CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	February 7, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	205437
Applicant Name:	Celgene Corporation
Date of Submission:	March 21, 2013
PDUFA Goal Date:	March 21, 2014
Proprietary Name:	Otezla (proposed by Celgene)
Established Name:	Apremilast
Dosage form:	Tablets
Strength:	10 mg, 20 mg, and 30 mg
Proposed Indications:	Treatment of adult patients with active psoriatic arthritis (PsA)
Action:	Approval

1. Introduction

Celgene Corporation submitted this NDA to support approval of apremilast (proposed trade name is Otezla) for treatment of adult patients (ages 18 years and older) for the treatment of active psoriatic arthritis (PsA) at a dose to be titrated from a starting dose of 10 mg to the recommended dose of 30 mg twice daily within a week. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Typically, a patient will be aware of having the skin manifestation of psoriasis before the associated arthritis occurs. PsA affects both the peripheral joints and the axial skeleton. The arthritis of PsA is inflammatory in nature, presenting with pain, swelling, and stiffness of the affected joints. Any peripheral joint may be affected in PsA. Early in the disease the arthritis tends to be oligoarticular, but may become polyarticular as more joints are accrued over time. The axial skeleton involvement in PsA includes inflammation in both the sacroiliac joint and the apophyseal joints of the spine. The distribution tends to be asymmetric, with only one sacroiliac joint involved and other being spared or with a different degree of involvement.

The classes of drugs used for treatment of PsA include: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). NSAIDs and corticosteroids are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-inflammatory and analgesic effects. Corticosteroids are versatile agents with potent anti-inflammatory effects, but their use is

limited by long-term toxicity. DMARDs are therapeutic agents that reduce signs and symptoms of PsA as well as slow disease progression or produce a disease-modifying effect by retarding radiographic progression of joint damage. Approved large molecule biologic DMARDs for use in PsA and some of their features are listed in Table 1. In addition to large molecule DMARDs, small molecules such as methotrexate, sulfasalazine, cyclosporine, and leflunomide are commonly used as DMARDs in patients with PsA. Methotrexate is the most commonly used DMARD because of its well-understood long-term effects. In the treatment of PsA, methotrexate is often the initial DMARD used and then combined with other DMARDs, commonly biologics, to enhance clinical effect.

Table 1. Large molecule biologic DMARDs approved for marketing in the United States for PsA

Product Name (Trade Name) [Sponsor] {year} [*]	**Presentation and *ROA*** [†]	**Description and *MOA*** [§]	**Claims for adult PsA** [#]
Etanercept (ENBREL) [Immunex/Amgen] {2002}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	Clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {2005}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2005}	Prefiled syringe 40 mg/0.8 mL Prefilled syringe 20 mg/0.4 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response
Cetrolizumab (CIMZIA) [UCB Inc] {2013}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL *SC injection*	Humanized Fab fragment *TNF-α inhibitor*	Clinical response Physical function response Radiographic response
Ustekinumab (STELARA) [Janssen] {2013}	Prefilled syringe 45 mg/0.5 mL Prefilled syringe 90 mg/0.5 mL Vial 90 mg/1mL Vial 45 mg/0.5 mL *SC injection*	Human IgG1 k mAb IL-12 and IL-23 antagonist	Clinical response Physical function response

[*]Year = Year of first approval for PsA
[†]ROA = Route of administration
[§]MOA= Mechanism of action
[#]Claims: Clinical response (or reducing signs and symptoms) assessed by components of disease activity such as ACR-20 in PsA over at least 3-6 month; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) and SF-36 Health Survey over at least 6 month period; Radiographic response (or inhibiting progression of structural damage) assessed radiographically by Total Sharp Score (TSS) and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over at least 12 months

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. It will represent the first small molecule drug approved for the treatment of adult patients with active PsA.

The Division and Celgene had typical milestone meetings on apremilast for the PsA program. The following timeline highlights some major discussion.

- End-of-Phase 2 meeting, March 25, 2010: The Division (the then Division of Anesthesia Analgesia and Rheumatology Products) and Celgene discussed the phase 3 program and agreed on ACR 20 as the primary endpoint and HAQ-DI as a secondary endpoint.

