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APPLICATION NUMBER:

205437Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 06, 2014
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205437
Supplement#	
Applicant	Celgene Corporation
Date of Submission	March 21, 2013
PDUFA Goal Date	March 21, 2014
Proprietary Name / Established (USAN) names	Otezla/apremilast
Dosage forms / Strength	Immediate release tablets 10mg, 20mg, 30 mg
Proposed Indication(s)	1. Treatment of Adult Patients with Active Psoriatic Arthritis (PsA)
Recommended:	<i>Approval, with Revisions to Proposed Label</i>

1. Introduction

Celgene Corporation has submitted New Drug Application (NDA) 203437 for the new molecular entity (NME) apremilast (also known as CC-10004), an oral small molecule inhibitor phosphodiesterase 4 (PDE4) proposed for the treatment of adult patients with active psoriatic arthritis. The product is being proposed as immediate-release tablets for oral administration in 10, 20, and 30 mg dosage strengths. Celgene proposes an initial titration dosing regimen from Day 1 to Day 5 to reduce the gastrointestinal symptoms with initial therapy, followed by 30 mg twice daily dosing thereafter.

The phosphodiesterase superfamily contains 11 different members which appear to have different target activities. Theophylline is a non-specific phosphodiesterase inhibitor. PDE4 is the predominant isoenzyme found in inflammatory cells and pulmonary smooth muscle cells. The putative mechanism of action is related to an increase in cyclic adenosine monophosphate (cAMP) that occurs as a result of PDE4 inhibition, which in turn modulates other pro-inflammatory and anti-inflammatory mediators.^{1,2}

Apremilast is not currently marketed anywhere in the world. If approved, apremilast would be the first PDE4 inhibitor for psoriatic arthritis (PsA), and the first orally administered agent

¹ McCann FE, et al, "Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumor necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis" *Arthritis Res Ther.* 2010;12(3):R107

² Schafer PH, et al, "Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis" *Br J Pharmacol.* 2010 Feb;159(4):842-55

approved for the treatment of patients with PsA. The other PDE4 inhibitor on the market, roflumilast (Daliresp®), was approved since February 2011 as a treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

While the NDA for apremilast posed a number of review issues, none were considered substantive based on the findings from the Agency's review and consequently, the NDA was not discussed at a meeting of the Arthritis Advisory Committee.

2. Background

PsA is an inflammatory arthritis, like rheumatoid arthritis (RA), however differs from RA in prevalence (lower, at 0.3 to 1% of the population), demographics (approximately equal male:female ratio, slightly younger mean age of late 40's), and joints involved (asymmetric, tendency toward distal involvement, involvement of the spine, and involvement of the tendons as well as synovium—dactylitis and enthesitis). In 80-85% of cases, skin involvement with psoriasis has occurred previously or contemporaneously with the joint disease. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies.

The management of patients with PsA includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (mostly intra-articular), and small molecule and biologic disease modifying antirheumatic drugs (DMARDs).³ The treatment should also consider concomitant psoriatic skin involvement, enthesitis/dactylitis, and axial involvement. NSAIDs are used for the relief of the musculoskeletal signs and symptoms of the disease. The use of oral DMARDs, with methotrexate being the first choice (sulfasalazine, leflunomide, and cyclosporine are also used), is recommended for patients with active disease poorly responding to NSAIDs. Among the DMARDs this far, only the TNF-inhibitors have also been shown to also reduce the radiographic progression of peripheral arthritis in PsA and have become a mainstay in the therapy of PsA. FDA has also recently approved another biologic, ustekinumab, targeting a IL23/23 signaling pathway. The FDA approved biologics for the treatment of patients with PsA are summarized in Table 1.

³ Gossec L, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis.* Jan 2012;71(1):4-12

Table 1. FDA Approved Biologics for PsA

Product Name (Trade Name) Year approved for PsA	ROA	Description and MOA	Labeled Claims for PsA
Etanercept (ENBREL) 2002	SC injection	Fusion protein TNF inhibitor	Clinical response Physical function response Radiographic response
Infliximab (REMICADE) 2005	IV infusion	Monoclonal Antibody TNF inhibitor	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) 2005	SC injection	Monoclonal Antibody TNF inhibitor	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) 2009	SC injection	Monoclonal Antibody TNF inhibitor	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) 2013	SC injection	Fab fragment TNF inhibitor	Clinical response Radiographic response Physical function response
Ustekinumab (STELARA) 2013	SC injection	Monoclonal Antibody IL12/23 inhibitor	Clinical response Physical function response

Abbreviations: IV-intravenous, MOA-Mechanism of action, ROA-Route of administration; SC-subcutaneous, TNF-tumor necrosis factor

Historically, clinical development programs evaluating the efficacy of proposed products for PsA have primarily utilized American College of Rheumatology (ACR) response criteria to assess treatment effect on signs and symptoms, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess treatment effect on physical functioning which have been validated for use in PsA and were used in the apremilast trials. These outcome measures will be described in greater detail later in this memorandum. Radiographic outcomes were not assessed in the apremilast development program. While demonstrating benefit on radiographic progression of disease is important, it has not been required for approval, which has historically been based on clinical responses.

Relevant Regulatory History for Apremilast in PsA

Investigational new drug application (IND) 101761 was opened in December 2008 for the study of apremilast in patients with rheumatic diseases, including PsA, and included Phase 1 clinical data from healthy volunteers, patients with asthma, and patients with psoriasis.

In March 2010, an End of Phase 2 (EOP2) meeting was conducted to discuss apremilast’s development program in PsA. The Agency agreed in principle with the proposed Phase 3 program elements and endpoints:

- Common design of proposed Phase 3 PsA trials, including AC20 as the primary and HAQ-DI as the secondary endpoints, and statistical methodology
- Definition of proposed target population (CASPAR criteria⁴)
- Doses to be studied: 20 mg bid and 30 mg twice daily based on results from two Phase 2 conducted in PsA and plaque psoriasis
- Number of patients required for safety database for NDA submission.

⁴ Taylor W, et al., “Classification criteria for psoriatic arthritis: development of new criteria from a large international study”, *Arthritis Rheum.* 2006 Aug;54(8):2665-73

In June 2012, prior to unblinding the data, the Agency provided written agreement to the Applicant's proposal to change the timing of the primary and major secondary endpoint evaluations in the Phase 3 studies from Week 24, as originally designed, to Week 16. The Applicant's rationale for this revision was to minimize the confounding effect of patients escaping from placebo to active treatment at Week 16. The revised statistical analysis plan for the Phase 3 studies were also generally agreed upon with the exception of the proposed handling of missing data using the Last Observation Carried Forward (LOCF) imputation method.

General agreement was reached at the Pre-NDA meeting in December 2012 regarding the proposed format and content of the NDA to support review of the application including the adequacy of the nonclinical program and clinical safety database, which included additional retrospective analyses of Major Adverse Cardiac Events (MACE), possible MACE, malignancies, infections, and retrospective evaluation of suicidality using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The Agency expressed concern regarding the limited observed treatment benefit of apremilast as it related to the HAQ-DI findings and requested that the Applicant provide a justification for the clinical meaningfulness of the reported treatment difference if they intended to pursue an *improvement in physical function* labeling claim. The Agency also requested analyses of safety based on two patient populations: (1) patients' original randomized treatment arms, i.e. "as randomized", and (2) patients' original randomized treatment arms plus placebo patients who transitioned to apremilast by design or by escape, i.e. "as treated".

3. CMC/Device

CMC Reviewers: Ciby J. Abraham, Ph.D., Minerva Hughes, Ph.D., Neal J. Sweeney, Ph.D., Linda Ng; Supervisory: Prasad Peri, Ph.D., Bryan S. Riley, Ph.D., and Eric Duffy, Ph.D.

- **General product quality considerations**

The drug substance apremilast is a white to pale yellow powder. The Biopharmaceutics Classification System (BCS) class is 4 (low solubility/low permeability). The drug substance is formulated with compendia grade excipients to form immediate release 10, 20 and 30 mg tablets. (b) (4). The drug substance is chiral and contains an (b) (4), and the impurity (b) (4) which are structural alerts for potential genotoxicity. The drug substance is not photosensitive and the stability data provided supports both the proposed retest period of (b) (4), and the post-approval stability protocol.

The proposed commercial drug product, apremilast tablets, contains 10 mg, 20 mg, and 30 mg apremilast and standard compendia 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, and 30 mg strengths as a 2-week starter pack for the initial titration. The tablets are prepared by (b) (4). The tablets are coated with proprietary

(b) (4). The drug product is 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. The proposed expiration date is (b) (4) and the storage conditions is 30° C or below. Phase 3 development program was conducted with the to-be-marketed formulation.

The Applicant attests that apremilast drug substance and drug product are manufactured in accordance with the current Good manufacturing Practices (cGMP). The following facilities are listed as manufacturing sites for the drug substance: (b) (4) Celgene Chemicals GmbH, in Zofingen, Switzerland, (b) (4). Apremilast drug product is manufactured, packaged and released in Celgene International Sarl, Switzerland, (b) (4) and is also packaged by (b) (4)

- **Facilities review/inspection**

A prior approval inspection of Celgene International, Boudry, CHE facility, listed in the NDA as performing stability studies, uncovered that there were (b) (4). This has been identified by the Office of Compliance as a substantive current good manufacturing practice (cGMP) compliance issue that had to be addressed under the current NDA, and was communicated to the Applicant through an information request dated November 08, 2013. The issue was subsequently discussed at the Late-Cycle Meeting (LCM) on December 06, 2013 as a substantive review issue. Following the LCM, Celgene has proposed, and the Agency agreed, to keep Celgene International Sarl, FEI: 3006323509 for testing of stability samples and to store the stability samples (b) (4)

(b) (4) The facility inspection is pending at the time of this review.

- **Other notable issues (resolved or outstanding)**

From a Chemistry, Manufacturing, and Controls (CMC) perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding the facilities’ inspections.

There is one Biopharmaceutics post-marketing commitments recommended:

- Applicant to submit the final dissolution method development and validation report and proposed final dissolution acceptance criterion for your drug product within 6 months of the action letter date.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: L Steven Leshin, D.V.M., Ph.D.; Supervisor: Marcie Wood, Ph.D.

