4.4)	13 (6.3)	5 (5.5)	11 (5.3)	17 (5.7)	16 (5.4)
Psoriasis	2 (2.2)	5 (2.4)	0	1 (0.5)	7 (2.4)	1 (0.3)
General disorders and administration site conditions	2 (2.2)	5 (2.4)	3 (3.3)	11 (5.3)	7 (2.4)	14 (4.7)
Fatigue	2 (2.2)	1 (0.5)	2 (2.2)	8 (3.9)	3 (1.0)	10 (3.4)
Vascular disorders	1 (1.1)	2 (1.0)	2 (2.2)	5 (2.4)	3 (1.0)	7 (2.3)
Hypertension	0	2 (1.0)	2 (2.2)	4 (1.9)	2 (0.7)	6 (2.0)

System organ classes and preferred terms were coded using MedDRA version 23.0.
Source: PSOR-022 Clinical Study Report (M 5.3.5.1), Modified from Tables 12-6, 12-7, and Table 14.3.1.2.1. Consistent with Clinical Reviewer's JMP analysis.

Laboratory Findings

During the placebo-controlled period, evaluation of systemic safety included assessments of clinical laboratory data, which included hematology, serum chemistry, and urinalysis. Abnormal laboratory measurements were mild, transient, and not reported as SAE or AELD. No clinically significant mean changes from baseline, or clinically significant shifts in laboratory values were reported. No abnormal liver enzyme measurements met Hy's law criteria.

During the apremilast-exposure period, assessments of the results of clinical laboratory measurements were consistent with the results from the PC period.

Vital Signs

During the PC period, no clinically significant abnormalities in vital signs were reported in any treatment group. No significant changes in body temperature were observed in any treatment group. A mean decrease in systolic blood pressure of -0.3 mm Hg, a mean decrease in diastolic blood pressure of -0.2 mm Hg, and a mean increase in pulse rate of 2.3 beats per minute were reported for subjects in the apremilast group.

During the apremilast-exposure period, vital signs assessment results were consistent with the results from the PC period.

Electrocardiograms (ECGs)

Electrocardiograms were not included in the safety assessments for Trial PSOR-022.

QT

Not applicable.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Weight Decrease
During the PC period, the mean weight change from baseline to Week 16 was -1.53 kg in the apremilast group, compared to +0.15 kg in the placebo group, with a weight decrease between 0 to -5 kg reported in 168 (57%) subjects in the apremilast group, compared to 124 subjects (42%) in the placebo group.

During the apremilast-exposure period, the mean weight decrease from baseline to Week 32 was -1.61 kg, with a weight decrease between 0 to -5 kg reported in 285 (53%) of subjects; consistent with similar results during the PC period.

Reviewer's Comment:
During Trial PSOR-022, the incidence of Weight Decrease and Gastrointestinal-related Adverse Events did not appear to be related. Of the 4 subjects reported with the TEAE of "Weight Decrease", none was reported with an AE of Diarrhea; and 3 were reported with TEAE of "Nausea" of mild severity (not resulting in dose change) during the first week (dose titration), whereas the TEAE of "Weight Decrease " was reported at later timepoints in the Trial (Weeks 2, 4, and 12 for one subject each, respectively).

During the review of sNDA 205437/S-008 efficacy supplement (Study CC-10004-SPSO-001 for the treatment of subjects with moderate to severe psoriasis and moderate to severe psoriasis of the scalp), an Information Request (IR) was sent to the applicant on 8/2/20219, including the following FDA comment for the applicant to clarify whether any potential influence of the GI-related AEs on the degree of weight decrease were identified. The applicant's response was found to be a plausible explanation by the review team (excerpt enclosed below):

"FDA Comment 4:
At the end of the placebo-controlled phase (Week 16) of trial SPSO-001, 9% of apremilast-treated subjects compared to 6% of subjects in the placebo group had weight decrease of between 5%-10% from baseline (Table 63 of CSR). Clarify whether these subjects reported diarrhea or other GI-related TEAEs which could potentially influence the degree of their weight decrease.
Applicant's Response:
"In the Phase 3 psoriasis clinical development program, there was no clear evidence of an association between weight loss and selected GI AEs (e.g., diarrhea, nausea, and vomiting)

based on the findings that the weight loss was observed after 16 weeks of treatment, while the selected GI AEs occurred early and tended to decrease over time. A review of the information from trial SPSO-001 did not change this conclusion… "