- Written correspondence, June 29, 2012: The Division (DPARP) agreed to modify the timing of efficacy endpoint from week 24 to week 16 in the phase 3 studies.
- Pre-NDA meeting, December 19, 2012: The general content of the NDA was discussed. The Division asked Celgene to provide justification for the clinical meaningfulness of the treatment difference seen for HAQ-DI.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, apremilast tablets, contains 10 mg, 20 mg, and 30 mg apremilast and standard compendial excipients. The drug product will be packaged as bottles containing 60 tablets of 30 mg strength for regular use, and as a blister pack containing 10 mg, 20 mg, and 30 mg strengths as a 2-week starter pack. The drug product (immediate-release tablets) is manufactured with a (b) (4) process. The drug substance is (b) (4) by Celgene Chemicals in Zofingen, Switzerland. The drug product is manufactured and packaged at Celgene International facility in Boudry, Switzerland, and (b) (4) facilities at (b) (4). The drug product can also be packaged at (b) (4) All manufacturing and testing facilities associated with this application have pending inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 18 months is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

Celgene conducted a complete and adequate toxicology program that included general toxicology studies in mice and monkeys, reproductive and developmental studies, genetic toxicology studies, and carcinogenicity studies. The toxicities seen in mice included arteritis in aortic root and heart, perivascular inflammation in the lung, hepatocyte hypertrophy, and hematological changes with an increase in white cell count, increase in neutrophil count, and decrease in lymphocyte count. The toxicities seen in monkeys included arteritis in the heart in a shorter duration study with higher doses, but not in a chronic 12-month study. Hematological changes similar to that seen in mouse were also seen in monkeys. NOAELs (no observed adverse effect levels) in chronic mouse and monkey studies provided coverage for the proposed human doses on a systemic exposure basis. Apremilast had no effects on fertility in male mice; however, apremilast prolonged the estrus cycle and increased interval to mating in female mice. Dystocia, and reduced viability, reduced litter size, and reduced fetal weight were also observed in mice. In both mice and monkeys, there were dose-related increases in abortion and embryofetal death early in the gestational period. Apremilast was not teratogenic in mice and monkey studies. The submitted data support a pregnancy category C classification for apremilast. Apremilast was negative in a complete battery of genotoxicity tests. Finally, 2-year carcinogenicity studies in mice and rats showed no increased incidence of tumors in apremilast-treated animals.

5. Clinical Pharmacology and Biopharmaceutics

Celgene submitted a complete and adequate clinical pharmacology program for apremilast. Apremilast is well absorbed after oral administration with the absolute oral bioavailability of about 73%, with peak plasma concentration occurring at approximately 2.5 hours, and with elimination half-life of about 5 to 7 hours. Apremilast is extensively metabolized through hepatic cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. The primary path of metabolism is by CYP3A4 with a minor contribution from CYP1A2 and CYP2A6. Apremilast does not inhibit or induce CYP enzymes in vitro, suggesting that it is unlikely to have drug-drug interactions with drugs metabolized by the CYP enzymes. Co-administration of the strong CYP3A4 inducer rifampin with apremilast resulted in a 72% reduction of apremilast plasma exposure (AUC). Labeling language reflects avoiding concomitant use of strong CYP450 inducers with apremilast. In vitro data suggest that apremilast is a substrate and a weak inhibitor of p-glycoprotein, however in vivo human data suggest that apremilast is unlikely to have drug-drug interactions with drugs that are inhibitors of p-glycoprotein. Patients with severe renal impairment are recommended a reduced 30 mg once daily dosing regimen based on exposure data. No dose adjustments are necessary for patients with hepatic impairment. There is no substantial impact of food, age, weight, and gender on apremilast exposure. A thorough QT study was conducted for apremilast and reviewed by the QT study interdisciplinary review team. No significant QTc prolongation effect of apremilast at the doses tested was detected.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the studies that form the basis of the review and regulatory decision for this application are shown in Table 2. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 2. Relevant clinical studies

Study ID and Year *	**Study Characteristics** **-Patient age** **-Past treatment** **-Concurrent background treatment** **-Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variable §**	**Region % ¶**
Dose Ranging Efficacy and Safety					
PSA-001 Study 1 2007-2009	-18 years and older - Biologic or a non-biologic DMARD - Methotrexate, sulfasalazine, leflunomide, corticosteroids, NSAIDs -12 weeks	Ap 20 mg BID Ap 40 mg QD Placebo	69 67 86	ACR20 at wk 12	NA (33%) Europe (67%)
Definitive Efficacy and Safety					
PSA-002 Study 2	-18 years and older -Biologic or a non-biologic DMARD	Ap 20 mg BID Ap 30 mg BID	168 168	ACR20 at wk 16 HAQ-DI at wk 16	NA (44%), Europe (24%),