- **General nonclinical pharmacology/toxicology considerations**

Pivotal nonclinical toxicology studies were conducted in mice up to 6 months in duration and cynomolgus monkeys up to 12 months in duration. The major apremilast-related finding across mouse studies was arteritis observed within the thoracic organs and the aortic root, together with a perivascular inflammatory cell infiltration in the lung. Arteritis in the myocardium was also reported in monkeys in the short-term studies with higher doses (up to 1000 mg/kg/day), but not in 13-week (doses of 25, 85 or 300 mg/kg/day) or 12-month (doses of 60, 180 or 600 mg/kg/day) studies. Other findings included centrilobular hepatocyte hypertrophy, likely due to extensive apremilast metabolism in mice, dose-dependent increase in white blood cells due to an increase in neutrophils, and a reduction in lymphocyte counts in both species.

The 6-month mouse study identified a NOAEL at 10 mg/kg/day, and the 12-month monkey study identified a NOAEL at 600 mg/kg/day. The Pharmacology/Toxicology review team has determined that the NOAELs of both chronic mouse and monkey studies provide adequate systemic safety margins on an AUC basis (approximately 1 for the mouse and approximately 5 for the monkey) for the proposed dose of apremilast of 30 mg twice daily.

- **Carcinogenicity**

Two 2-year oral carcinogenicity bioassays were conducted with apremilast in mice and rats. Apremilast was not carcinogenic in mice at doses up to 1000 mg/kg/day or in rats at doses up to 20 mg/kg/day in males and 3 mg/kg/day in females.

- **Reproductive toxicology**

In reproductive toxicology studies, apremilast had no effects on fertility of male mice at doses up to 50 mg/kg/day, but prolonged estrus cyclicity, increased time to mating, and increased early resorption were observed in female mice at doses greater than or equal to 20 mg/kg/day.

In a pre- and postnatal development study in mice, dystocia, reduced viability, and reduced birth weights occurred at doses greater than or equal to 80 mg/kg/day.

In embryo-fetal development studies, a dose-dependent reduction in litters and litter sizes due to post-implantation loss occurred in mice at doses greater than or equal to 20 mg/kg/day. A dose-dependent increase in fetal losses (abortions) was also observed in monkeys at doses greater than or equal to 50 mg/kg/day. Apremilast was not teratogenic in mice and monkey studies.

The findings of embryo-fetal death and abortions provided a supportive rationale for the post-marketing study recommended by the Pediatric and Maternal Health Staff (PMHS).

In light of the limited clinical information on embryo-fetal apremilast exposure, and the findings of embryo-fetal death and abortions with apremilast, the Pediatric and Maternal Health Staff (PMHS) recommended a pregnancy registry study as a post-marketing requirement as discussed in Section Recommendations/Risk Benefit Assessment. The Pharmacology/Toxicology and the clinical teams agree with recommendation.

- **Other notable issues (resolved or outstanding)**

The Pharmacology/Toxicology review team believes the information in this application is adequate to support approval of the proposed chronic dosing of 30 mg twice daily, and I concur with their recommendation.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology reviewer: Sheetal Agarwal, Ph.D.; Supervisor: Satjit Brar, Pharm.D., Ph.D.

Pharmacometrics reviewer: Li Zhang, Ph.D.; Supervisor: Atul Bhattaram, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The absolute bioavailability of apremilast was 70%. The systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to dose in the dose range of 50 mg BID or 80 mg QD, with no accumulation up to 40 mg QD dosing. T_{max} was reached by approximately 2.5 hours following oral administration. Co-administration with food had no significant effect on the extent of absorption ($AUC_{0-\infty}$). Dividing a daily dose to BID or using dose titration appeared to improve the gastrointestinal tolerability of apremilast.

Apremilast has a total plasma protein binding of approximately 68%. The volume of distribution (V_d) for apremilast was 87 L, suggesting distribution into tissues.

Apremilast is primarily eliminated as metabolites formed via both CYP-mediated oxidative metabolism (and subsequent glucuronidation) and non-CYP mediated hydrolysis.

Of the 97.1% drug recovered following oral administration using radioactive [^{14}C]-apremilast and its metabolites, approximately 58% and 39% was recovered in urine as parent drug (less than 3%) and metabolites (predominantly glucuronide conjugate of O-demethylated apremilast), respectively. The terminal elimination half-life of apremilast was approximately 5 to 7 hours after single- or multiple-dose administration.

- **Drug-drug interactions**

Apremilast had no substantial effects on the plasma levels of oral contraceptives (Ortho Tri-Cyclen®), or methotrexate. No drug-drug interactions (DDIs) with concomitantly administered CYP3A4 substrates were observed and at systemic concentrations, apremilast is not expected to inhibit/induce CYPs. Thus no dose adjustment is needed for these drugs when co-administered with apremilast.

While apremilast has been shown to be a substrate for P-gp *in vitro*, it is not expected to inhibit P-gp at systemic concentrations *in vivo*, based on dedicated study using ketoconazole.

Apremilast is not a substrate for breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, or OATP1B3, and does not inhibit or is a weak inhibitor of BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, multidrug resistance protein (MRP)1, MRP2, MRP3 and MRP4 (IC₅₀ > 10 µM).

Apremilast co-administration with a strong CYP3A inducer, rifampin, resulted in substantial decreases in apremilast exposure by 3 fold. Thus the Clinical Pharmacology review team recommended that the co-administration with rifampin should be avoided because that may result in ineffective concentrations of apremilast.

Co-administration with methotrexate had no significant effect on apremilast exposure and no dose adjustment is needed for apremilast when co-administered with methotrexate.

- **Intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

There was no substantial impact of age, weight, and gender on PK parameters, after accounting for differences in renal function (i.e., creatinine clearance).

Renal Impairment

The effect of renal function on the PK of apremilast was evaluated in Study CC-10004-CP-019 which enrolled subjects with severe renal impairment and healthy volunteers. An increase in AUC of about 88% and decrease in clearance of about 47% was observed in severe renal impairment subjects. Based on these data and PK simulations conducted by the Applicant and the FDA Clinical Pharmacology and Pharmacometrics review teams, attempting to match plasma apremilast exposures to subjects without renal impairment, the Clinical Pharmacology review team recommended an alternative titration (administer only the morning apremilast dose from the titration schema) and dosing regimen (apremilast 30 mg once daily) for severe renal impairment subjects. I concur with this recommendation.

Hepatic Impairment

No dose adjustment is needed in these subjects, based on PK of apremilast data from a dedicated study (CC-10004-CP-011) in subjects with mild, moderate and severe hepatic function.

- **Demographic interactions/special populations**

The population PK analysis in PsA patients showed about 1.4 fold increase in steady state AUC relative to healthy volunteers. However, the exposure difference attributed to body weight and gender was generally less than 26% and well within the expected between subject variation and thus no dose adjustment is warranted with these covariates.

- **Thorough QT study**

QT effect for apremilast was evaluated in a randomized, blinded, four-arm crossover group study, in 60 male healthy subjects who received apremilast 30 mg BID, apremilast 50 mg BID, placebo, and a single oral dose of moxifloxacin 400 mg. No significant QT prolongation effect of apremilast (30 mg BID and 50 mg BID) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between apremilast (30 mg BID and 50 mg BID) and placebo of QTcF were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

- **Other notable issues (resolved or outstanding)**

The Office of Clinical Pharmacology has determined the information in NDA 205437 acceptable. No outstanding issues have been identified or post-marketing commitments recommended.

6. Clinical Microbiology—N/A

7. Clinical/Statistical- Efficacy

Clinical Primary Reviewer: Keith M. Hull, M.D., Ph.D.

Statistical Reviewer: Robert Abugov, Ph.D., Statistical Team Leader: Joan Buenconsejo, Ph.D.

Overview of the Clinical Program

Three randomized placebo-controlled trials (PSA-002, 003, and 004) of highly similar design have been submitted as the primary evidence of efficacy and safety of apremilast, as summarized in Table 2 below. One notable difference between the studies is that Study PSA-004 included the PASI-75 response as a secondary endpoint and the adjustment of the analyses of the primary and secondary endpoints for baseline DMARD use and baseline psoriatic skin involvement $\geq 3\%$ body surface area (BSA). The studies consist of a 24-week randomized, placebo-controlled period, a 28-week randomized double-blind active treatment, and an open-label extension period of up to 4 years. All studies were multicenter and enrolled patients from North America, Europe, Asia, and South Africa. The current submission includes controlled efficacy data from the initial 24-week period.

One additional Phase 3 study, PSA-005, is ongoing and still blinded; therefore no efficacy data were included in the NDA submission. This is a study of similar design, including primary endpoint, to the other three efficacy studies, with the exception of enrollment of active PsA patients who were naïve to DMARDs.

Table 2: Key Design Features of the Phase 3 Efficacy and Safety Studies in Apremilast PsA Development

Study ID <i>Study ID in labeling</i>	Subjects Enrolled (n)	Patient population	Study Design	Dosing ^a	Primary Endpoint (Week 16)
PSA-002 <i>Study 1</i>	504	Active PsA with an inadequate response to DMARDs ± biologic therapy	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR30 twice daily with initial titration regimen from Days 0 through 5 and then continued on the full dose. At Week 16, all placebo (but not apremilast) subjects whose swollen and tender joint count had both not improved by ≥ 20% entered early escape and were re-randomized 1:1 to receive APR 20 BID or APR 30 BID and dose-titrated during their first week of active treatment.	APR20 BID APR30 BID PBO	ACR20
PSA-003 <i>Study 2</i>	488				
PSA-004 <i>Study 3</i>	505				

^a Patients received initial titration regimen from Days 0 through 5 and then continued on the full apremilast dose. At Week 16, all subjects whose swollen and tender joint count had both not improved by ≥ 20% were re-randomized 1:1 to receive APR 20 BID or APR 30 BID and dose-titrated during their first week of active treatment. Subjects on active treatment who met early escape criteria continued to receive the same dosage of apremilast to which they were originally assigned

Brief Description of Efficacy Endpoints Proposed for Labeling

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in rheumatoid arthritis, which have since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.⁵ To address the differences in the clinical presentation in PsA, the ACR response criteria were modified for PsA by the addition of the DIP joints of the toes and the carpometacarpal (CMC) joints to the total joint counts (78 tender joints and 76 swollen joints). The use of the modified ACR response criteria has been established as a valid endpoint to assess clinical response in patients with PsA and has previously been accepted to provide the evidentiary support of efficacy for regulatory approval of other product for the treatment of patients with PsA.

The modified ACR20 response is calculated as a ≥20% improvement in:

- tender joint count (of 78 joints) and
- swollen joint count (of 76 joints) and
- 3 of the 5 remaining ACR core set measures
 - Patient Global Assessment of Arthritis on a visual analog scale (VAS)
 - Physician Global Assessment of Arthritis on a VAS

⁵ DT Felson, et al., Arthritis & Rheum, 1995 June, 38(6):727-735

- Patient Assessment of Pain on a VAS
- Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
- Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Agency has historically recognized a distinct claim in PsA for “improvement in physical function” based on outcome measures such as the HAQ-DI.⁶ This instrument assesses a patient’s level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The 8 category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to 3 (completely disabled). The most widely accepted figure on the minimal clinically important difference (MCID) in the HAQ-DI score in RA is an improvement (decrease) of at least 0.22 units for a group mean and 0.25 units for an individual RA patient.