Depression and Suicidal Ideation and Behavior (SIB)
During the PC period, no SAEs of depression or SIB were reported. For subjects in the apremilast group compared to the placebo group, TEAEs were reported for depression (2 vs. 1), depressed mood (4 vs. 0), and suicidal ideation (1 vs. 1).

During the apremilast-exposure period, the frequency of reported TEAEs of depression (3), depressed mood (4), and suicidal ideation (1) were consistent with similar results during the PC period.

8.2.6. Safety Analyses by Demographic Subgroups

In view of the small sample size, the utility of analyzing TEAEs by demographic subgroups is limited. The review of safety data revealed no substantial differences in the risk of adverse reactions in demographic subgroups. However, because the trial was not powered for these analyses, the data must be interpreted with caution.

In general, the frequency of reported TEAEs during the PC period by age, sex, race, and baseline sPGA score were generally balanced between groups.

Baseline sPGA (2 or 3)
Refer to Sec. 8.2.4 of this review for a summary of TEAEs by subjects' baseline sPGA.

Race
Analysis of TEAEs (observed in ≥ 5% of subjects in any treatment group during the PC period) by race indicated that for apremilast-treated subjects, non-white subjects reported more frequent nausea (18.2% vs. 11.8%) and vomiting (6.8% vs. 3.1%) than white subjects; diarrhea (16.9 vs. 13.6%), headache (14.2% vs. 6.8%), and upper respiratory infections (6.7% vs. 0) were more frequent in white subjects as summarized in the following table:

Table 19: Analysis by Race of TEAEs reported in at Least 5% of Subjects in Any Treatment Group During the Placebo-controlled Period (Weeks 0 to 16) (Safety Population)

Preferred Term (PT)	Number (%) of Subjects in each subgroup			
	Placebo (N = 296)		Apremilast (N =298)	
	White (n =256)	Non-white (n = 40)	White (n = 254)	Non-white (n = 44)
Subjects with Any TEAE	126 (49.2)	13 (32.5)	170 (66.9)	25 (56.8)
Diarrhoea	13 (5.1)	2 (5.0)	43 (16.9)	6 (13.6)
Nausea	12 (4.7)	1 (2.5)	30 (11.8)	8 (18.2)
Headache	14 (5.5)	1 (2.5)	36 (14.2)	3 (6.8)
Vomiting	2 (0.8)	0	8 (3.1)	3 (6.8)
Nasopharyngitis	7 (2.7)	1 (2.5)	21 (8.3)	1 (2.3)

Preferred Term (PT)	Number (%) of Subjects in each subgroup			
	Placebo (N = 296)		Apremilast (N =298)	
	White (n =256)	Non-white (n = 40)	White (n = 254)	Non-white (n = 44)
Upper respiratory tract infection	13 (5.1)	2 (5.0)	17 (6.7)	0

Source: CSR CC-10004-PSOR-022, Adapted from Table 14.3.1.5.5 (consistent with Clinical Reviewer's analysis by JMP Clinical 7.0) . MedDRA dictionary (v. 23.0).

Age

Analysis of TEAEs (observed in ≥ 5% of subjects in any treatment group during the PC period) by age category indicated that for apremilast-treated subjects, subjects ≥ 65 years of age reported more frequent diarrhea (24.5% vs. 14.9%), headache (18.4% vs. 12.0%), and nasopharyngitis (12.2% vs. 6.4%) than subjects < 65 years of age as summarized in the following table:

Table 20: Analysis by Age of TEAEs reported in at Least 5% of Subjects in Any Treatment Group During the Placebo-controlled Period (Weeks 0 to 16) (Safety Population)