Study ID and Year *	**Study Characteristics** **-Patient age** **-Past treatment** **-Concurrent background treatment** **-Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variable §**	**Region % ¶**
"Palace 1" 2010-2012	-Methotrexate, sulfasalazine, leflunomide, corticosteroids, NSAIDs background treatment -24 weeks	Placebo	168		ROW (32%)
PSA-003 Study 3 "Palace 2" 2010-2012	-18 years and older -Biologic or a non-biologic DMARD - Methotrexate, sulfasalazine, leflunomide, corticosteroids, NSAIDs -24 weeks	Ap 20 mg BID Ap 30 mg BID Placebo	163 162 159	ACR20 at wk 16 HAQ-DI at wk 16	NA (24%), Europe (64%), ROW 12%)
PSA-004 Study 4 "Palace 3" 2010-2012	-Over 18 years -Biologic or a non-biologic DMARD - Methotrexate, sulfasalazine, leflunomide, corticosteroids, NSAIDs -24 weeks	Ap 20 mg BID Ap 30 mg BID Placebo	169 167 169	ACR20 at wk 16 HAQ-DI at wk 16	NA (32%), Europe (46%), ROW (22%)

* Study ID shown (from top to bottom) as Celgene's study number, as referred to in the apremilast product label, and as identified by Celgene in the proposed product label and some other documents. Year shows when study started – completed.
† Ap = Apremilast oral tablets
‡ Full analysis set
§ ACR20 = Proportion of patients achieving 20% improvement from baseline in American College of Rheumatology defined criteria; HAQ-DI = Change from baseline in Health Assessment Questionnaire Disability Index;
¶ % As randomized; NA = North America; ROW = Rest of the world countries included Australia, New Zealand, Republic of Korea, Russian Federation, South Africa, Taiwan, and China.

b. Design and conduct of the studies

Study PSA-001 was randomized, double-blinded, placebo-controlled, and conducted in patients 18 years of age and older with active PsA. Apremilast at various doses were given for a total of 12 weeks as shown in Table 2. The primary efficacy variable was ACR20 response rate as shown in Table 2.

Studies PSA-002, -003, and -004 were similar in design and conduct except that study PSA-004 enrolled patients with psoriatic skin lesions and assessed skin response to treatment as a secondary endpoint. All studies were randomized, double-blind, placebo-controlled, and conducted in patients 18 years of age and older with active PsA. Eligible patients were required to have inadequate control of active PsA (defined by Classification Criteria for Psoriatic Arthritis [CASPAR] diagnostic criteria by DMARDs (small molecule or biologics) and ≥3 swollen and ≥3 tender joints. Enrollment of patients with treatment failure to TNF blockers was limited to ≤10%. Treatment assignments were stratified based on small molecule DMARD use at baseline. Eligible patients enrolled in the study were treated with apremilast or placebo for a total of 24 weeks as shown in Table 2. To limit gastrointestinal adverse reactions, apremilast dosing was titrated in 10 mg/day increments over the first week to the target dose of 20 or 30 mg twice daily. Patients were allowed to continue baseline DMARDs (methotrexate, leflunomide sulfasalazine) during the study. At week 16 (primary efficacy assessment time point), all patients whose tender and swollen joint counts had both not improved by ≥20% were escaped in a blinded fashion to active treatments. At week 24, all remaining patients in

the placebo group were re-randomized to active treatments. Patients are then enrolled in ongoing extension safety phase consisting of an initial phase of 28-week randomized double-blind active treatment, and a subsequent phase of 4-year, open-label, active treatment.

The primary efficacy variable for studies PSA-002, -003, and -004 was ACR response rate assessed at weeks 16 and 24. Primary efficacy endpoint was change in ACR 20 response at week 16 from baseline compared to placebo response. A key secondary efficacy variable was health assessment questionnaire (HAQ-DI). Other secondary efficacy variables included medical outcome short form 36-item health survey (SF-36), and Psoriasis Area and Severity Index (PASI). Safety assessment in all studies included recording of adverse events, vital signs, physical examination, clinical laboratory measures, and ECG.

The efficacy variables most relevant to this submission were ACR response, and the HAQ-DI. An understanding of these endpoints will help the interpretation of the study results described in the subsequent section.