In PsA however, the MCID for the HAQ-DI has not been fully established. In clinical practice setting, an improvement of 0.13 was regarded as clinically meaningful⁷, while the MCID in biologic clinical trial setting has been reported as 0.35 units⁸.

The Agency has historically used a cut-off of 0.3 units to define the proportion of patients with clinically meaningful improvement in HAQ-DI.



⁶ B Bruce and JF Fries, “The Health Assessment Questionnaire (HAQ).” Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18

⁷ 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(5):1024-8.

⁸ Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. 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(11):2461-5.

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Dose and Dosing Regimen Selection

The proposed recommended dosing is initial titration from Day 0 through Day 5 as summarized in Table 3, followed by the full apremilast dose of 30 mg BID thereafter which was employed in the Phase 3 PsA development program.

Table 3. Proposed Recommended Initial 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

The Phase 3 PsA studies also included a 20 mg BID dosing regimen using the same initial titration. Celgene selected the doses and the dosing regimen for the Phase 3 program, based on data from dose-ranging studies in PsA and psoriasis.

- ***Initial Dose Titration***

Justification for the initial dose titration was provided from a dedicated PK study CC-10004-PK-007 where the total number of adverse events reported for the titrated group 40 mg QD is titrated (10 mg first 3 days, 20 mg next 3 days and finally 40 mg on the 7th day) was 34 as compared to 72 in the non-titrated group. Based on this observation, all future studies for apremilast were conducted employing an initial 5-day dose titration scheme which has been further extensively studied in the apremilast Phase 2 and Phase 3 program. The purpose of the recommended titration is to improve the tolerability by reducing the gastrointestinal symptoms

associated with initial therapy. To ascertain the correct dosing during the initial titration, the Applicant proposes to use a 2-week starter blister pack for the initial titration containing 10 mg, 20, and 30 mg 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).

- *Dose Selection, Including Dose Frequency*

Phase 3 evaluated 20 and 30 mg BID dosing regimens for apremilast. These dosing regimens were selected on the basis of results from 2 Phase 2 dose-ranging studies:

- Study CC-10004-PSA-001 tested 20 mg BID and 40 mg QD dosing regimens of apremilast versus placebo in PsA patients,
- Study PSOR-005 tested 10, 20 and 30 mg BID dosing regimens of apremilast in psoriasis patients.

In Study CC-10004-PSA-001 apremilast 20 mg BID produced exposure similar to 40 mg QD dosing regimen with a lower C_{max} (by ~28%) and higher C_{min} (by ~112%). However, as compared to the placebo group, the apremilast 20 mg BID treatment group achieved statistically better ACR 20 and ACR 50 responses at Week 12 (43.5% versus 11.8%, $p < 0.001$ and 17.4% versus 2.9%, $p = 0.012$, respectively) whereas apremilast 40 mg QD treatment group achieved statistical significance only for ACR 20 (35.8% versus 11.8%, $p = 0.002$). The AEs such as fatigue, dizziness, and pruritus were more common in subjects taking 40 mg QD than on either 20 mg BID or placebo and the 20 mg BID dosing regimen of apremilast was better tolerated than the 40 mg QD regimen with respect to the most common AEs of diarrhea and nausea. In summary, the data from Study PSA 001, indicated that the twice daily dosing had a better efficacy and was better tolerated than the once daily dosing which supported the Applicant’s rationale to pursue a twice daily dosing for the Phase 3 development program.

In Study PSOR-005, there was a noticeable dose-response relationship in psoriasis patients between the 3 tested doses for the primary endpoint in that study, the proportion of subjects achieving Psoriasis Area and Severity Index (PASI-75) response at Week 16, with statistical superiority over placebo for the 20 mg BID and 30 mg BID doses but not the 10 mg BID dosing. The safety assessment did not suggest dose-dependent safety issues.

Based on the overall safety and efficacy data from the two dose-ranging studies, the 20 mg BID and 30 mg BID dosing regimens, following the initial dose titration, were selected to be carried forward in the Phase 3 development program. The Agency considered these doses and dosing regimens reasonable to be studied in the confirmatory studies, as discussed at the EOP2 meeting.

Study conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. Overall completion rates at Week 24 were high in the 85 to 90% range for active and control groups in all three studies and generally comparable between the

apremilast- and placebo-treated arms. Dropout rates were due primarily due to adverse events and were overall similar between the apremilast- and placebo-treated arms. This pattern and amount of missing data is consistent with other PsA clinical development programs. One notable observation is the significant proportion of patients who met the pre-specified criteria for early escape at Week 16 (subjects whose tender and swollen joint counts had both not improved by $\geq 20\%$). This led to a differential escape pattern with more patients escaping from the placebo arms (ranging between 55 and 64%) as compared with apremilast-treated patients (ranging from 32 to 46%) as shown in Table 4 below. Because of this high proportion of placebo-treated patients who entered early escape and crossed-over to active treatment, the interpretation of efficacy at timepoints after Week 16, e.g. Week 24, is of questionable utility ^{(b) (4)} particularly with respect to continuous endpoints.

Table 4. Subject Disposition at Week 24 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR20 BID N=168	APR30 BID N=168	PBO N=159	APR20 BID N=163	APR30 BID N=162	PBO N=169	APR20 BID N=169	APR30 BID N=167
Discontinued prior to Week 24	14 (8)	19 (11)	21 (13)	16 (10)	19 (12)	21 (13)	13 (8)	12 (7)	11 (7)
Discontinued due to AE	8 (5)	8 (5)	11 (7)	3 (2)	5 (3)	12 (7)	10 (6)	12 (7)	11 (7)
Entered Early Escaped at Week 16	107 (64)	78 (46)	58 (35)	88 (55)	59 (36)	64 (40)	97 (57)	76 (45)	53 (32)

Source: Adapted from Table 6, Dr Abugov's statistical review of the NDA

Statistical Considerations

Celgene's primary analysis was conducted on the "Full Analysis Set" (FAS), which included all patients who were randomized, and received at least one dose of study drug. Missing data, particularly following early escape at Week 16, and their impact on the analyses of the respective study endpoints will be discussed in the sections below pertaining to the analyses of the Week 24 results.

All three studies were designed to establish superiority of the two doses of apremilast (20 mg and 30 mg BID) to placebo for the primary endpoint, ACR20 response rates at Week 16 using the same statistical approach.

In order to control the probability of type 1 error with multiple doses and endpoints, Celgene assessed each endpoint sequentially using Hochberg procedure using pairwise comparisons between APR30 vs. placebo treatment arms and between APR20 and placebo treatment arms. Differences were considered statistically significant if both comparisons were significant at the 0.05 level or if one comparison was significant at the 0.025 level. Endpoints were tested in hierarchal order starting with the primary endpoint tested first followed by subsequent secondary endpoints as prespecified in the statistical analysis plan. Non-responder imputation was used to assess missing data for the primary analysis at Week 16. Missing data for continuous endpoints at Weeks 16 and 24 were imputed using LOCF, with sensitivity analyses at Week 16 based on baseline observation carried forward (BOCF) for discontinued subjects.

Joints classified as not assessable at baseline were excluded from the analyses, while those that were not assessed for other reasons were accounted for using BOCF.

A large number of originally proposed labeling statements were based on [REDACTED] (b) (4)

The analyses and presentation of the Week 24 data are confounded by the limitations of the study design, the early escape provisions, and the non-responder imputations. While this is generally also true for the analyses of other rheumatology products, in the case of apremilast PsA development program, a significant amount of patients met early escape criteria at Week 16: approximately 55% to 66% of placebo patients who then crossed-over to active treatment and about 32% to 46% in the active group who continued on the same apremilast dose. [REDACTED] (b) (4)

Efficacy findings

- *ACR Response Rates*

The primary endpoint for all three confirmatory studies was the proportion of patients experiencing a modified ACR20 response at Week 16. As shown in Table 5 below, apremilast treatment was associated with a higher proportion of ACR20 responders in all 3 studies at both 20 mg BID and 30 mg BID doses, and the differences were statistically significant compared to the placebo control groups. The results were not clearly dose-dependent as the apremilast 20 mg BID dose group showed a numerically higher ACR20 response rates compared with apremilast 30 mg BID dose group in study PSA-003.

Table 5: Summary of Modified ACR20 Response Rates at Weeks 16 and 24 in Phase 3 PsA Studies PSA-002, PSA-003, and PSA-004

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR20 BID N=168	APR30 BID N=168	PBO N=159	APR20 BID N=163	APR30 BID N=162	PBO N=169	APR20 BID N=169	APR30 BID N=167
Proportion of Subjects Achieving ACR20 at Week 16; n (%)	32 (19)	51 (30)	64 (38)	30 (19)	61 (37)	52 (32)	31 (18)	48 (28)	68 (41)
Treatment Difference, %	-	11	19	-	19	13	-	10	22
p-value APR dose vs. PBO	-	0.02	0.0001	-	0.0002	0.006	-	0.03	<0.0001
p-value APR30 vs. APR20	-	-	0.14	-	-	0.31	-	-	0.02
Proportion of Subjects Achieving ACR20 at Week 24; n (%)	22 (13)	43 (26)	59 (35)	23 (16)	51 (31)	40 (25)	26 (15)	46 (27)	52 (31)
Treatment Difference, %	-	13	22	-	16	9	-	12	16
p-value APR dose vs. PBO	-	0.0038	0.0001	-	0.0009	0.0394	-	0.011	0.0007

Source: Adapted from Dr Hull's clinical review and Dr Abugov's statistical review

Compared to placebo, patients treated with apremilast 20 mg BID and 30 mg BID achieved higher ACR 20 responses at week 24 in all three studies (Table 5).

Consistent with the primary analysis, improvements were observed for all ACR core components at week 16 in patients treated with apremilast 20 mg BID and 30 mg BID compared to placebo (data not shown).

Consistent with the primary endpoint results, the proportion of patients experiencing ACR50 levels of improvement was numerically higher in the apremilast groups compared to the placebo control. However, these differences did not reach statistical significance and were of questionable clinical importance. The ACR70 response rates however, were very small (1 to 6 %) and overall similar between placebo and apremilast groups.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

As a key secondary endpoint, the change in HAQ-DI score was assessed from baseline to Week 16 in all three studies. Apremilast treatment was associated with a statistically significant improvement (decrease) in HAQ-DI (mean change from baseline), with the apremilast 30 mg BID treatment groups experiencing a 0.13 to 0.6 unit improvement over placebo in the three studies as shown in Table 6 below.