Preferred Term (PT)	Number (%) of Subjects in each subgroup			
	Placebo (N = 296)		Apremilast (N =298)	
	Age< 65 years (n =258)	Age ≥65 years (n = 38)	Age< 65 years (n = 249)	Age ≥65 years (n = 49)
Subjects with Any TEAE	122 (47.3)	17 (44.7)	163 (65.5)	32 (65.3)
Diarrhoea	12 (4.7)	3 (7.9)	37 (14.9)	12 (24.5)
Nausea	12 (4.7)	1 (2.6)	34 (13.7)	4 (8.2)
Headache	14 (4.7)	3 (7.9)	30 (12.0)	9 (18.4)
Vomiting	2 (0.8)	0	10 (4.0)	1 (2.0)
Nasopharyngitis	8 (3.1)	0	16 (6.4)	6 (12.2)
Upper respiratory tract infection	15 (5.8)	0	14 (5.6)	3 (6.1)
Urinary tract infection	4 (1.6)	0	2 (0.8)	3 (6.1)
Arthralgia	3 (1.2)	2 (5.3)	5 (2.0)	0
Fatigue	3 (1.2)	0	7 (2.8)	3 (6.1)

Source: CSR CC-10004-PSOR-022, Adapted from Table 14.3.1.5.1 (consistent with Clinical Reviewer's analysis by JMP Clinical 7.0) . MedDRA dictionary (v. 23.0).

Sex

Analysis of TEAEs (observed in ≥ 5% of subjects in any treatment group during the PC period) by sex category indicated that for apremilast-treated subjects, female subjects reported more frequent diarrhea (19.4% vs. 14.4%), nausea (16.1% vs. 10.3%), headache (16.9% vs. 10.3%), vomiting (6.5% vs. 1.7%), and combined nasopharyngitis/upper respiratory infection (18.6% vs. 9.2%) than male subjects as summarized in the following table:

Table 21: Analysis by Sex of TEAEs reported in at Least 5% of Subjects in Any Treatment Group During the Placebo-controlled Period (Weeks 0 to 16) (Safety Population)

Preferred Term (PT)	Number (%) of Subjects in each subgroup			
	Placebo (N = 296)		Apremilast (N =298)	
	Male (n =151)	Female (n = 145)	Male (n = 174)	Female (n = 124)
Subjects with Any TEAE	67 (44.4)	72 (49.7)	103 (59.2)	92 (74.2)
Diarrhoea	8 (5.3)	7 (4.8)	25 (14.4)	24 (19.4)
Nausea	7 (4.6)	6 (4.1)	18 (10.3)	20 (16.1)

Preferred Term (PT)	Number (%) of Subjects in each subgroup			
	Placebo (N = 296)		Apremilast (N =298)	
	Male (n =151)	Female (n = 145)	Male (n = 174)	Female (n = 124)
Headache	8 (5.3)	7 (4.8)	18 (10.3)	21 (16.9)
Vomiting	2 (1.3)	0	3 (1.7)	8 (6.5)
Nasopharyngitis	2 (1.3)	6 (4.1)	8 (4.6)	14 (11.3)
Upper respiratory tract infection	11 (7.3)	4 (2.8)	8 (4.6)	9 (7.3)

Source: CSR CC-10004-PSOR-022, Adapted from Table 14.3.1.5.3 (consistent with Clinical Reviewer's analysis by JMP Clinical 7.0) . MedDRA dictionary (v. 23.0).

8.2.7. Specific Safety Studies/Clinical Trials

Study CC-100004-PSOR-23

In addition to the results of Trial PSOR-022 submitted in support of this prior approval supplement, the applicant also submitted the results of the Clinical Study PSOR-23 (conducted in Japan and enrolled a similar population to Trial PSOR-022) for the Agency awareness, entitled: "A Phase 3b, Open-Label, Single-Arm Study of the Efficacy and Safety of Apremilast in Subjects with Plaque Psoriasis that is not Adequately Controlled by Topical Therapy."