The American College of Rheumatology (ACR) response is a composite endpoint with seven components that are used to calculate the proportion of patients achieving a target percentage of improvement from baseline.[1, 2] The ACR criteria have been used extensively in clinical trials in RA as a measure of efficacy of a therapeutic agent. The ACR criteria were modified for PsA by the addition of the DIP joints of the toes and the carpometacarpal joints to the total joint counts. The ACR 20 response for PsA is calculated as at least 20% reduction in tender joint count of 78 joints, and at least 20% reduction in swollen joint count of 76 joints, and at least a 20% reduction in at least 3 of the following 5 measures: patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., HAQ-DI), and acute phase reactant (e.g., CRP). The ACR 50 and ACR 70 are similarly calculated using the higher 50% and 70% levels of improvement, respectively. The Agency has accepted ACR 20 response as an acceptable demonstration of efficacy of a therapeutic agent supporting a "clinical response" claim.

Health Assessment Questionnaire-Disability Index (HAQ-DI) assesses a patient's level of functional ability and includes questions regarding fine movements of the upper extremities, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning intended to represent a comprehensive set of functional activities, including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients are asked to grade their status on a scale from 0 (no difficulty) to 3 (unable to do) for each question. The 8 category scores are averaged into an overall HAQ-DI score on a scale from 0 (no

[1] DT Felson, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in Rheumatoid Arthritis. Arthritis & Rheum 1995; 38:727-735.
[2] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis classification criteria. Arthritis & Rheum 2010; 62:2569-2581.

disability) to 3 (completely disabled). The Agency has accepted a "physical function response" claim based on HAQ-DI.

c. Efficacy findings and conclusions

The submitted data show efficacy for apremilast for the treatment of active PsA at the proposed doses of 30 mg twice daily.

In the following sections, dose selection and dosing regimen for apremilast are discussed first, followed by a discussion of the efficacy data for the proposed claims of clinical response, physical function response, SF-36, and closing with summary comments on efficacy.

Dose selection and dose ranging:
Celgene conducted one study comparing apremilast 20 mg twice daily and 40 mg once daily over 12 weeks of treatment (Table 2). In this study a statistically significantly greater proportion of patients achieved ACR 20 response compared to placebo for both apremilast doses at week 12 with a numerically higher trend for the 20 mg twice daily dose compared to the 40 mg once daily dose (43.5% versus 11.8% for apremilast 20 mg twice daily versus placebo, and 35.8% versus 11.8% for apremilast 40 mg once daily versus placebo). As expected, pharmacokinetic analysis showed that twice daily and once daily for the same nominal daily dose produced similar exposure. The twice daily dose was better tolerated with fewer adverse events leading to discontinuations compared to the once daily dose. With these considerations, Celgene decided to carry the 20 mg twice daily dose and a higher 30 mg twice daily dose in the definitive efficacy and safety studies. This was reasonable and acceptable to the Agency.

Clinical response:
Apremilast treatment was associated with a higher proportion of patients with ACR 20 response in all definitive studies at both 20 mg and 30 mg twice daily doses and the differences between apremilast treatment arms and placebo treatment arms were statistically significant (Table 3). The 30 mg twice daily dose was associated with a slightly higher proportion of patients with ACR 20 response compared to the 20 mg twice daily dose. Results of ACR 50 and ACR 70 responses were consistent with the ACR 20 response (Table 3). Results of individual components of the ACR response were generally similar to the results of ACR response (data not shown in this review).

Table 3. ACR response rates (%with response) at week 16 (primary analysis time point) and week 24 (ITT) *

Study †	Time	Treatment ‡	ACR 20 %	ACR 50 %	ACR 70 %	P vs placebo ACR 20
Study PSA-2	Week 16	Ap 20 mg BID	30	15	6	0.0166
		Ap 30 mg BID	38	16	4	0.0001
		Placebo	19	6	1	
	Week 24	Ap 20 mg BID	26	14	5	0.0038
		Ap 30 mg BID	35	19	10	<0.001
		Placebo	13	4	1	

Study †	Time	Treatment ‡	ACR 20 %	ACR 50 %	ACR 70 %	P vs placebo ACR 20
Study PSA-3	Week 16	Ap 20 mg BID	37	15	4	0.0002
		Ap 30 mg BID	32	11	2	0.0060
		Placebo	19	5	1	
	Week 24	Ap 20 mg BID	31	14	5	0.0009
		Ap 30 mg BID	25	12	2	0.0394
		Placebo	16	9	3	
Study PSA-4	Week 16	Ap 20 mg BID	28	12	5	0.0295
		Ap 30 mg BID	41	15	4	<0.0001
		Placebo	18	8	2	
	Week 24	Ap 20 mg BID	27	14	4	0.0110
		Ap 30 mg BID	31	16	5	0.0007
		Placebo	15	8	4	