Table 6. Mean Change of HAQ-DI from Baseline to Week 16 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=165	APR20 BID N=163	APR30 BID N=159	PBO N=153	APR20 BID N=159	APR30 BID N=154	PBO N=163	APR20 BID N=163	APR30 BID N=160
Mean Change from Baseline in HAQ-DI at Week 16	-0.09	-0.2	-0.24	-0.05	-0.16	-0.19	-0.07	-0.13	-0.19
Treatment Difference	-	-0.11	-0.16	-	-0.10	-0.14	-	-0.07	-0.13
p-value APR dose vs. PBO	-	0.025	0.002	-	0.036	0.004	-	0.17	0.007
p-value APR30 vs. APR20	-	-	0.36	-	-	0.45	-	-	0.2

Source: Adapted from Dr. Hull's clinical review

As discussed in the Statistical Considerations section above, the interpretation of Week 24 data particularly for continuous endpoints such as HAQ-DI is confounded by the significant amount of placebo patients crossing over to active treatment at Week 16 due to early escape (Table 4 above), thus limiting the conclusions on the apremilast effects on physical function at Week 24.

At the pre-NDA meeting, the Agency had expressed concerns with the clinical meaningfulness of the HAQ-DI data. To address these concerns, the Applicant provided analyses on the proportion of patients meeting a cut-off of at least 0.3 units of change from baseline, consistent with the regulatory precedent for psoriatic arthritis products. This analysis, shown in Table 7, demonstrated a relatively small but statistically significant increase in the proportion of HAQ-DI responders meeting the threshold of 0.3 units of improvement in the apremilast 30 mg BID

treatment arms over placebo in two of the three studies. The proportion of HAQ-DI responders (HAQ-DI ≥ 0.3 units improvement) in apremilast 20 mg BID dose group was not statistically significant from placebo but the results were overall consistent the effect of apremilast on improving physical function in PsA. The overall HAQ-DI results are consistent with a modest effect of apremilast on physical functioning in PsA and are also consistent with the magnitude of the clinical response as measured by ACR responses rates.

Table 7. Proportion of Patients with HAQ-DI Improvement ≥ 0.30 at Week 16

Study	Placebo n/N (%)	APR 20 BID			APR 30 BID		
		n/N (%) ^a	Treatment Difference	P-value	n/N (%) ^a	Treatment Difference	P-value
PSA-002	45/168 (27)	55/168 (33)	6	0.2360	64/168 (38)	12	0.0249
PSA-003	39/159 (25)	52/163 (32)	7	0.1400	61/162 (38)	13	0.0110
PSA-004	45/169 (27)	54/169 (32)	5	0.3047	56/167 (34)	7	0.1726

Source: Summary of Clinical Efficacy. Adapted from Table 17
 a- Missing values for subjects who did not discontinue or enter EE were imputed using the latest available postbaseline value prior to the visit in question. Subjects who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as nonresponders

- *Disease Activity Score (DAS)-28 < 2.6*

(b) (4)
 The results of DAS28 analyses are summarized here for completeness of the review. (b) (4)

The differences between apremilast 30 mg BID and placebo in the proportions of patients achieving DAS28 CRP < 2.6 at Week 16 were nominally significant at week 16 in studies PSA-002 and PSA-004, with treatment difference ranging from 4 to 11%.

- *SF-36*

(b) (4)
 The results of SF-36 analyses are summarized here for completeness of the review. (b) (4)

The mean change from baseline at Week 16 in the physical component summary (PCS) score showed a significantly significant improvement with apremilast 30 mg BID compared to placebo in all studies with treatment differences (the difference between apremilast and placebo) ranging from 1.7 to 2.2 units. The results in the domains contributing the most to the PCS were generally consistent with the PCS results. The mean change from baseline at Week 16 in the mental component summary (MCS) score however, showed a significantly

significant improvement in apremilast 30 mg BID compared to placebo in only one of the studies with treatment differences ranging from 0.6 to 1.9 units. The mean values in the domains contributing the most to the MCS remained generally unchanged with the exception of improvement in the Mental Health domain scores.



- *PASI Scores and Skin Manifestations*

(b) (4)

The results of PASI scores analyses are summarized here for completeness of the review. (b) (4)

(b) (4)

Post-hoc analyses were conducted in studies PSA-002, and PSA-003, where PASI score was determined only for the subpopulation of subjects whose BSA involved by psoriasis at baseline was $\geq 3\%$. In the subgroup of patients with body surface area (BSA) $\geq 3\%$ involved by psoriasis at baseline, the PASI75 scores at Week 16 improved significantly (not adjusted for multiplicity) in apremilast-treated patients compared with placebo without a clear dose-dependence.

- **Efficacy Conclusions**

The clinical and statistical review teams are in agreement that apremilast at the studied doses, 20 mg and 30 mg BID, is efficacious for signs and symptoms (ACR Responses) as well as for physical function (HAQ-DI) with an estimated treatment effect that is smaller than previously observed with biologic therapies approved for PsA. Efficacy results showed a numerical, but not statistically significant, advantage for the apremilast 30 mg BID compared to the apremilast 20 mg BID. Further, the proportion of HAQ-DI responders (HAQ-DI ≥ 0.3 units improvement) in apremilast 30 mg BID, but not 20 mg BID dose group, was statistically significant from placebo. These observations suggest that the apremilast 30 mg BID dosing may offer some advantages over 20 mg BID dosing and is reasonable as the recommended maintenance dose in PsA from efficacy perspective.

The clinical and statistical review teams are also in agreement that the presentation of the Week 24 data, particularly for continuous endpoints, such as HAQ-DI, is problematic due to

the significant proportions of patients crossing over to active treatment at Week 16 because of meeting early escape criteria (Table 4 above).

(b) (4)

Radiographic outcomes, while of interest in this disease, were not assessed in the apremilast PsA development program; however documenting structural benefit has not been a requirement for approval of products for PsA.

8. Safety

Studies contributing to integrated safety analyses, and Celgene's pooling and attribution strategies

A summary of the studies contributing to the primary integrated safety analyses may be found in Table 8 below. These included five studies with apremilast in subjects with PsA. The primary integrated safety analysis for apremilast was derived from the three nearly identically designed placebo-controlled Phase 3 studies: PSA-002, PSA-003, and PSA-004. These studies employed the same dosing regimens and each enrolled approximately 500 subjects with active PsA who had an inadequate clinical response to DMARDs and/or biologic therapy. The high degree of similarity of the study design of the three pivotal studies provides a scientific justification for integrating the safety data from these studies. The Phase 2 study PSA-001 was a dose-finding study of apremilast as either a single 40 mg daily dose or as a 20 mg dose given twice daily. As the study did not include the proposed 30 mg BID dosing regimen, the data from the study were used only as supportive and were not included in the primary integrated safety analysis. Safety data from the fifth study, PSA-005, are only used as supportive and not included in the integrated safety analyses, as the study was ongoing and blinded at the time of the original submission.

The primary safety analyses were focused on the placebo-controlled period, up to Week 24, from the three pivotal PsA studies. Placebo-controlled period was up to Week 24, however, at Week 16, all placebo subjects whose swollen and tender joint count had both not improved by $\geq 20\%$ were re-randomized 1:1 to receive APR 20 BID or APR 30 BID and dose-titrated during their first week of active treatment and subjects on active treatment who met early escape criteria continued to receive the same dosage of apremilast to which they were originally assigned. Of note, a significant proportion of patients crossed-over from to active treatment because they met the early escape criteria as shown in Table 4. To address some of

the complexity of the study design and account for cross-over of the early escapees at Week 16 the Applicant provided data analyzed using two patient populations as requested at the pre-NDA meeting:

- “As originally randomized”, i.e. patients who were censored once they crossed-over, referred to as “placebo-controlled period” by the Applicant,
- “As treated”, i.e. including patients who escaped to active treatment and contributed to the safety data under active treatment for the period when they received apremilast, referred to as “apremilast-exposure period” by the Applicant.

Data from the non-placebo-controlled periods of the three PsA Phase 3 studies were used to assess potential safety signals that may occur with longer exposures to apremilast, using exposure-adjusted incidence rates (EAIRs). These analyses were not adequately controlled and provided very limited ability to assess potential dose-relatedness of AEs.

Additional safety data were derived the as supportive from the clinical studies in psoriasis, rheumatoid arthritis (Table 8). This data pool was referred to as the Apremilast Unblinded Data Pool.

Table 8: Summary of Phase 2 and Phase 3 Studies Contributing to the Safety Assessment of Apremilast

Study	Centers (n)	Subjects Enrolled (n)	Dosing ^a	Study Design	Primary Endpoint
Primary Integrated Safety Analyses					
PsA:					
PSA-002	83	504	PBO APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active PsA with an inadequate response to DMARDs ± biologic therapy. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Week 16.	ACR20 @ Wk 16
PSA-003	84	488	PBO APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active PsA with an inadequate response to DMARDs ± biologic therapy. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Week 16.	ACR20 @ Wk 16
PSA-004	78	505	PBO APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active PsA with an inadequate response to DMARDs ± biologic therapy. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Week 16.	ACR20 @ Wk 16
Supportive Safety Analyses					
PsA:					
PSA-001	38	204	PBO APR20 BID APR 40 QD	Randomized, double-blind, PBO-controlled, dose-testing, parallel-group study enrolling subjects with active PsA. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR 40. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Day 85.	ACR20 @ Day 85
PSA-005	96	528	PBO APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active PsA who were naïve to DMARDs. Subjects were randomized 1:1:1 to receive PBO, APR20, or APR30 twice daily. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Week 16.	ACR20 @ Wk 16
Psoriasis					
PSOR-001	3	19	APR20 QD	Open-label, single-arm, pilot study enrolling subjects with severe plaque-type psoriasis. Subjects were treated with APR20 mg QD. Primary efficacy endpoint was improvement in the PASI score at Day 29.	PASI @ Day 29
PSOR-003	34	260	PBO APR20 QD APR20 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with mod-severe plaque-type psoriasis. Subjects were randomized 1:1:1 to receive PBO, APR20 mg QD, or APR20 mg BID. Primary efficacy endpoint assessing the proportion of subjects achieving a PASI reduction of ≥75% at Day 84.	PASI @ Day 84
PSOR-004	4	30	APR20 BID	Open-label, multicenter study enrolling subjects with plaque-type psoriasis. All subjects received APR20 mg BID. Primary efficacy endpoint assessing the change in PASI score at Day 85.	PASI @ Day 85
PSOR-005	20	352	PBO APR 10 BID APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with mod-severe plaque-type psoriasis. Subjects were randomized 1:1:1:1 to receive PBO, APR 10 mg BID, APR20 mg BID, or APR30 mg BID. Primary efficacy endpoint assessing the proportion of subjects achieving a PASI score ≥75 at Week 16.	PASI @ Wk 16
RA					
RA-002	42	237	PBO APR20 BID APR30 BID	Randomized, double-blind, PBO-controlled, parallel-group study enrolling subjects with active RA and an inadequate response to MTX. Subjects were randomized 1:1:1 to receive PBO, APR20 mg BID, or APR30 mg BID. Primary efficacy endpoint assessing the proportion of subjects achieving an ACR20 was performed at Week 16.	ACR20 @ Wk 16
^a Patients received initial titration regimen from Days 0 through 5 and then continued on the full apremilast dose. At Week 16, all subjects whose swollen and tender joint count had both not improved by ≥ 20% were re-randomized 1:1 to receive APR 20 BID or APR 30 BID and dose-titrated during their first week of active treatment. Subjects on active treatment who met early escape criteria continued to receive the same dosage of apremilast to which they were originally assigned. Abbreviations: APR=apremilast, ASTH=asthma, BCT=Behcet's disease,					