Study PSOR-023 enrolled 152 subjects between 20 to 82 years of age with baseline sPGA scores of mild (2) or moderate (3) with no prior treatment with biologics and inadequate response to topical treatment. Following a 4-week screening period, subjects received apremilast 30 mg tablets orally twice daily and continued their baseline topical treatment for 16 weeks. During Weeks 16-32, subjects continued to receive treatment with apremilast in combination with their topical therapy with the option to reduce their topical treatment at their discretion under the direction of their physician, followed by a 4-week observational follow-up period.

No formal statistical testing was conducted for the primary efficacy endpoint (result: 43.7% of subjects achieved sPGA score = 0, 1 at Week 16). Safety assessments included TEAEs and changes from baseline in vital signs and laboratory measurements. TEAEs were reported for 75.7% of subjects, with the most frequent (≥5%) TEAEs for diarrhea (19.1%), nausea (19.1%), nasopharyngitis (18.4%), soft feces (13.2%), and headache (13.2%).

In addition, no deaths, (non-gastrointestinal) SAEs (4), severe TEAEs (4), and (frequent gastrointestinal) AELDs (7) were reported in Study PSOR-023.

Reviewer's comment:

The following conclusions by the applicant about the results of Study PSOR-023 appear plausible: "apremilast in combination with topical therapy is an effective and safe treatment for subjects with mild to moderate plaque psoriasis not adequately controlled with topical therapy alone...the safety profile of apremilast was consistent with the known safety profile of apremilast, and no new safety findings were observed."

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no statistical issues affecting overall conclusions. The treatment effects were generally consistent and there were no substantial differences in efficacy among subgroups. For handling of missing data, the results were similar across the two prespecified methods for handling missing data (i.e., MI [primary] and NRI [sensitivity]), see Table 9 in Section 8.1.4.

8.3.2. Conclusions and Recommendations

Trial PSOR-022 achieved statistical significance for both the primary and secondary efficacy endpoints, and the secondary efficacy endpoints were supportive of the primary efficacy endpoint. In addition, the result for the primary efficacy endpoint in this trial were similar to the results from the previous Phase 3 trials used to approve apremilast tablets for the treatment of moderate-to-severe plaque psoriasis. The safety data in trial PSOR-022 identified no new safety signals and was consistent with the known safety profile of apremilast.

In the opinion of the Clinical and Statistical review teams, there is sufficient evidence to conclude that the benefits of apremilast outweighs its potential risks for the treatment of mild to moderate plaque psoriasis in adult subjects. We recommend inclusion of the results of the primary and secondary efficacy endpoints (Whole Body Itch Response and ScPGA Response at Week 16) in Section 14, and the safety data for Adverse Reactions in Section 6 of the OTEZLA label.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee was deemed necessary for this supplemental NDA.

10 Pediatrics

The applicant is pursuing a new indication, [redacted] (b) (4) [redacted] (b) (4). An Agreed iPSP Agreement letter was issued to the applicant on 2/8/2019, including the following requests:

- A partial waiver of the requirement to perform pediatric studies in Mild-to-Moderate Plaque Psoriasis patients from birth to less than 6 years of age (necessary studies are impossible or highly impracticable)
- A deferral to perform pediatric studies in mild to moderate Plaque Psoriasis patients between 6 to 17 years of age (inclusive) until data from mild to moderate Plaque Psoriasis in adults (Study PSOR-022) and [redacted] (b) (4) [redacted].

The results for Study PSOR-022 was submitted and reviewed under this sNDA submission. Following the submission of the final clinical study report (CSR) for Study [redacted] (b) (4), the applicant proposes the following:

- [redacted] (b) (4)
- [redacted]

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The applicant submitted proposed Prescribing Information (PI) with Efficacy Supplement-11 on 2/19/2021.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Madhuri R. Patel, PharmD, found the proposed PI, container labels, and carton labeling acceptable from a medication error perspective in her review of 9/8/2021.

The Office of Prescription Drug Promotion (OPDP) regulatory review officer, Laurie Buonaccorsi, reviewed the proposed PI and carton and container labeling, and had no comments in her review of 10/15/2021.