* ITT = Intent-to-treat population defined as all randomized patients who took at least one dose of study drug
† Study ID shown as Celgene's study number
‡ Ap = Apremilast oral tablets

Physical function response:

Apremilast treatment was associated with an improvement in HAQ-DI scores at both 20 mg and 30 mg twice daily doses and most of the differences between apremilast and placebo were statistically significant (Table 4). The 30 mg twice daily dose was associated with slightly higher numerical response rates in the HAQ-DI compared to the 20 mg twice daily dose. The HAQ-DI effect size (difference between drug and placebo for change over baseline) for apremilast 30 mg twice daily in these studies ranged from 0.13 to 0.16 units at week 16. The clinical significance of this magnitude of benefit is uncertain because the minimal clinically important difference MCID for HAQ-DI for PsA is not established. The HAQ-DI has been validated in RA, with a MCID of 0.25 units (for a given patient) or 0.22 units (based on group means).[3] For PsA, MCID of 0.13 has been reported from clinical practice setting,[4] and 0.35 has been reported from biologic product treatment.[5] On responder analysis (using ≥0.3 units as a threshold), in two studies (PSA-002 and PSA-003) the difference between apremilast 30 mg twice daily and placebo was statistically significant at week 16 and at week 24 (data not shown in this review).

Table 4. HAQ-DI scores (mean change from baseline) week 16 (primary analysis time point) and week 24 (ITT) *

Study †	Time	Treatment ‡	HAQ-DI Δ from baseline	P vs placebo HAQ-DI
Study PSA-002	Week 16	Ap 20 mg BID	0.20	0.0252

[3] B Bruce and JF Fries. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18
[4] Kwok T, Pope JE. Minimally important difference for patient-reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue, and global visual analog scales. J Rheumatol 2010; 37:1024-1028.
[5] Mease PJ, Woolley JM, Bitman B, et al., Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. J Rheumatol 2011; 38:2461-2465.

Study †	Time	Treatment ‡	HAQ-DI Δ from baseline	P vs placebo HAQ-DI
		Ap 30 mg BID	0.24	0.0017
		Placebo	0.09	
	Week 24	Ap 20 mg BID	0.21	0.0091
		Ap 30 mg BID	0.26	0.0005
		Placebo	0.08	
Study PSA-003	Week 16	Ap 20 mg BID	0.16	0.0320
		Ap 30 mg BID	0.19	0.0042
		Placebo	0.05	
	Week 24	Ap 20 mg BID	0.17	0.1179
		Ap 30 mg BID	0.21	0.0191
		Placebo	0.09	
Study PSA-004	Week 16	Ap 20 mg BID	0.13	0.0091
		Ap 30 mg BID	0.19	0.0005
		Placebo	0.07	
	Week 24	Ap 20 mg BID	0.14	0.0860
		Ap 30 mg BID	0.19	0.0050
		Placebo	0.06	

* ITT = Intent-to-treat population defined as all randomized patients who took at least one dose of study drug
† Study ID shown as Celgene's study number
‡ Ap = Apremilast oral tablets

SF-36:
Apremilast treatment was associated with nominal improvement in physical function domain scores at week 16 for the 30 mg twice daily treatment groups across all studies and for the 20 mg twice daily treatment groups in one study. The mental function domain scores did not worsen for either of the doses in these studies.

Summary comments on efficacy:
The submitted data show efficacy of apremilast in patients with active PsA. There was numerical and statistically significant improvement in clinical response, physical function response, and physical function component of SF-36 in the clinical studies. The magnitude of effect sizes with apremilast for various efficacy measures tended to be smaller than DMARDs, such as TNF inhibitors and other molecules directly targeting the immune system.

Of the two apremilast doses studied in the definitive efficacy and safety studies, the 30 mg twice daily provided consistently higher numerical response compared to the 20 mg twice daily dose. Given the nature of safety findings and lack of clear dose-related serious safety concerns (discussed in section 8 below), Celgene's proposal to list the 30 mg twice as the recommended dose in the product label is reasonable and acceptable.