An AE was included in the safety database if the event occurred on or after the date of the first dose of study drug and no later than 28 days after the last dose of study drug. The serious AEs (SAEs) were defined using the standard regulatory definition. All AEs were coded according to MedDRA version 14.0.

Adverse events of special interest were pre-defined based on the mechanism of action of apremilast, possible class effects, and known comorbidities of PsA, and included gastrointestinal events, infections, malignancies, cardiovascular events, suicidal ideation and behavior (suicide and attempted suicide), depression, vasculitis, and weight changes. All AEs related to malignancies, serious infections, and potential major adverse cardio-vascular events (MACE) were adjudicated by independent, blinded, subspecialty adjudicators. Because a potential increased risk for suicide and other psychiatric events has been noted with the use of the PDE4 inhibitor, roflumilast, the Applicant identified these events as AEs of special interest and submitted a retrospective Columbia Classification Algorithm of Suicide Assessment (C-CASA) analysis for studies RA-002, PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, and PSOR-009. The Applicant also expanded the standard search terms in an effort to capture all potential suicide events. The subject profiles were then reviewed by Celgene physicians and classified as either suicidal ideation or suicidal behavior using the five levels of suicidal behavior defined in the FDA guidance. The adverse events of special interest were analyzed using either the MedDRA preferred terms/Standardized MedDRA Queries or Applicant - created queries, and presented in a format consistent with the primary safety analyses discussed above.

Laboratory data, ECG data, and vital signs were presented using summary statistics and pre-determined markedly abnormal values.

- **Adequacy of the database, major findings/signals, special studies**

As of the original submission data cut-off (July 06, 2012), the extent of the safety database comprised of 2401 patients (all indications) exposed to any dose of apremilast. Of these, 1441 patients were exposed to apremilast in the three Phase 3 pivotal studies providing 955 patient-years of exposure as summarized in Table 9 below. Exposure to placebo was lower in the long-term PsA safety database due to intentional design features of the controlled trials (e.g., limited duration of the placebo controlled period and provisions for early escape to active treatment at Week 16). The long-term exposure was limited, because less than a quarter of the patients were exposed to apremilast for longer than 48 weeks; however, the overall long-term exposure was comparable between the two apremilast doses allowing for a reasonable assessment of dose-related adverse events with apremilast exposure beyond the placebo-controlled period of the studies.

Table 9: Exposure to Apremilast by Dose and Duration in Phase 3 Pivotal Studies in PsA

Duration of exposure	Placebo	APR20 BID	APR 30 BID	APR All
As originally randomized*	N=495	N=501	N=497	N=998
≥ 4 weeks	484 (98%)	485 (97%)	472 (95.0)	957 (96%)
≥ 16 weeks	363 (73%)	449 (90%)	444 (89%)	893 (90%)
≥ 24 weeks	113 (23%)	292 (58%)	278 (56%)	570 (57%)
As treated population [#]	N=495	N=720	N=721	N=1441
≥ 4 weeks	484 (98%)	693 (96%)	686 (95%)	1379 (96%)
≥ 24 weeks	113 (23%)	516 (72%)	527 (73%)	1043 (72%)
≥ 48 weeks	-	176 (24%)	183 (25%)	359 (25%)
≥ 60 weeks	-	92 (13%)	84 (12%)	176 (12%)
Patient-years of exposure		477	478	955

Source: Integrated Summary of Safety (clinical data cut-off July 06, 2012), adapted from Tables 3 and 4
 **As originally randomized", i e patients who were censored once they crossed-over to active treatment at Week 16
 #As treated population" includes patients who escaped to active treatment at Week 16and contributed to the safety data under active treatment for the period when they received apremilast, referred to as "apremilast-exposure period" by the Applicant

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Overview of Safety in PsA Phase 3 Development Program

In the PsA Phase 3 development program, the overall incidence of AEs and AEs leading to withdrawal and dose interruption, but not SAEs, was higher in the apremilast-treated groups without a clear dose-dependence as shown in Table 10. The exposure-adjusted incidence rates were similar between the two apremilast dose groups in “as treated” analyses except for some dose-related higher rates of AEs leading to dose interruption in the apremilast 30 mg BID group.

Table 10. Safety Overview of the PsA Phase 3 Development Program (Studies PSA-002, -003, -004)

	As originally randomized*			As treated [#]	
	PBO (N=495)	APR 20 BID (N=501)	APR 30 BID (N=497)	APR 20 BID (N=720)	APR 30 BID (N=721)
Any AE	235 (48%)	308 (62%)	302 (61%)	456 (201)	476 (219)
SAE	19 (4%)	17 (3%)	19 (4%)	34 (7)	35 (8)
AE leading to withdrawal	21 (4%)	28 (6%)	36 (7%)	48 (10)	51 (11)
AE leading to drug interruption	24 (5%)	46 (9%)	64 (13%)	73 (16)	95 (22)
AE leading to death	0	1 (<1%)	0	1 (0.2)	0

Source: Integrated Summary of Safety, adapted from Table s29 and 30
 **As originally randomized", i e patients who were censored once they crossed-over to active treatment at Week 16
 #As treated population" includes patients who escaped to active treatment at Week 16and contributed to the safety data under active treatment for the period when they received apremilast, referred to as "apremilast-exposure period" by the Applicant

Deaths

As of the 120-day safety update (data cut-off March 01, 2013), a total of seven deaths were reported in the apremilast clinical development program for all indications. Of these one occurred in the PsA program, and the remaining five deaths occurred during the psoriasis studies (PSOR-004, PSOR-005, PSOR-008, and PSOR-009). Narratives of the subject deaths are as follows:

- Subject PSA-002-9051004 was a 52-year-old, White female with PsA, randomized to the APR20 BID, died due to multiple organ failure on Study Day 73. Death was attributed to pre-existing Vitamin B12 deficiency as a toxicity of MTX.
- Subject PSOR-004-0020009 was a 48-year-old, morbidly obese, White male with psoriasis who died an unwitnessed death on Study Day 140. The subject's past medical history was significant for a cardiac arrhythmia that was treated with a cardiac ablation procedure. The subject was originally randomized to the APR20 BID treatment arm but his apremilast dose was increased from 20 mg BID to 30 mg BID 53 days prior to his death.
- Subject PSOR-005-E-LTE-0421019 was a 63-year-old male subject with psoriasis randomized to the placebo treatment arm and found dead on Study Day 84 in his closed garage with a motorcycle running. Autopsy did not establish a cause of death.
- Subject PSOR-008-4031002 was a 30-year-old, White female with psoriasis who was randomized to the APR30 BID treatment arm and found dead on Study Day 111, seven days after receiving her last dose of apremilast. The subject's past medical history included obesity (BMI=41 kg/m²), depression, and alcohol use. Autopsy results were significant for diffuse lung congestion and bilateral edema that was consistent with acute cardiac failure in association with sleep apnea and morbid obesity.
- Subject PSOR-008-0251014 was a 28-year-old, White female with psoriasis, randomized to placebo, committed suicide via a gunshot wound on Study Day 55, with the last placebo dose administered on Study Day 29. Subject's past medical history was significant for depression, bipolar disorder, previous suicide attempts, unstable family life, obesity, alcohol abuse, and insomnia.
- Subject PSOR-009-1191012 was a 51-year-old, White female with psoriasis who died secondary to an intracranial hemorrhage. The subject received apremilast for 225 days followed by placebo for 112 days.
- Subject PSOR-008-1051011, a 69-year old, White, male subject, experienced a fatal cerebrovascular accident (CVA) on while receiving apremilast 30 mg BID for 666 days in the long-term extension phase of the study. The subject's medical history included

long-standing hypertension, hyperlipidemia, type 2 diabetes mellitus, obesity (BMI was 42.6 kg/m² at screening), ex-smoker, alcohol use, chronic obstructive pulmonary disease, chronic bronchitis, anemia, and benign prostatic hyperplasia.

Of the seven deaths that occurred during the apremilast development program, three subjects were being treated with apremilast, two subjects were receiving placebo, and one subject was initially randomized to apremilast but was subsequently re-randomized to the placebo treatment arm during the randomized withdrawal period of study PSOR-009. One additional death was reported in a non-Celgene-sponsored RA study from an acute myeloid leukemia diagnosed about one year after completion of 3 weeks of apremilast treatment. The overall mortality rates were low and the causes of death were consistent with what is expected for the background patient population.

Of note, the deaths of subjects PSOR-008-0251014 and PSOR-005-E-LTE-0421019, who were receiving placebo, were apparent suicides. Patients with psoriasis have been reported to demonstrate increased incidences of suicidal ideations, suicide attempts, and completed suicides compared to the general population and patients with other chronic diseases.^{13, 14} A separate analysis of depression, suicidal ideations, suicide attempts, and/or completed suicides to assess a potential association with apremilast use is discussed below in this document.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients experiencing SAE was approximately 4% and comparable across all treatment groups during the 24-week placebo-controlled period of the Phase 3 PsA studies as summarized in Table 10 above. The SAEs included psoriatic arthropathy (n=4), cholelithiasis (n=3), atrial fibrillation (n=2), breast cancer (n=2), depression (n=2), acute myocardial infarction (n=2), congestive heart failure (n=2), hypertensive crisis (n=2), and acute pancreatitis (n=2). The incidence and pattern of SAEs did not suggest a clear safety signal with apremilast use.