Review of the safety results from Study PSOR-022, submitted under NDA 205437/S-011, did not identify any new safety concerns that would warrant any safety-related changes to the current OTEZLA label.

The following 2 changes to the OTEZLA label were proposed by the FDA Office of Surveillance and Epidemiology (OSE) based on their consult reviews of the post-marketing safety data for OTEZLA, and were agreed to by the DRTM and DDD:

i. OSE RCM #: 2019-2182 (4/9/2020)
Subject: Suicidal ideation and behavior with apremilast use
Based on this review, OSE recommended that OND consider revising the title of the WARNING in the apremilast labeling from "Depression" to (b) (4) (b) (4) to more accurately reflect the information described in the WARNING.

ii. Pharmacovigilance Review SS ID #: 1004130 (3/31/2021)
Subject: Angioedema and anaphylaxis
Based on this review, DPV-I recommends the following: "Add angioedema and anaphylaxis to the ADVERSE REACTIONS *Postmarketing Experience* section of the apremilast product label". Suggested text for labeling is represented below:

ADVERSE REACTIONS
(b) (4)

The final agreed-upon label will be appended to this review.

12 Risk Evaluation and Mitigation Strategies (REMS)

No additional safety concerns were identified, and no REMS were deemed necessary by the review team for this supplemental NDA.

13 Postmarketing Requirements and Commitment

A PMR was agreed to in the Agreed iPSP Agreement letter for this supplemental NDA. Refer to Sec. 10 of this review for additional detail.

14 Appendices

14.1. References

References to the literature articles cited were provided as footnotes.

14.2. Financial Disclosure

The Applicant submitted financial certifications and financial disclosure information (FDA Forms 3454, 3455) in Section 1.3.4 of this sNDA submission.

Covered Clinical Study (Name and/or Number): CC-10004-PSOR-022

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 67		
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): 4		
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: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

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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/

DAWN WILLIAMS
12/16/2021 01:27:58 PM

HAMID N TABATABAI
12/16/2021 01:41:38 PM

DAVID L KETTL
12/16/2021 02:10:23 PM

MATTHEW W GUERRA
12/16/2021 02:22:52 PM

MOHAMED A ALOSH
12/16/2021 05:15:57 PM

TATIANA OUSSOVA
12/16/2021 07:49:52 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2054374Orig1s011

OTHER REVIEW(S)

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

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

Memorandum

Date: October 15, 2021

To: Hamid Tabatabai, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)

Dawn Williams, Regulatory Project Manager, DDD

David Kettl, MD, Clinical Team Leader DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

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

NDA: 205437/S-011

In response to DDD's consult request dated April 7, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the supplemental NDA submission for OTEZLA® (apremilast) tablets, for oral use (Otezla). This supplement provides for changes in the indication (b) (4)

PI: OPDP's comments on the proposed labeling are based on the draft PI provided below received by electronic mail from DDD on October 8, 2021. We have no comments at this time.

Carton and Container: OPDP's comments on the proposed labeling are based on the carton and container labeling provided below submitted to the electronic document room on February 19, 2021. We have no comments at this time.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 3, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 205437/S-011
Product Name, Dosage Form, and Strength:	Otezla (apremilast) tablets, 10 mg, 20 mg, and 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amgen Inc.
FDA Received Date:	February 19, 2021
OSE RCM #:	2021-338
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Amgen Inc. submitted a supplement for Otezla (apremilast) tablets to propose a new indication (b) (4)

Subsequently, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Otezla prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The revised PI provides revisions for the proposed indications of (b) (4) (b) (4). The revised container labels and carton labeling provides for changes to the dosage statement for consistency with the PI (from "The recommended dose is a 30 mg tablet taken by mouth twice daily" to "See full Prescribing information for dosing and administration."). Consistent with recommendations made during the review of NDA 205437/S-009[a], the location of the "Rx Only" statement was revised in the 28-count blister bridge pack and on 60-Count bottle, as well as a reduction to its prominence on the 60-count bottle. The size of the text of the net quantity statement was also decreased on

[a] Mcmillan, T. Label and Labeling Review for Otezla (NDA 205437/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 19. RCM No.: 2020-1269.

the PDP of 60-count bottle label. We find this change acceptable due to its prominence commensurate with the text size of the strength.