8. Safety

a. Safety database

The safety assessment of apremilast for PsA is primarily based on three confirmatory efficacy and safety studies discussed above (Table 1). Safety data were available from large studies in other diseases (6 in psoriasis, 1 in rheumatoid arthritis, and 1 in asthma)

and small clinical pharmacology studies, and those were also reviewed. The size of the safety database is adequate.

There are some limitations that need to be considered in the analysis of apremilast safety data. The PsA study design allowed for dose titration in 10 mg/day increments over the first week to the target dose of 20 or 30 mg twice daily, and allowed escapes from one treatment group to another at weeks 16 and 24 (discussed in section 7b above). The dose titration does not directly impact safety assessment, but will need to be considered for reporting of adverse event for the 20 or 30 mg doses of apremilast. The escape from one treatment group to another can impact safety assessment depending on how a safety finding is assigned to a treatment group, and also resulted in unequal distribution of patients across treatment groups as the study progressed (Table 5). In the apremilast PsA program, the number of patients remaining in the placebo and active treatment groups were reasonable up to week 16 that allow informative safety assessment of apremilast compared to placebo, but after week 16 informative comparative safety assessment is only possible between two active apremilast dose groups because of large escapes and drop outs in the placebo group. Corrections of adverse events for exposure may partly address this problem, but has its own limitation, and is not necessary for this program because of the nature of adverse event findings seen (discussed below in Summary comments on safety), and the number of patients remaining in the assigned groups were reasonable up to week 16.

Table 5. Number (percentage) of patients remaining on assigned treatment groups during the placebo-controlled treatment period of the three studies PSA-002, PSA-003, PSA-004

	Placebo	Apremilast 20 mg twice daily	Apremilast 30 mg twice daily
Day 1, Randomization	495 (100%)	501 (100%)	497 (100%)
Week 4	484 (98%)	485 (97%)	472 (95%)
Week 8	468 (95%)	471 (94%)	460 (93%)
Week 12	458 (93%)	462 (92%)	451 (91%)
Week 16, Escape from placebo to active	363 (73%)	449 (90%)	444 (89%)
Week 20	154 (31%)	437 (87%)	435 (88%)
Week 24, End of placebo treatment	113 (23%)	292 (58%)	278 (56%)

b. Safety findings and conclusion

The submitted data support the safety of apremilast at a dose of 30 mg twice daily for the treatment of active PsA. The major safety findings of note in the program were upper gastrointestinal adverse reactions, and weight loss.

Deaths, SAEs, and discontinuations due to AEs:

Death was rare in the apremilast program. There were a total of 6 deaths out of 2401 patients exposed to apremilast by the data cutoff of July 6, 2012. In the PsA clinical program, 1 death occurred in a 52 year old female patients assigned to apremilast 20 mg twice daily. The death was from multi organ failure possibly related to a concomitant diagnosis of vitamin B12 deficiency. The other 5 deaths occurred in the psoriasis clinical

program, 2 in the apremilast group and 3 in the placebo group. Analyses of these cases do not raise a safety concern for apremilast. There was one death from suicide committed by a 30-year-old female patient treated with placebo in a psoriasis study.

Non-fatal serious adverse events (SAEs) and discontinuations and drop out from adverse events (AEs) were small in number. Approximately 4% of patients reported non-fatal SAEs during the placebo controlled treatment period of 24 weeks in the PsA studies. The events were psoriatic arthropathy, cholelithiasis, atrial fibrillation, breast cancer, depression, acute myocardial infarction, congestive cardiac failure, hypertensive crisis, and acute pancreatitis. These events were spread out across treatment groups and do not raise safety concerns for apremilast.

Discontinuations due to AEs appeared to occur in a treatment- and dose-dependent manner during the PsA studies, and most were from gastrointestinal AEs (Table 6). The frequencies of discontinuations were not very high and thus did not appear to impact assessment of other safety findings.