Discontinuations due to Adverse Events (DAE)

The proportion of patients discontinuing due to an adverse event was numerically higher in the apremilast treatment groups compared to the control groups, as shown in Table 11 below. The most common AEs leading to drug withdrawal were nausea, diarrhea, headache, dizziness, and vomiting that appeared to increase in a treatment- and dose-dependent manner. Depression, as an AE of special interest and discussed in further detail in the respective section, was also a cause of discontinuation from treatment and occurred only in apremilast-treated subjects but not in a dose-related manner. The incidence and types of AEs leading to drug discontinuation were consistent for the “as treated” population, and the apremilast unblinded data pool.

¹³ Kurd SK, et al., “The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study”, Arch Dermatol. 2010 Aug;146(8):891-5

¹⁴ Dowlatshahi EA, et al., “The Prevalence and Odds of Depressive Symptoms and Clinical Depression in Psoriasis Patients: A Systematic Review and Meta-Analysis”, J Invest Dermatol. 2013 Nov 27

Table 11: Patient Discontinuation due to AE in Phase 3 PsA Studies PSA-002, -003, -004 During the Placebo-controlled Period

	PBO (n=495) n (%)	APR20 BID (n=501) n (%)	APR30 BID (n=497) n (%)
Any SAE	21 (4)	28 (6)	36 (7)
Nausea	3 (<1)	7 (1)	13 (3)
Diarrhea	3 (<1)	5 (1)	11 (2)
Headache	2 (<1)	1 (<1)	8 (2)
Dizziness	2 (<1)	2 (<1)	3 (1)
Vomiting	0	1 (<1)	3 (1)
Fatigue	0	1 (<1)	3 (1)
Migraine	0	1 (<1)	2 (<1)
Abdominal pain, upper	0	1 (<1)	2 (<1)
Abdominal discomfort	1 (<1)	1 (<1)	1 (<1)
Abdominal pain	1 (<1)	2 (<1)	0
Urticaria	1 (<1)	1 (<1)	1 (<1)
Hyperhidrosis	1 (<1)	2 (<1)	0
Decreased appetite	0	1 (<1)	1 (<1)
Depressed mood	0	1 (<1)	1 (<1)
Depression	0	2 (<1)	0
Abdominal distention	0	1 (<1)	1 (<1)
Dyspepsia	0	2 (<1)	0
Cellulitis	1 (<1)	0	1 (<1)
Anxiety	1 (<1)	1 (<1)	0
Dyspnea	1 (<1)	1 (<1)	0
Psoriatic arthropathy	1 (<1)	0	1 (<1)
Hypertension	2 (<1)	0	0

Source: Integrated Summary of Safety, adapted from Table 88

○ **Special Safety Concerns: Adverse Events of Special Interest**

The Applicant predefined a set of AEs of special interest that were based on the mechanism of action of apremilast, possible class effects, known comorbidities of PsA, and other factors. These AEs of special interest were followed during the apremilast clinical program and included gastrointestinal events, infections, malignancies, cardiovascular events, suicidal ideation and behavior (suicide and attempted suicide), depression, vasculitis, and weight changes.

Gastrointestinal Events

Gastrointestinal events are commonly associated with the use of PDE4 inhibitors and were the most commonly reported AE and occurred with the highest incidence with initiation of therapy, i.e. during the initial dose titration (data not shown). They were also the most common reason for discontinuation in the apremilast studies (Table 11). Diarrhea, nausea, and vomiting were observed to increase in a dose- and treatment-dependent manner during the placebo-controlled period of the PsA Phase 3 studies as shown in Table 12. The vast majority of the gastrointestinal adverse events were mild to moderate; however there was one serious

case of diarrhea reported in the apremilast 20 mg BID treatment group and one case of serious nausea and vomiting reported in the apremilast 30 mg BID treatment group.

Table 12. Summary of Select Gastrointestinal Adverse Events in Phase 3 PsA Studies PSA-002, -003, -004 During the Placebo-controlled Period

	Placebo	APR20 BID	APR 30 BID	APR All
As originally randomized*	N=495	N=501	N=497	N=998
Gastrointestinal Disorders SOC, n (%)	64 (13%)	128 (26%)	181 (36%)	309 (31%)
Diarrhea	14 (3%)	63 (13%)	82 (17%)	145 (15%)
Nausea	23 (5%)	50 (10%)	80 (16%)	130 (13%)
Vomiting	4 (1%)	12 (2%)	22 (4%)	34 (3%)
As treated population [#]	N=495	N=720	N=721	N=1441
Gastrointestinal Disorders SOC, n (%)	64 (13%)	183 (25%)	242 (34%)	425 (30%)
Diarrhea	14 (3%)	80 (11%)	109 (15%)	189 (13%)
Nausea	23 (5%)	63 (9%)	94 (13%)	157 (11%)
Vomiting	4 (1%)	17 (2%)	28 (4%)	45 (3%)
Source: Integrated Summary of Safety (clinical data cut-off July 06, 2012), adapted from Tables 36 through 39 **As originally randomized", i.e. patients who were censored once they crossed-over to active treatment at Week 16 #As treated population" includes patients who escaped to active treatment at Week 16 and contributed to the safety data under active treatment for the period when they received apremilast, referred to as "apremilast-exposure period" by the Applicant				

Serious Infections, Including Opportunistic Infections and Tuberculosis

A total of 18 subjects reported a serious infection for the Apremilast Unblinded Data Pool: two placebo-treated subjects, six APR20 BID subjects, and ten APR30 BID subjects. Of the 18 cases, six were opportunistic infections described below. The 12 cases of non-opportunistic serious infections included three cases each of appendicitis and pneumonia, two cases of cellulitis, and single cases of an abdominal abscess, gastroenteritis, anal abscess, and empyema.

In the PsA Phase 3 studies, there was no requirement for latent TB screening prior to enrollment. There were no new cases of tuberculosis or tuberculosis reactivation reported in either the PsA development program or the Apremilast Unblinded Data Pool (all indications). Opportunistic infections were rare in the Apremilast Unblinded Data Pool (all indications). The three cases of systemic opportunistic infections included single cases of *Rothia* species-related tenosynovitis following a puncture wound (placebo), Herpes Zoster with associated viral meningitis (apremilast 20 mg BID), and MRSA-related naso-facial cellulitis/abscess (apremilast 30 mg BID). Three cases of non-systemic opportunistic infections consisted of two cases of bacterial pneumonia, and a single case of *Clostridium difficile* infection.

In summary, the incidence and types of serious infections including the reported opportunistic infections do not suggest that apremilast administration is associated with significant immunosuppression and do not indicate an increased risk of serious infections with apremilast use.

Malignancy

Because apremilast is ostensibly an immunomodulatory product, malignancy was identified as an event of special interest for adjudication. A total of 18 out of 22 cases meeting criteria for adjudication were identified as adjudicated malignancy events for the Apremilast Unblinded Data Pool (all indications). Seven of the 18 cases were non-melanoma skin cancers. Of the remaining 11 events, there were four cases of prostatic adenocarcinoma, two cases of breast cancer, two cases of lung cancer, and one case each of B-cell lymphoma, neoplasia of the oral cavity, and mesothelioma. The time from initiation of apremilast therapy to the onset of malignancy varied between 36 to 440 days with no clear temporal or dose-response relationship between dosing and the onset of the event. Of the 18 adjudicated cases, ten occurred in the PsA Phase 3 Data Pool: three subjects in the placebo arm, five subjects in the APR20 arm, and two subjects in the APR30 arm. The overall incidence and types of malignancy in the apremilast PsA development program do not suggest an increased risk of malignancy with apremilast use.

Cardiovascular Adverse Events

Cardiovascular disorders were identified as events of interest for monitoring and analyses. Adverse events related to MACE included sudden unwitnessed death, cardiovascular death (i.e., sudden cardiac death, death due to MI, death due to heart failure, death due to stroke, death due to other cardiovascular causes), MI, and non-fatal stroke. Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularization procedures, transient ischemic attack (TIA), re-hospitalization for recurrent ischemia, embolic events, and deep vein thrombosis.

A total of 8 out of 19 cases meeting criteria for adjudication were identified as adjudicated MACE and potential MACE events for the Apremilast Unblinded Data Pool (all indications) with all events being reported in the APR20 and APR30 treatment arms. Five of the reported cases occurred in the PsA Phase 3 studies. Overall, the numbers of adjudicated MACE were small and all attributed to cases of MI with estimated exposure adjusted incidence rates of 0 events/100 patient years for placebo, 0.4 events/100 patient years for apremilast 20 mg BID (n=3), and 0.2 event/100 patient years for apremilast 30 mg BID (n=1) treatments arms.

The overall small number of MACE events and the lack of dose-relatedness preclude definitive conclusions on an association between apremilast therapy and significant cardiovascular adverse events.

Psychiatric Adverse Events

Psychiatric adverse events were identified as a potential class effect of PDE4 inhibition and prospectively monitored as adverse events of interest in the apremilast development program. The concerns was based on imbalances in psychiatric adverse events in the roflumilast, a PDE4 inhibitor, development program in COPD which are included as warnings and precautions in roflumilast product labeling: psychiatric adverse events in patients taking roflumilast (5.9%) vs. patients taking placebo (3.3%), including higher proportions of patients reporting insomnia, anxiety, and depression. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving roflumilast (n = 4438) compared to one patient (suicidal ideation) who received placebo (n = 4192).

To assess for potential association of apremilast use and psychiatric events, including depression, suicidal ideations, suicidal attempts, completed suicides, and self-injury as adverse events of special interest, the Applicant used two approaches: (1) a narrow standardized MedDRA query term search and (2) a retrospective search using the Columbia Classification Algorithm of Suicide Assessment (C-CASA)¹⁵ of the apremilast clinical development program. A C-CASA analysis (using the method described by Posner et al.), if done correctly, is the most definitive way to look for and classify suicidal ideation and behavior.

Numerical imbalances were observed between placebo- and apremilast-treated patients during the placebo-controlled period in the PsA development program as shown in Table 13. Overall, more patients experienced a depression and discontinued therapy in the apremilast-treatment groups than in placebo. However, there were not dose-dependent increases in the incidence of any of the reported psychiatric events, further corroborated by the exposure-adjusted incidence rates (3 events per 100 subject-years in the apremilast 20 mg BID treatment arm vs. 1.9 events per 100 subject-years in the apremilast 30 mg BID treatment arm). In addition, more patients discontinued treatment in the apremilast 20 mg BID compared with the 30 mg BID dose group. The lack of dose-relatedness raises questions about the clinical significance of the observed numerical imbalances.