Additionally, the currently approved dosage form and strength support the proposed new indication. We find the PI, container labels, and carton labeling acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI), container labels and carton labeling are acceptable from a medication error perspective. We have no recommendations at this time

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Otezla received on February 19, 2021 from Amgen Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Otezla</th></tr>
<tr><td>Initial Approval Date</td><td>March 21, 2014</td></tr>
<tr><td>Active Ingredient</td><td>apremilast</td></tr>
<tr><td>Indication</td><td>• treatment of adult patients with active psoriatic arthritis
• (b) (4) [redacted]
• treatment of adult patients with oral ulcers associated with Behçet’s Disease</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>10 mg, 20 mg, and 30 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Initial Dose Titration
Table 1: Dosage Titration Schedule
<table>
<tr><th>Day 1</th><th colspan="2">Day 2</th><th colspan="2">Day 3</th><th colspan="2">Day 4</th><th colspan="2">Day 5</th><th colspan="2">Day 6 & thereafter</th></tr>
<tr><th>AM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th></tr>
<tr><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>30 mg</td><td>30 mg</td><td>30 mg</td></tr>
</table>
Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6.</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Package configuration</th><th>Tablet strength</th><th>NDC number</th></tr>
<tr><td>Bottles of 60</td><td>30 mg</td><td>55513-137-60
59572-631-06</td></tr>
<tr><td>Bottles of 500</td><td>30 mg</td><td>55513-137-50</td></tr>
<tr><td>Two-week starter pack</td><td>13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (14) 30-mg tablets</td><td>59572-630-27</td></tr>
<tr><td>28-count carton</td><td>Two 30-mg blister cards containing (14) 30-mg tablets</td><td>55513-137-28
59572-631-28</td></tr>
<tr><td>28-day starter pack</td><td>13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (42) 30-mg tablets</td><td>55513-369-55
59572-632-55</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store tablets below 30°C (86°F).</td></tr>
<tr><td>Container Closure</td><td>Bottles, carton, blister pack</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 2, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'otezla'. Our search identified 9 previous reviews[b,c,d,e,f,g,h,i,j] and we considered our previous recommendations to see if they are applicable for this current review.

[b] Mcmillan, T. Label and Labeling Review Memo for Otezla (NDA 205437/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 14. RCM No.: 2020-1269-1.

[c] Mcmillan, T. Label and Labeling Review for Otezla (NDA 205437/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 19. RCM No.: 2020-1269.

[d] Patel, M. Label and Labeling Review for Otezla (NDA 205437/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 10. RCM No.: 2019-1427-2.

[e] Patel M. Labeling Review for Otezla (NDA 205437/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 18. RCM No.: 2019-14271-1.

[f] Patel M. Labeling Review for Otezla (NDA 205437/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 18. RCM No.: 2019-1427.

[g] Mena-Grillasca. Label and Labeling Review for Otezla (NDA 206088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 10. RCM No.: 2014-423

[h] McMillan, T. Label, Labeling and Packaging Memorandum for Otezla (NDA 205437). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAR 05. RCM No.: 2013-790-2.

[i] McMillan, T. Label, Labeling and Packaging Memorandum for Otezla (NDA 205437). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 DEC 18. RCM No.: 2013-790-1.

[j] McMillan, T. Label, Labeling and Packaging Review for Otezla (NDA 205437). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 12. RCM No.: 2013-790.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Otezla labels and labeling submitted by Amgen Inc..

- Container label received on February 19, 2021
- Carton labeling received on February 19, 2021
- Bridge pack Professional Sample Wallet received on February 19, 2021
- Bridge pack Professional Sample Carton Labeling received on February 19, 2021
- Prescribing Information (Image not shown) received on February 19, 2021, available from \\CDSESUB1\evsprod\nda205437\0275\m1\us\annotated-draft-uspi.pdf

G.2 Label and Labeling Images

Container Labels

(b) (4)

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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