Table 6. Number (percentage) of patients withdrawn due to adverse events during placebo-controlled treatment period of the three PsA studies PSA-002, PSA-003, PSA-004 (events that appear to be drug and dose related are shown)

	Placebo N=495	Apremilast 20 mg twice daily N=501	Apremilast 30 mg twice daily N=497
Nausea	3 (0.6%)	7 (1.4%)	13 (2.6%)
Diarrhea	3 (0.6%)	5 (1.0%)	11 (2.2%)
Headache	2 (0.4%)	1 (0.2%)	8 (1.6%)
Dizziness	2 (0.4%)	2 (0.4%)	3 (0.6%)
Vomiting	0	1 (0.2%)	3 (0.6%)
Fatigue	0	1 (0.2%)	3 (0.6%)
Migraine	0	1 (0.2%)	2 (0.4%)
Upper abdominal pain	0	1 (0.2%)	2 (0.4%)
Decreased appetite	0	1 (0.2%)	1 (0.2%)
Depressed mood	0	1 (0.2%)	1 (0.2%)
Depression	0	1 (0.2%)	0
Abdominal distension	0	1 (0.2%)	1 (0.2%)
Dyspepsia	0	2 (0.4%)	0

AEs of interest:

Celgene identified a set of AEs of interest based on the mechanisms of action of apremilast (inhibition of PDE4), possible class effects associated with PDE4, known comorbidities of PsA, and observed findings from earlier apremilast studies. The AEs of interest included gastrointestinal events, weight changes, infections, malignancies, cardiovascular events, suicidal ideation and behavior, vasculitis, hypersensitivity, and hepatobiliary and renal events. All AEs related to infections, malignancies, and cardiovascular events classified as MACE and potential MACE were adjudicated by independent blinded adjudicators. All events related to suicidal ideation and behavior was assessed by the Columbia Classification Algorithm of Suicide Assessment (C-

CASA). The AEs that were identified as AEs of interest and the methodologies for their assessment were reasonable and acceptable. Brief comments are made below on these AEs of interest.

Gastrointestinal events: The frequency of nausea, vomiting, and diarrhea was observed to increase in a dose dependent manner with frequencies varying from approximately 11 to 18% in apremilast groups compared to 3 to 5% in place groups. These were also common causes of discontinuations as discussed above (Table 5).

Weight changes: Apremilast treatment was associated with weight loss. In the PsA studies during the placebo control treatment period, weight decrease was reported by 0.4% patients in the placebo group, 1.0% patients in the apremilast 20 mg twice daily group, and 1.4% patients in the apremilast 30 mg twice daily group. The data were not adequate to identify the cause of weight loss and if the weight loss was associated with gastrointestinal adverse reactions.

Malignancies: There were a total of 18 cases of malignancy identified in the overall apremilast safety database. Of these 18 cases, 7 were non-melanoma skin cancers. The types of malignancies were diverse and spread across treatment arms. The overall number of malignancies was relatively small.

Infections: There were a total of 18 patients with serious infections reported from the overall apremilast database. There were no appreciable differences in the frequency of overall infection, opportunistic infection, new diagnosis of tuberculosis, and reactivation of latent tuberculosis in the program. The overall number of infections was relatively small.

MACE: A total of 8 cases meeting the MACE criteria were identified. The overall number was small and all were attributed to myocardial infarction. Five of the 8 cases occurred in the PsA studies during controlled treatment periods, with 3 in the 20 mg group, 1 in the 30 mg group, and none in placebo. The numbers are small too make a conclusion related to the difference across treatment groups.

Suicidal ideation and behavior: There were two patients with suicidal ideation in PsA studies, both in the apremilast 20 mg twice daily group. There were three other suicidal ideations in the entire database including one completed suicide in a placebo treated patient (mentioned under death above). Analyses of these using the C-CASA do not identify a signal for suicide for apremilast. Adverse event reporting of depression was low in the PsA studies during the placebo-controlled period (0.8% in placebo, 1.8% in apremilast 20 mg twice daily, and 1.0% in apremilast 30 mg twice daily groups) and do not show a clear dose effect for apremilast. Serious depression was reported in 2 patients, both in apremilast 20 mg twice daily group.

Vasculitis: There were no findings suggestive of vasculitis associated with apremilast treatment.

Hypersensitivity: There were no findings suggestive of hypersensitivity associated with apremilast treatment.

Hepatobiliary and renal AEs: There were no reports of liver failure or LFT abnormalities meeting Hy's Law criteria with apremilast treatment. There were liver function test abnormalities with numerically higher frequencies with apremilast compared to placebo (described further below under laboratory findings). Renal adverse events and laboratory findings were numerically small and not clearly suggestive of a safety signal.

Common AEs:

Reporting of common AEs were generally similar to AEs of interest noted above. Gastrointestinal adverse events were reported commonly and more in apremilast groups.