Additional analyses, submitted in response to an information request, combined safety data from PsA studies PSA-001 through SPA-004 along with new data from the already unblinded study PSA-005 which has the identical design as the core PsA studies. The analyses on these updated data showed consistently similar crude incidence and exposure-adjusted rates between placebo and apremilast 30 mg BID.

To further assess the adequacy of the Applicant's review of the psychiatric adverse events, the Division of Psychiatry Products (DPP) was consulted. The consult's team identified some limitations of the Applicant's C-CASA analysis. Specifically, the analysis was retrospective and was conducted by physicians internal to Celgene. There were two cases of suicidal ideation and one case of apparent completed suicide (described in section Deaths above) which

¹⁵ Posner K, et al., "Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants", *Am J Psychiatry*. 2007 Jul;164(7):1035-43

were not identified by the Applicant’s C-CASA analysis but were identified by the SMQ search as well as the DPP consult team. Granted the limitations of the Applicant’s C-CASA analysis, the DPP consult team concurred with the Division’s assessment that there was no signal for suicidal ideation or behavior looking at either the placebo-controlled period of the PsA Phase 3 Data Pool or the Apremilast Unblinded Data Pool (all indications).

In summary, more patients experienced a depression and discontinued therapy in the combined apremilast-treatment groups (14/998 or 1.4%) than in placebo (4/495 or 0.8%). However, these differences were not dose-dependent and were driven primarily by in the apremilast 20 mg BID dose group. Further, patients with PsA, similarly to patients with psoriasis, have an increased estimated incidence of depression.¹⁶ More apremilast-treated patients reported suicidal ideations (3/998 or 0.2%) compared with 0 placebo-treated patients. However, two placebo-treated patients (0.4%) committed suicide and none in the apremilast groups in the PsA program. Based on these observations, the numerical imbalances do not appear to represent a clear safety signal of psychiatric events, including suicidality in the PsA apremilast development program. However, because these adverse events are clinically significant, they warrant inclusion in the product labeling.

Table 13. Summary of Select Psychiatric Adverse Events in Phase 3 PsA Studies PSA-002, -003, -004 During the Placebo-controlled Period

	Placebo n (%)	APR20 BID n (%)	APR 30 BID n (%)	APR All n (%)
As originally randomized*	N=495	N=501	N=497	N=998
Any depression AE	4 (0.8%)	9 (1.8%)	5 (1%)	14 (1.4%)
Depression SAE	0	2 (0.4%)	0	2 (0.2%)
Depressions AE leading to discontinuation	0	3 (0.6%)	1 (0.2%)	4 (0.4%)
Suicide, completed	2 (0.4%)	0	0	0
Suicidal ideation/attempt	0	2 (0.4%)	0	2 (0.2%)
As treated population [#]	N=495	N=720	N=721	N=1441
Any depression AE	4 (1%)	14 (1.9%)	9 (1.2%)	23 (1.6%)
Depression SAE	0	2 (0.3%)	1 (0.1%)	3 (0.2%)
Depressions AE leading to discontinuation	0	3 (0.4)	1 (0.1%)	4 (0.3%)
Suicide, completed	2 (0.4%)	0	0	0
Suicidal ideation/attempt	0	2 (0.3%)	1 (0.1%)	3 (0.2%)
Source: Integrated Summary of Safety (clinical data cut-off July 06, 2012), adapted from Tables 137 through 140 **As originally randomized”, i e patients who were censored once they crossed-over to active treatment at Week 16 #As treated population” includes patients who escaped to active treatment at Week 16and contributed to the safety data under active treatment for the period when they received apremilast, referred to as “apremilast-exposure period” by the Applicant				

¹⁶ Freire M, et al., “Prevalence of symptoms of anxiety and depression in patients with psoriatic arthritis attending rheumatology clinics”, Reumatol Clin. 2011 Jan-Feb;7(1):20-6

Vasculitis

Vasculitis was selected and prospectively monitored as an adverse event of special interest because of the findings of arteritis in the non-clinical development as discussed in detail in section Nonclinical Pharmacology/Toxicology above. An analysis of vasculitis conducted based on a search using the narrow SMQ terms identified two cases of vasculitis across all studied indications: one case of cutaneous vasculitis in a patient with RA treated with apremilast 30 mg BID and once case of cutaneous vasculitis in a placebo-treated patient. No cases of vasculitis were identified in the PsA development program. The sporadic nature of cases of reported vasculitis, including one in a patient at risk of vasculitis as an extraarticular manifestation of RA, and one case in placebo, do not indicate a safety signal of vasculitis with apremilast administration.

Weight Changes

Weight decreases were identified as a potential event of special interest as significant weight decreases were reported with roflumilast. During the placebo-controlled period, placebo-treated subjects had a fairly stable weight (mean weight gain of 0.09 kg) compared with a mean weight loss of about 1 kg observed in the apremilast groups. In addition, during the controlled period of the PsA Phase 3 studies, weight decrease between 5 and 10% of body weight was reported in 10% (49/497) of patients treated with apremilast 30 mg twice daily compared to 3.3% (16/495) treated with placebo. A total of three placebo-treated subjects, 23 apremilast 20 mg BID-treated subjects, and 22 apremilast 30 mg BID-treated subjects experienced weight loss $\geq 10\%$ from baseline at any time during the study. While the weight decreases were not clearly dose-dependent, they were apremilast-related. Because weights were measured at pre-specified timepoints and not at the time of other AEs occurrences, associations between weight changes and gastrointestinal AEs could not be adequately assessed.

In summary, the weight decreases in the apremilast PsA development program were consistent with what was observed with roflumilast and indicate a PDE4 inhibitor class effect which warrants inclusion the Warnings and Precautions section consistent with roflumilast labeling.

Common AE

Adverse events in the Gastrointestinal Disorders SOC were the most common adverse events in the PsA Phase 3 studies. In the first 24 weeks of the Phase 3 studies, approximately 25 to 35% of patients in the apremilast groups experienced a gastrointestinal adverse event in a dose-related manner (mostly diarrhea and nausea) compared to 13% of patients in the placebo group. Headache was the next most common dose-dependent AE, occurring in 10 to 12% in the apremilast-treated patients compared to 5% of patients in the placebo. The majority of these events occurred during the first two weeks of initiating therapy; they were of mild to moderate intensity, and for the most part did not result in discontinuation from therapy. As apremilast was titrated for the first 5 days and patients did not receive the full apremilast dose

until 5 days, presenting the common adverse events of these two periods may be informative for prescribers and patients and should be considered for inclusion in the product labeling.

Laboratory Abnormalities

Summary statistics of observed values and changes from baseline over time were assessed for hematology and clinical chemistry parameters at pre-specified timepoints in the placebo-controlled and apremilast-exposure periods in the three PsA Phase 3 studies. The baseline laboratory values were well balanced in all three treatment arms. The data were analyzed using mean change from baseline and shifts from baseline to the end of the study period. The mean changes from baseline in hematology and clinical chemistry (including glucose, serum creatinine, cholesterol, and electrolytes) values were small, infrequent, and not clinically significant (data not shown). The analyses of shifts from baseline have not identified clinically meaningful differences between the groups with a notable exception of some hepatic enzyme abnormalities discussed below.

Hepatic enzyme abnormalities

At baseline, ALT or AST elevations were reported in approximately 10 to 15% of patients and bilirubin elevations only in 1 to 2% of patients, and these were equally distributed among the treatment groups. Significant liver test abnormalities were uncommon in the PsA clinical development program. During the placebo-controlled period of the pivotal PsA studies, numerical imbalances in the incidence of marked liver function test abnormalities defined as ALT or AST elevation > 3 times the upper limit of normal (ULN) was observed that appeared to be treatment and dose-related: placebo in 2/492 (0.4%) patients, apremilast 20 mg BID in 2/496 (0.4%), and apremilast 30 mg BID in 7/492 (1.4%) of the patients. These findings however, were not consistent with the analyses of the “as treated” population where no dose-dependent differences in the marked liver tests abnormalities were observed between the two apremilast doses. Bilirubin elevations greater than 1.8 x ULN were reported in 2/496 (0.4%) of the patients in the apremilast 20 mg BID and 2/492 (0.4%) of the patients in apremilast 30 mg BID groups but not in placebo. However, none of the subjects had an AST/ALT value >3 x ULN with an associated increase in bilirubin >1.5 x ULN and no cases of liver test elevations met Hy’s Law criteria in any Data Pool. Only two patients in the apremilast 20 mg BID group discontinued treatment due to hepatobiliary AE. A single subject from the apremilast 30 mg BID group reported an increase of ALT (1.3 x ULN) and AST (1.1 x ULN) in conjunction with an elevated bilirubin (>1.5 x ULN). This subject had a medical history significant for several years of hyperbilirubinemia.

In summary, the transient nature of the reported sporadic hepatic enzyme abnormalities and the fact that many of the subjects in the PsA program were receiving concomitant medications known to be hepatotoxic including MTX or statins, do not indicate a safety signal and can be monitored via routine clinical monitoring.

Hypersensitivity

Subsequent to the original submission, the Applicant has identified one case of hypersensitivity upon re-challenge which resulted in discontinuation. In response, the Applicant amended the proposed labeling sections Contraindications and Adverse Reactions.

- **Immunogenicity**

As an orally administered small molecule, apremilast is not expected to be associated with immunogenicity.

- **Safety Conclusions**

Dr. Hull and I are in agreement that the currently submitted safety data and analyses are adequate to inform the decision regarding the benefit-risk profile of the product. The safety data submitted for apremilast suggests it is associated with dose-dependent gastrointestinal effects mostly upon initiation of therapy and weight decreases both of which appear to be class effects of PDE4 inhibition. The most commonly occurring adverse events associated with apremilast were diarrhea, nausea, vomiting, headache, and upper respiratory tract infections (URI). These AEs typically occurred in the first 14 days after starting apremilast, were usually mild or moderate in severity, and generally resolved within 30 days while subjects continued receiving apremilast. Treatment with apremilast was also associated with weight loss, with approximately 10% of apremilast-treated subjects losing between 5% and 10% of body weight. Except for the AEs of diarrhea, nausea, vomiting, headache, and URI, no imbalance was observed for adverse events of special interest including adjudicated events of serious infections, MACE, and malignancies.

More patients experienced a depression and discontinued therapy in the combined apremilast-treatment groups (14/998 or 1.4%) than in placebo (4/495 or 0.8%). However, these differences were not dose-dependent and were driven primarily by in the apremilast 20 mg BID dose group. More apremilast-treated patients reported suicidal ideations (3/998 or 0.2%; two in the apremilast 20 mg BID and one in the apremilast 30 mg BID group) compared with 0 placebo-treated patients. However, two placebo-treated patients (0.4%) committed suicide and none in the apremilast groups in the PsA program. Based on these observations, the numerical imbalances do not appear to represent a clear safety signal of psychiatric events, including suicidality in the PsA apremilast development program. Further, patients with PsA, similarly to patients with psoriasis, have an increased estimated incidence of depression.¹⁷

¹⁷ Freire M, et al., "Prevalence of symptoms of anxiety and depression in patients with psoriatic arthritis attending rheumatology clinics", *Reumatol Clin.* 2011 Jan-Feb;7(1):20-6

The overall safety profile of the two tested apremilast doses 20 mg BID and 30 mg BID appears comparable with no notable dose-dependent major toxicities in patients with PsA supporting the proposed maintenance dosing of 30 mg BID.

Because PsA is a disease which also affects females with child-bearing potential, to further address the effect of apremilast on pregnancy and embryo-fetal development, the PMHS recommend, and the Division concurred, that a long-term active-controlled safety study should be conducted as a postmarketing requirement.

9. Advisory Committee Meeting

Advisory Committee meeting is generally convened for discussion of new molecular entity products, such as apremilast. However, following internal discussions based on the initial reviews of the efficacy and safety data submitted in support of the NDA, the Agency has determined that there were no questions that would warrant further discussion at a public forum and the tentatively scheduled Advisory Committee meeting for this NDA has been canceled.

10. Pediatrics

(b) (4)

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

Juvenile psoriatic arthritis (JPsA) has been considered the juvenile equivalent of adult PsA, and thus study(ies) in JPsA patients would be required by the Pediatric Research Equity Act (PREA) if this NDA in adult patients with PsA is approved. Historically, the Agency has waived the requirements for such studies, as these would be impossible or highly impracticable due to the difficulty of making specific diagnoses of JPsA in the pediatric age range, and the rarity of the condition.

There has been no submission, discussions, and respectively no agreed upon pediatric study plan (PSP) prior to the NDA submission. With this NDA, Celgene submitted a pediatric plan,

(b) (4)

(b) (4)

the Division recommended a full waiver of pediatric studies in JPsA.

The apremilast pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on November 20, 2013. The PeRC agreed with Division's recommendation to grant a full waiver of pediatric studies with juvenile psoriatic arthritis.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **OSI audits**

OSI inspected 2 clinical sites in the US (Dr. Sanford Wolfe, Dayton Ohio and Dr. Antony Hou, Upland California) and the Applicant, Celgene's site in Warren, NJ. The Applicant's site and Dr. Wolfe's site received NAI. Dr. Hou's site received VAI due to lack of updating informed consent documents at follow-up visits and a delay in reporting one subject's noncompliance to the IRB. However these were not considered to affect the integrity of the data from the Hou site. The Applicant inspection concluded that this clinical site appeared to be in compliance with Good Clinical Practices. The overall OSI conclusion was that the study data collected and submitted with the NDA appear generally reliable in support of the requested indication.

- **Other discipline consults**—Division of Psychiatric Products

The FDA Division of Psychiatric Products consult team concluded that there is no safety signal of psychiatric adverse events, including suicidality as discussed in detail in section "Special Safety Concerns: Adverse Events of Special Interest/ Psychiatric Adverse Events" above.

- **Any other outstanding regulatory issues**—Not applicable.

12. Labeling

The Applicant submitted a product label in PLR format for review on March 21, 2013.

- **Proprietary name**

The proposed proprietary name for apremilast is Otezla. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of

Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be acceptable.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments**

Consistent with the findings from this review Division, the Division of Risk Management (DRISK) identified no serious safety issues which warrant requiring a REMS to ensure that the benefits of apremilast outweigh the risks.

- **Physician labeling**

Major issues with the currently proposed labeling (original version submitted March 21, 2013):

1) Dosage and Administration section:

- This section should be revised to provide adequate directions on the titration regimen and the reason for titration, i.e. to reduce the gastrointestinal symptoms with initial therapy. The statement (b) (4) should be deleted as it is not supported by data.

2) Warnings and Precautions section: Originally proposed as (b) (4)

- This section should be revised to include:
 - Weight decrease, which was a common finding in the apremilast PsA development, consistent with the findings with roflumilast, another PDE4 inhibitor, indicating a class effect.

3) Adverse Reactions section: This section should be revised as follows:

- Include subsection on psychiatric events, including depression, suicidal ideations and suicidality
- Present the common adverse events separate for the titration period (days 0-5) and the full apremilast dose (Days 6 to Week 16) to provide a descriptive sense of what prescribers and patients should be expecting during titration and then on a stable full dose of the drug.
- The language (b) (4) the risk of adverse events should be revised in some need to
- Include Psychiatric adverse events

4) Clinical studies section:

- (b) (4)
-
-
-
-

- Language and data pertaining to other endpoints in the clinical studies section will need revision

As of the time of this review, the review team is discussing the labeling revisions with the Applicant in order to finalize the product labeling.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above.

- **Carton and immediate container labels (if problems are noted)**

DMEPA's review team concluded that the proposed container and blister labels, container labels, and carton labeling are acceptable.

- **Patient labeling/Medication guide (if considered or required)**

No serious safety issues have been identified which warrant requiring a patient labeling/Medication Guide.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of apremilast for the treatment of adult patients with active psoriatic arthritis provided agreement can be reached with the applicant on revisions to the proposed label.

- **Risk Benefit Assessment**

1) Analysis of condition

Psoriatic Arthritis (PsA) is a serious inflammatory disease that results in premature morbidity, mortality, and disability if left untreated. It occurs in approximately 25 to 30% of patients with psoriasis and is manifested by several types of arthritis of varying distribution, including the extreme case of rapidly progressive destructive arthritis mutilans. Psoriatic arthritis is in the group of the seronegative spondyloarthropathies affecting the peripheral and core joints as well as the axial skeleton, entheses, and tendon sheaths, and is characterized by bone formation and destruction radiographically. Early, aggressive treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs) appears to have altered the course of peripheral joint disease in PsA, although the details of this are difficult to characterize over the long-term. Because of the severity of the untreated disease, potent immunosuppressives have been commonly used in

the treatment PsA, with their incumbent risks, such as an increased susceptibility to serious infection.

2) Unmet medical need

As noted in Section 2 of this memorandum, there are 6 targeted biologic DMARDs currently approved for PsA, but these are all injectable products for either subcutaneous or intravenous administration. No oral small molecules are approved for PsA even though other traditional DMARDs are currently used for the treatment patients with PsA; methotrexate is the predominant and typically foundational DMARD used, followed by other small molecule drugs such as sulfasalazine and leflunomide. If approved, apremilast will be the first in class, orally administered product, specifically approved for PsA and would be a welcome addition to the therapeutic armamentarium for PsA.

3) Benefits

As described in section 7 Clinical/Statistical- Efficacy above, all three submitted Phase 3 studies provided corroborating evidence of the efficacy of apremilast for reducing the signs and symptoms of PsA, based on the proportion of patients experiencing improvement in the modified ACR20 response criteria with some numerical advantages of apremilast 30 mg BID over 20 mg BID in studies PSA-002 and PSA-004.

The three Phase 3 studies also provided corroborating evidence of the efficacy of apremilast for improving physical function, as measured by HAQ-DI.

4) Risks

The risks associated with apremilast are consistent with the risks of PDE4 inhibition. Apremilast treatment was associated with:

- An increased incidence of gastrointestinal adverse events that appeared to be dose-dependent,
- An increased incidence of weight reductions without a clear dose-dependence.

5) Benefit-Risk Overview and Dosing Recommendations

Based on the data in this submission, the seriousness of PsA, and the need for additional orally administered therapies, the benefit-risk profile of apremilast in RA is adequately favorable to support approval of apremilast for the treatment of patients with active PsA.

The proposed recommended dosing is initial titration from Day 0 through Day 5 as summarized in Table 3 above, followed by the full apremilast dose of 30 mg BID thereafter. This dosing regimen was employed in the Phase 3 PsA development program supporting this NDA.

- Initial titration: The applicant-proposed initial titration regimen is intended to reduce the incidence of gastrointestinal effects with initiating apremilast treatment in order to

improve tolerability based on clinical data from early clinical development. The titration regimen has been extensively studied in the PsA development and supported by the clinical data.

- **Maintenance dosing:** The overall safety profile of the two tested apremilast doses, 20 mg BID and 30 mg BID, appears comparable with no notable dose-dependent major toxicities in patients with PsA. In the PsA confirmatory studies PSA-002, -003, and 004, apremilast was efficacious for signs and symptoms (ACR Responses) as well as for physical function (HAQ-DI). Efficacy results showed a numerical, albeit not statistically significant, advantage for the apremilast 30 mg BID compared to the apremilast 20 mg BID. The proportion of HAQ-DI responders (HAQ-DI \geq 0.3 units improvement) in apremilast 30 mg BID, but not 20 mg BID dose group, was statistically significant from placebo. These overall safety and efficacy data suggest that the apremilast 30 mg BID dosing may offer some advantages over 20 mg BID dosing to warrant the recommended maintenance dose of 30 mg BID in PsA.
- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The review of the NDA has not identified serious safety concerns with apremilast for use in adult patients with psoriatic arthritis. While psychiatric adverse events were observed in the apremilast clinical development, the incidence of these events is consistent with what has been reported in the literature for the target patient population, and did not suggest a clear safety signal. Therefore a Risk Evaluation and Mitigation Strategy (REMS) is not required for this application.

- **Recommendation for other Postmarketing Requirements and Commitments**

This NDA, if approved, would trigger PREA. However, the Applicant has been granted a full waiver of pediatric studies in patients with juvenile psoriatic arthritis, because such studies would be impossible or highly impracticable, consistent with prior regulatory precedent, and would not be required to conduct such studies under PREA.


1. Pregnancy Registry Study.

In considering whether a postmarketing commitment or requirement should be enacted, I considered the following factors:

- Animal data suggesting that apremilast increases the incidence of embryo-fetal deaths in mice and abortions in monkeys in a dose-dependent manner
- Limited pre-marketing embryo-fetal apremilast exposure data in humans.

Therefore, a post-marketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant to accrue additional data to assess whether apremilast exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group.

Subsequent to the discussion at the Late-Cycle Meeting, the Applicant amended the NDA with a commitment to conduct a pregnancy exposure registry study as a Post Marketing Requirement [REDACTED] (b) (4)

 ^{(b) (4)} outlining the general study design and proposed estimated timelines which are currently under review.

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
02/06/2014