Laboratory findings:

Laboratory results included hematology and clinical chemistry. These were analyzed using mean values and shift tables. The finding of note was in liver function test results. During the placebo controlled period in the PsA studies, 2 patients in the placebo group, 2 patients in the apremilast 20 mg group, and 7 patients in the apremilast 30 mg group had a 3-fold increase in ALT or AST over upper level of normal. In addition, 2 patients in the apremilast 20 mg group and 2 patients in the apremilast 30 mg group had bilirubin increase over 1.8 fold of upper level or normal. None of the cases met the definition of Hy's law of liver injury. Lipid profiles, renal function parameter, and hematological parameters did not suggest any adverse effect of apremilast.

Summary comments on safety:

The apremilast clinical program identified safety findings of gastrointestinal adverse events and weight loss as noted above. There was also a signal of adverse effect on liver function tests. Analyses of some other events of interest, such as infection, malignancy, cardiovascular adverse events, and suicidal ideation did not show a safety signal for apremilast. The safety findings identified in the program do not preclude approval, or limit the dose to 20 mg twice daily as opposed to the proposed dose 30 mg twice daily, or would require demonstration of efficacy comparable to biologic DMARDs for PsA. The safety findings identified from the existing analysis also do not rise to a level that would justify re-analysis of the entire database to address the limitation of dose titration for the first week and escape at weeks 16 and 24. Some limited re-analysis can be done for accurate quantification of events for labeling purpose, such as some common adverse events, gastrointestinal adverse events leading to discontinuations, weight change, depression, and liver function tests.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. The efficacy and safety finding for apremilast in the PsA clinical studies were clear and did not warrant discussion at an advisory committee meeting.

10. Pediatric

The applicant requested a full waiver from Pediatric Research Equity Act (PREA) requirements with the reasoning that studies in children with PsA are impossible and impractical because the juvenile equivalents of PsA are rare, as children with juvenile idiopathic arthritis do not typically develop sufficient distinguishing features of PsA. This was discussed at the Pediatric Review Committee (PeRC) meeting on November 20, 2013, and the PeRC was in agreement with granting the waiver.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit for 2 clinical study sites, one in Ohio and another one in California, as well as the Celgene site in New Jersey, was done. The clinical study sites were selected based on high enrollment. Final report of the DSI inspection concluded adherence to Good Clinical Practice. Minor deficiencies were note, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or other groups in CDER.

12. Labeling

a. Proprietary Name

Celgene submitted Otezla as the proprietary name, which was considered acceptable by DMEPA.

b. Physician Labeling

The labeling for apremilast is being reviewed by various disciplines of this Division, the Division of Medical Policy and Programs (DMPP), DRISK, DMEPA, SEALD, and OPDP. Various changes to different sections of the label submitted by Celgene will be made to reflect the data accurately and to better communicate the findings to the

healthcare providers. The Division and Celgene are working towards a final agreed upon label.

c. Carton and Immediate Container Labels

These are under review by various disciplines of this Division and DMEPA, and tentatively seems to be acceptable.

d. Patient Labeling and Medication Guide

There is a Patient Counseling Information that is under review by the Division and other groups within the Center. There will be no Medication Guide for apremilast.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant submitted adequate data to support approval for apremilast at a dose to be titrated from 10 mg as the starting dose to the recommended dose of 30 mg twice daily for the treatment of adult patients 18 years of age and older with active psoriatic arthritis. The recommended action on this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of apremilast for the treatment of active PsA. The submitted efficacy data showed consistent efficacy in PsA. Of the two apremilast doses studied, the 30 mg twice daily provided consistently higher numerical response compared to the 20 mg twice daily dose. The overall magnitude of effect sizes with apremilast for various efficacy measures tended to be smaller than with DMARDs, such as TNF inhibitors and other molecules directly targeting the immune system. The major safety findings identified in the clinical program were gastrointestinal adverse events and weight loss. Given the nature of the safety findings and lack of clear dose-related serious safety concerns, the 30 mg twice daily dose, which is higher of the two doses studied, is acceptable as the proposed dose. The upward titration of the dose within a week from 10 mg as the starting dose to the recommended dose of 30 mg twice daily to limit gastrointestinal adverse reactions is acceptable. The clinical program was conducted with such a titration scheme.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

There will be one PMR study to gather human data regarding pregnancy outcome because of concerns with dose related abortions and embro-fetal deaths seen in mice and monkey studies with apremilast. There will be one PMC study to develop final dissolution methods and acceptance criteria for the apremilast drug product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
02/07/2014